S. HRG. 108–791

FDA, MERCK, AND VIOXX: PUTTING PATIENT SAFETY FIRST?

HEARING

BEFORE THE

COMMITTEE ON FINANCE
UNITED STATES SENATE

ONE HUNDRED EIGHTH CONGRESS

SECOND SESSION

NOVEMBER 18, 2004

Printed for the use of the Committee on Finance

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U.S. GOVERNMENT PRINTING OFFICE

99–575—PDF WASHINGTON : 2005

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FDA, MERCK, AND VIOXX: PUTTING PATIENT SAFETY FIRST?

THURSDAY, NOVEMBER 18, 2004

U.S. SENATE,
COMMITTEE ON FINANCE,
Washington, DC.

The hearing was convened, pursuant to notice, at 10 a.m., in room SH–216, Hart Senate Office Building, Hon. Charles E. Grassley (chairman of the committee) presiding.

Also present: Senators Hatch, Nickles, Lott, Snowe, Bunning, Baucus, Breaux, and Bingaman.

OPENING STATEMENT OF HON. CHARLES E. GRASSLEY, A U.S. SENATOR FROM IOWA, CHAIRMAN, COMMITTEE ON FINANCE

The CHAIRMAN. Good morning, everybody. We are here today because Congress has a constitutional duty to conduct oversight of the executive branch of government. Congressional oversight can expose wrongdoing in both the Federal bureaucracy, as well as in the private sector. Congressional oversight can shed disinfecting sunlight. It can result in accountability and necessary reforms for the public good.

Today's hearing will consider allegations of mismanagement by the Food and Drug Administration and by Merck Pharmaceutical Company regarding the safety of the painkiller, Vioxx.

On September 30 of this year, Merck withdrew Vioxx from the worldwide market. A blockbuster drug became a blockbuster disaster. Before September 30, Vioxx was the subject of controversy in the scientific community behind closed doors.

Today we will look out in the open at the decisions made about Vioxx. Depending on the perspective you take, Vioxx either changed lives for the better or ended lives prematurely.

Historically, the Food and Drug Administration has met its charge to protect the health and safety of the American public. Those who work at the Agency are, by and large, committed to doing no harm. Even so, the FDA has also stood watch over failures when it comes to drug safety.

Likewise, the pharmaceutical industry in the United States has achieved extraordinary advances in medicine. Drugmakers have helped save lives and improve the quality of life of people around the world. They profited by doing so.

At the same time, the industry has contributed to skyrocketing costs of health care and settled billions of dollars of false claims against the government, including both civil and criminal action.

Merck & Co. has a reputation for excellence in research and development, yet today Merck is faced with one of the worst drug disasters in history. Merck acknowledged that Vioxx carried with it serious cardiovascular risk when it withdrew the drug from the market.

During today's hearing, we will hear about the red flags that were raised about those risks in the years before and the years after Vioxx was approved by the Food and Drug Administration.

The Finance Committee has jurisdiction over the Medicare and Medicaid programs. Accordingly, the committee has a responsibility to more than 80 million Americans who received health care coverage, including prescription drugs, under these programs.

Of the 20 million people who reportedly took Vioxx, an untold number are Medicare and Medicaid beneficiaries. I asked the Office of Inspector General of the Department of Health and Human Services about how much the Federal Government reimbursed Merck for Vioxx. I was told that the Medicare program alone paid in excess of $1 billion for Vioxx while Vioxx was on the market.

I have also seen a June 4, 1999 Merck document entitled "In It To Win It" that said, "As of yesterday, Vioxx became reimbursable on Medicaid in 42 States, with the other States close behind."

The Medicaid market was clearly going to be a money market and a money maker for Merck, and Medicaid has paid Merck well for Vioxx.

Last year, Vioxx sales totaled $2.5 billion. Merck's marketing effort included $160 million for direct-to-consumer advertising. It has been said, in the history of pharmaceutical advertising, Vioxx was one of the most directly marketed to consumer prescription drugs ever.

We remember the Bruce Jenner and Dorothy Hamill TV ads. In addition to targeting consumers directly, Merck reportedly spent more than that on marketing Vioxx to physicians.

Now, there is nothing wrong with either of these efforts. Such marketing is part of the system. But today's hearing will consider whether Merck followed the letter and spirit of the law with this marketing of Vioxx.

The witnesses here today will help us tell the Vioxx story. That story will continue to unfold in the months ahead. It will affect public confidence. When the FDA approves a drug, it is considered a "Good Housekeeping Seal of Approval."

However, what has come to light about Vioxx since September 30 makes people wonder if the FDA has lost its way when it comes to making sure that drugs are safe.

Today's witnesses will describe how danger signals were ignored. They will offer perspective on how appropriate action was not taken. We will see that the FDA failed to heed the words of even its own sanctus. It also looks like the FDA allowed itself to be manipulated by Merck on labeling changes that became necessary after a review by Merck that is known as a VIGOR trial.

The VIGOR trial found that heart attacks were 5 times higher for Vioxx patients than for patients on another drug. Even so, nearly 2 years passed before any label change was made by the Food and Drug Administration.

Merck completed the VIGOR trial in March, 2000. It gave the findings to FDA in June, 2000. The trial was the subject of an advisory board meeting February, 2001. However, it was April 11, 2002, 14 months later, before the Vioxx label was actually changed.

Now, over a period of 22 months, Merck aggressively marketed Vioxx, knowing that consumers and doctors were largely unaware of the cardiovascular risks found in the VIGOR trial.

One of my concerns is that the FDA has a relationship with drug companies that is far too cozy. That is exactly the opposite of what it should be. The health and safety of the public must be FDA's first, and only, concern.

I am interested in changes inside the FDA that will result in greater transparency and greater openness at the Food and Drug Administration. One reform that may be needed is an independent Office of Drug Safety.

It does not make sense, from an accountability standpoint, to have the office that reviews the safety of drugs that are already on the market to be under the thumb of the office that puts the drugs on the market in the first place.

The bottom line is, consumers should not have to second-guess the safety of what is in their medicine cabinet. The public should feel confident that, when the FDA approves a drug, you can bank on it being safe, and, if the drug is not safe, that the FDA will take it off the market.

For the sake of time, we have three panels. The first panel is Dr. David Graham, Dr. Gurkipal Sigh, and Dr. Bruce Psaty.

After these three witnesses, we will hear from Dr. Sandra Kweder of the Food and Drug Administration, and Mr. Raymond Gilmartin, the chief executive officer of Merck & Co.

The record for this hearing will remain open for 10 days. Committee members should submit remarks and questions for the record no later than November 29. In addition, a number of documents will be discussed today.

They have been made available to committee members, their staffs, and to hearing witnesses. Many of these documents have been provided to the committee by Merck and other parties to litigation involving Vioxx.

As a result, they may be considered confidential in the context of those court proceedings. I ask that the committee members, their staffs, and the hearing witnesses not leave the room with their bound copies of these documents during the hearing today.

Committee staff will collect the exhibits from each witness, each committee member, and from all committee staff at the close of the hearing.

I look forward to opening remarks of the Ranking Member of the Finance Committee now, my colleague who has been so helpful not only on this hearing but on so many things coming before the committee, Senator Baucus.

OPENING STATEMENT OF HON. MAX BAUCUS, A U.S. SENATOR FROM MONTANA

Senator BAUCUS. Thank you very much, Mr. Chairman.

First, I just want to commend you for holding this hearing on behalf of members of the Congress, and more importantly, the public. You are performing a great public service here, Mr. Chairman, in holding this hearing.

Even though the election was just held and there are only a few more days left in this Congress, I very much compliment you for taking the lead and moving in this direction. It is very, very important. That is obviously mostly because the withdrawal of the painkiller, Vioxx, has raised such serious questions.

Two million patients were taking Vioxx in late September when Merck pulled it due to concerns about the increased risk of heart attacks and strokes. And while we do not know the true extent of the risk, tens of thousands of patients potentially could have suffered a heart attack or stroke as a result of the drug.

This hearing is an opportunity to take a hard look at what happened with Vioxx. But this hearing goes beyond that. It goes beyond Merck. It goes beyond Vioxx. We must think critically about the way we test and evaluate drugs generally to ensure their safety.

In the weeks since Merck withdrew Vioxx, many questions have been raised. When did Merck know about the potential dangers of Vioxx, and should the company have acted sooner to withdraw the drug? Why did the FDA not detect the risks associated with Vioxx during the initial approval process, or even in the 5 years since approval?

Does the FDA have sufficient resources, authority, and independence to ensure that the drugs it approves are safe? Should we be doing more to monitor drug safety after a drug has been approved?

These questions, and many others, must be answered so that medications do not pose a risk to Americans' health. They are also especially critical to Medicare and Medicaid beneficiaries. In the 5 years that Vioxx was on the market, Medicare spent more than $1 billion on the drug, and Medicaid bears the cost of any additional medical care necessary when drugs cause injury.

Furthermore, in just over a year, Medicare will begin covering prescription drugs through the optional Part D benefit. We need to be certain that beneficiaries of the new program are not exposed to potentially harmful medications.

I am concerned that what happened with Vioxx may have been due, in part, to insufficient emphasis on complete, rigorous, and expansive clinical trials.

Clinical trials focused on drug safety should not stop when the FDA approves a drug. Rather, we need to continue testing drugs to thoroughly evaluate the potential risks, not just the benefits.

Clinical trial results should be more transparent. The conduct and reporting of clinical trials is critical to approving a new drug, and we must continue to evaluate and monitor drugs, even after they are approved, to ensure their safety and their effectiveness.

In addition, I have encouraged drug manufacturers to expand the number of patients who participate in clinical trials, including patients in rural areas such as Montana. I also support greater use

of studies that test the comparative effectiveness and safety of drugs in similar therapeutic classes.

The Medicare bill that passed last year designated $15 million for these studies. I support raising that level to at least $75 million. Unfortunately, the current Senate appropriations bill only includes $15 million. I think we should do more.

Finally, the Vioxx situation raises serious concerns about the broad implications of the Medical Malpractice Reform bill currently being considered by the Congress.

Liability restrictions in this bill apply not just to doctors and hospitals, they also include pharmaceutical and medical product manufacturers, such as Merck. The legislation creates new protections for products approved by the FDA, such as Vioxx.

Given the events we are discussing today, I think the Congress and the public need to take a good, hard look at this legislation. I hope that today's hearing will shed light on these events.

I hope they lead to new reforms, to changes, to even better assure the American public that the FDA is doing what Americans think it is doing, that is, protecting them and making sure their drugs are safe. I look forward to hearing from our witnesses, Mr. Chairman. Thank you, again, for holding this hearing.

The CHAIRMAN. In the order of arrival, does Senator Bunning have an opening statement?

OPENING STATEMENT OF HON. JIM BUNNING, A U.S. SENATOR FROM KENTUCKY

Senator BUNNING. Just a very short one, Mr. Chairman.

I am pleased to have this opportunity to examine the issues surrounding Merck's removal of Vioxx from the market. It is of the utmost importance that Americans have reliable access to the drugs that they need. It is just as important that these drugs are safe.

The Food and Drug Administration has very high standards for what drugs it approves for consumers. It is essential that the FDA continues to lead the world in this capacity so that all Americans can be certain that the drugs they are taking will not harm them.

There is also a responsibility for the companies that manufacture these drugs to make sure they are safe, and to take appropriate action if it is found, later, that they are not.

Generally, I believe that the pharmaceutical industry is fulfilling its responsibility. However, it is critical that we make sure that this positive trend continues.

I believe that this hearing will serve a useful exercise in exploring these issues and making sure this aspect of our country's health care system is working as well as it should. I look forward to learning more about the circumstances of this drug's withdrawal.

I appreciate the time our witnesses have taken today to come to testify, and I thank the Chairman for allowing this hearing to take place.

The CHAIRMAN. Thank you.

Senator Bingaman was the next person.

OPENING STATEMENT OF HON. JEFF BINGAMAN, A U.S. SENATOR FROM NEW MEXICO

Senator BINGAMAN. Thank you, Mr. Chairman. I join Senator Baucus in commending you for having the hearing. I think it is a very useful thing for us to spend some time on.

I know the main focus of the hearing is on the issue of Vioxx and the actions, or failure to take action, on behalf of Merck, and that is an appropriate subject for inquiry.

The larger issue, which I think, also, of course, you mentioned, and which I think really deserves our attention, is the track record of the FDA and the ability of the FDA to prevent another Vioxx from occurring.

I notice in the testimony we received from Dr. Graham, he says that he would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. That should be a great concern to all of us.

I think he goes on with some extremely strong testimony about the culture within the FDA being one where the pharmaceutical industry, which the FDA is supposed to regulate, is seen by the FDA as its client instead. So, we have a serious set of problems here.

Obviously, we would be better equipped to begin dealing with these problems if the administration had appointed a head of the FDA. I hope that one of the things the President will do quickly, now that the election is behind us, is to appoint somebody to that position.

I think, clearly, strong leadership is going to be required if we are going to get this situation corrected, and I think this hearing could be a beginning of a solution. So, again, I commend you, Mr. Chairman. I look forward to the testimony and a chance to ask questions.

The CHAIRMAN. Senator Hatch?

OPENING STATEMENT OF HON. ORRIN G. HATCH, A U.S. SENATOR FROM UTAH

Senator HATCH. Mr. Chairman, thank you for giving us the opportunity to deliver opening statements here today.

Let me make this perfectly clear: none of us wants anybody in our society to be hurt by unsafe drugs. Our country's pharmaceutical approval process has been widely heralded as the gold standard throughout the world. If there are problems with it, they must be fixed. But, first and foremost, the heart of the issue before the committee is science.

In a few minutes we will hear from a number of witnesses, primarily scientists, who have differing opinions on the side effects of Vioxx, a drug that was prescribed primarily for arthritic pain.

Concerned for the health of patients throughout the world, Merck voluntarily removed Vioxx from its worldwide market within 1 week of receiving new data. To say the least, Vioxx's removal from the shelves in September has created a feeding frenzy for trial lawyers.

In fact, plaintiffs' attorneys are already promoting that they have a slam-dunk case against Merck. If you do not believe what I am saying is true, take a look at a sample of how trial attorneys are fishing for future clients.

Let me just read you the headline: "Get Your Million Dollars From Vioxx Lawsuit." It is worse if you read the whole advertisement. It is just one of, really, hundreds that I have seen on television all over the country.

Now, imbedded in this misleading promotion, Vioxx consumers are advised on how they can "benefit from this once-in-a-lifetime opportunity to become a millionaire."

The website also says, "There are still places selling Vioxx after the recall. You can find them on-line. Merck is still 100 percent fully responsible for any side effect. If you purchase Vioxx now, not only can you sue Merck, you can also sue the pharmacy store for selling recalled products."

Again, if there are problems, let us look at them in a deliberative way, examining all of the facts so that we can protect the health of our citizens.

Now, to be fair, Mr. Chairman, I do have concerns about why this committee is holding this hearing, and holding it now. True, Medicare and Medicaid have reimbursed for Vioxx, along with almost every other drug.

But my study of this issue leads me to believe that the questions that you have raised—and I emphasize that they are legitimate questions—largely relate to the approval process of the FDA, which obviously is a Health, Education, Labor and Pension Committee issue.

In addition, this is a complex issue. Finance Committee members were only given 8 days' notice of the hearing. Although this is technically within the committee rules, it is not enough time to understand this very complicated issue. After all, it takes up to 15 years and $1 billion in expenditures to get a drug approved through FDA.

The papers involved in an approval of the drug could almost fill this room from floor to ceiling. In fact, I assigned three staffers, including a physician and a lawyer, to go through the confidential documents in the committee office.

Over a period of several days, my staff was not able to review even one-third of the materials that we have. One staffer told me it took 2 hours to get through one-half of one binder due to the complexity of the documents.

To make matters worse, because these documents are protected by court order, Finance Committee staff members could not make copies of the materials or remove the information from the committee office.

Bottom line, it was physically impossible for any office to study those documents in time to prepare for today's hearing. This alone puts me, and other members of the committee, at a great disadvantage going into this hearing, and threatens the objectivity of this discussion.

It is important to keep an open mind, to hear all of the facts before deciding if anyone is guilty of wrongdoing. Unfortunately, I am worried that that is not the case with today's hearing, and that the committee staff may have jumped to conclusions by taking serious issues out of context.

For example, it has been alleged that Merck trained its sales representatives to "dodge" tough questions from doctors about Vioxx.

Now, I have reviewed the Merck training manual, and I can tell the members of this committee that this is not the case.

Merck's sales representatives, in training, participate in a game called "dodge ball," where they are given flash cards that have questions termed as obstacles about Merck's drugs.

According to the game's rules, if a person selects a "dodge" flash card, then he or she does not have to answer a question and receives two points. The rules for the game of dodge ball are clear: just read the manual.

From what I have read, nowhere in this manual are trainees encouraged to dodge tough questions that physicians may ask about Merck drugs, as reported by some sources.

Now, Mr. Chairman, I ask that the Merck training manual be entered into the record at this point.

The CHAIRMAN. Without objection.

[The manual appears in the appendix.]

Senator HATCH. I also am interested in hearing the comments of the first two panels, but I hope that members will stay to hear the testimony of the FDA and Mr. Gilmartin, the CEO of Merck, because they have important information to share with the committee as well. I think it is unfortunate that such critical witnesses have been placed on the last two panels.

Finally, I want to make one thing perfectly clear. Along with my colleagues, I want to ensure that the American drug supply is the safest in the world. I have spent 28 years here trying to make sure that that is a reality.

But today some are trying to punish one drug company for acting appropriately within the framework of our current regulatory system. If the mechanism by which the FDA examines drug safety needs to be critically evaluated, let us do that. But I think we must be fair and allow all of the facts to be reviewed carefully.

So, I will conclude by urging that my colleagues be open-minded during this hearing and evaluate all of the facts before making any decision on this issue.

Mr. Chairman, this is an important hearing. I know that you will be fair and I expect everybody to be fair. Let us get to the facts and help everybody to understand, really, what may or may not be going on here.

Thank you, Mr. Chairman.

The CHAIRMAN. Yes. You bet.

Before I call on Senator Breaux, I think that you have raised some questions that I ought to answer at this point.

Senator HATCH. Sure.

The CHAIRMAN. If, in regard to potential lawsuits, Congress limited its oversight to only those things that might not be in court, we would not be doing any oversight. The checks and balances system of government would not be working. We have constitutional responsibility to do oversight.

We are holding this hearing now because I think that we have had two examples this year of the FDA not doing its job. Maybe not having proper respect for scientists that work within the FDA, and having the scientific process work. As you said in your opening statement, we ought to be emphasizing science, and that is what we are talking about here.

We had the scientists that were suppressed, in the case of the antidepressants, children committing suicide. Since then, we have had a black box put on warnings of that drug. But that was a long time, making up their mind to do that, but the suppression of scientific evidence was not respected.

Now we have scientists in this particular case who are being harassed within the Agency because of sticking to their own science and the scientific process. I think the sooner Congress makes it clear to the Food and Drug Administration that transparency in government is about the only way that we are going to keep the public protected, the better.

So, I hope to bring to the attention of the FDA right now, and not after some lawsuit is settled 10 years from now, that something is wrong within FDA. As far as not having enough time to look, it seems to me that you did make a very good effort, Senator Hatch, to have your staff go over some of these documents, and maybe not get through them as thoroughly as you wanted to.

But a lot of members did not take advantage of that opportunity, as well, and were still complaining about having such a hearing. We are not here to decide whether anybody is guilty or not. Guilt comes through the judicial process. We are here to conduct our constitutional job of oversight.

Senator Breaux?

OPENING STATEMENT OF HON. JOHN BREAUX, A U.S. SENATOR FROM LOUISIANA

Senator BREAUX. Thank you very much, Mr. Chairman.

I think the hearing is entirely appropriate, because when you have an incident like this that has attracted attention and disclosed the potential problems with a product, the committees in Congress need to be involved to make sure that we, as government officials, are ensuring that everything we do and everything our government does is focused on the safety of the products that are approved by our government for use, particularly in the medical field.

I think it is slightly ironic that we are here today looking at how our FDA conducts their very extensive reviews of medical products that come on the market, which I think everyone would agree is probably the most sophisticated anywhere in the world.

It is the most regulated, the most scientifically oriented. It is subject to more rules and standards and steps that have to be taken than any other system in the world. Yet, we find that problems do occur, even with the system we have in this country.

Yet, at the same time there are many people who argue that one of the solutions to our medical problems in this country is to import drugs from foreign countries.

I mean, how ironic is that, that we have found problems in our own system, which is the best in the world, undeniably so, and yet some think that it would be all right to get drugs into this country that have been transshipped through Bangladesh, Libya, India, Thailand, and other countries of the world that do not have a semblance of what we have in this country to assure the safety.

If our own country sometimes finds fault with the system and drugs that are not quite ready for the market over a long period

of time with a particular dosage that causes problems, how much more serious would the problem be if we were to take action to say not only were we going to let the drugs that have been approved by our drug administration here in this country, but let them in from anywhere else in the world? I just think it is ironic, and I want to make that point.

Another question is, it seems to me that there is a question here of, how long do we test drugs before they are approved for the market? Do we do it for 12 months? Do we do it for 18 months? Do we do it for 2 years?

Do we take the proposition that, well, maybe we ought to look at this for 10 years, and maybe it will have adverse impacts over a 10-year period, or how about a 5-year period? Is 18 months the right amount of time? Apparently with Vioxx, up to 18 months, there were no adverse impacts. But after 18 months, it showed that there could be particular problems that were occurring. So how long do we test drugs?

Obviously, the medical profession and those who are affected by the problems these drugs are intended to cure put a great deal of pressure on all of us for getting the drugs to the market quicker and faster so that their diseases may be cured. So what do we do? What is the magic number? How long do we look at a drug before we say it is all right?

Another point. It seems to me that at the time the drug was approved in 1999 by the Food and Drug Administration, there was a statement at that time that FDA said that there is "a theoretical concern that the patients who take the COX-2 inhibitors may be at a higher risk for thromboembolic cardiovascular adverse experiences."

Basically in my terminology, it means a heart attack. They may be at a higher risk for these type of heart attacks than patients that are treated with a combination of COX-1 and COX-2 inhibitors.

They go on to say, however, "But with the available data, it is impossible to answer with complete certainty whether those risks," for heart attack, "are increased or not." They also said a larger database will be needed.

Now, despite saying that, the drug was still approved. It would seem to me that you all are going to have to answer to this Congress, and indeed to this country, that if FDA says that a larger database will determine whether it causes heart attacks, and yet the drug is still approved, that there is a problem. I think we need to answer that to a greater degree of efficiency than we have seen so far.

Thank you.

The CHAIRMAN. Senator Nickles?

OPENING STATEMENT OF HON. DON NICKLES, A U.S. SENATOR FROM OKLAHOMA

Senator NICKLES. Mr. Chairman, I want to apologize. I have to run. But just two or three comments.

I have not had a chance to review this. Since I heard your statement, that we cannot take these papers to our office, I will not re-

view this, because it might take a little time to chew on that. That is a little thicker than the Bible. It will take a while.

I am concerned, though. Sometimes there has been ebb and flow, and FDA jurisdiction is primarily with the Health Committee, so we have not wrestled with it a lot. But I am concerned that maybe one of the results, if we give FDA a really hard time, they are going to be really cautious, and then all of a sudden the time for approval of drugs is going to get longer and drugs are going to be more expensive. I do not want to do that. I hope we do not do that. I would hope that we could shorten the time for approval.

Yes, I guess if you do that you might increase the risk of some possible mistakes, but you also might be getting a lot of people some drugs that they need and you might save lives in the process. There are lives at stake on both ends of the drug approval process. You can save lives if some needed drugs are granted.

Granted, there may be some mistakes. My guess is, there have been lives that have been saved with Vioxx or other, similar-type drugs through reduced bleeding problems, stomach problems, according to the study.

It is also my understanding that the FDA did not call for removal of this drug. I think that Merck did. So, I just would make these comments.

Senator Hatch alluded to the fact that there are websites and others up trying to feed off this frenzy on the trial lawyer side. I hope that this hearing does not accelerate that. I do not think that is to the benefit of the consumers, nor do I think it is to the benefit of people who really want to make improvement in getting drugs to the marketplace that would help alleviate a lot of pain.

We have a lot of people who have a lot of pain that are looking for some relief, and I want to try and have an approval process that is as expedient as possible in approving drugs that are as safe as possible. But that is never pure and that is never 100 percent.

So, I just wanted to make those couple of comments. I apologize that I have to leave, but I am going to try and return for part of this hearing. I think it is a very interesting hearing, and one where I hope we do not add to the legal complexities that are already in the system.

The CHAIRMAN. Before I call on Senator Lott, let me repeat something I said after Senator Hatch's testimony. That is, if we limited our oversight to what might be in court or what might not be in court, we would not be doing any Congressional oversight, or very little compared to what we are doing now.

One thing I did not address that both you and Senator Hatch brought up that ought to be addressed so that it is very clear, it is not my intention to infringe upon the jurisdiction of the Committee on Health, Education, Labor and Pensions. It is my goal here to do what this committee can do, and that is having jurisdiction over the Medicaid program.

Medicaid spent $1 billion of taxpayers' dollars to buy Vioxx. With responsibility for that program, we have got a responsibility in this committee to make sure that our $1 billion goes to buy a drug that is safe for the consumers taking that drug.

Senator Lott?

Senator LOTT. No questions or comments at this time, Mr. Chairman. Thank you.

The CHAIRMAN. All right.

Before the testimony begins, I want to respond to comments issued last night by the Acting Administrator of the Food and Drug Administration, Dr. Crawford, about Dr. Graham, our first witness.

News reports today say that the FDA is calling him "a maverick who did not follow Agency protocols." Today's hearing includes a lot of testimony about scientific findings. It is not about protocols. It is not about administrative he saids/she saids. Dr. Graham completed an FDA-sponsored, 3-year study under FDA guidance, with Drs. Campen, Levy, Shore, Ray, Chittum, Spence, and Way.

Dr. Graham's immediate supervisor said the paper that formed the basis of the study was "an excellent study and analysis of a complex topic." So the clarifications provided last night by Dr. Crawford appear intended to intimidate a witness on the eve of a hearing.

I want to hear about Dr. Graham's study today. In fact, just 7 days ago, on November 9, Dr. Crawford met with Dr. Graham and acknowledged that there was a culture problem at the FDA and a problem with drug safety. Dr. Crawford even asked Dr. Graham to consider helping with "an internal FDA drug safety program and developing recommendations for improvements."

So, Dr. Crawford knows there is a problem and would better serve the FDA by spending time on the problem rather than going after Congressional witnesses who helped identify the problem in the first place.

I call on the witnesses that we have before us. Would you come to the table, even before I call your name?

Dr. Graham is a 20-year employee of the FDA and is currently the Associate Director for Science at the FDA's Office of Drug Safety. Dr. Graham has been given many awards and honors during his tenure at FDA.

Most recently, he received a group recognition award for his contribution to one of FDA's risk management working groups. Dr. Graham is here today to discuss the work that he has performed for FDA on Vioxx.

Dr. Psaty is a professor at the University of Washington, a practicing general internist at Harbor View Medical Center. He is a cardiovascular disease epidemiologist with proficiency in drug safety, and is also an expert in conducting and interpreting clinical studies.

Dr. Psaty is here with us to discuss the various studies and trials conducted on Vioxx. He will also highlight the red flags that many in the scientific community saw with Vioxx.

We will then hear from Dr. Singh, an adjunct clinical Professor of Medicine at Stanford University School of Medicine. Dr. Singh serves as a reviewer of *Arthritis and Rheumatoidism, Journal of Rheumatology,* and *Annals of Rheumatic Diseases.* He also serves as chief science officer at the Institute of Clinical Outcomes Research Education.

Dr. Singh will discuss the science behind Vioxx, as well as the many concerns that have been raised since Vioxx hit the market.

He will also be discussing the intimidation that he experienced working as a consultant for Merck.

We are going to start with Dr. Graham. We are going to give each of the witnesses 10 minutes. In fact, all of the witnesses today will have 10 minutes instead of our usual 5 minutes, but I would ask that we wind it up very quickly when the red light goes on.

Dr. Graham?

STATEMENT OF DAVID J. GRAHAM, M.D., MPH, ASSOCIATE DIRECTOR FOR SCIENCE, OFFICE OF DRUG SAFETY, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION, WASHINGTON, DC

Dr. GRAHAM. Mr. Chairman and members of the committee, good morning. My name is David Graham, and I am pleased to come before you today to speak about Vioxx, heart attacks, and the FDA.

By way of introduction, I graduated from Johns Hopkins School of Medicine and trained clinically in medicine and neurology. I completed a fellowship in epidemiology and a master's in public health. For the past 20 years, I have worked in the field of drug safety and am currently the associate director for Science and Medicine in the FDA's Office of Drug Safety.

During my career, I believe that I have made a beneficial difference for the cause of patient safety. My work led to the withdrawal from the U.S. market of Omniflox, Rezulin, Fen-Phen and Redux, and phenypropanolomine, the outpatient withdrawal of Trovan, and contributed to the withdrawal of Lotronex, Bacol, Seldane, and Propulsid. Over my career, I have recommended the market withdrawal of 12 drugs. Only two of these remain on the market today.

Prior to approval of Vioxx, a study was performed by Merck named 090 which found a nearly seven-fold increase in heart attack risk with low-dose Vioxx. The labeling and approval said nothing about these heart attack risks.

In November, 2000, another Merck trial named VIGOR found a five-fold increase in heart attack risk with the high-dose form of Vioxx. About 18 months after the VIGOR results were published, FDA made a labeling change about heart attack risk, but it did not place these in the warning section of the labeling.

Also, it did not ban the high dose formulation in its use. I believe such a ban should have been implemented. Of note, the label change that FDA made had absolutely no effect on how often high-dose Vioxx was prescribed, so I ask, what good did it achieve?

In March of 2004, another epidemiologic study reported that both high- and low-dose Vioxx increased heart attack risks compared to Celebrex, Vioxx's leading competitor. Our study found similar results. A study report describing our work was put on the FDA website. This report estimated that nearly 28,000 excess cases of heart attack and sudden cardiac death had been caused by Vioxx.

I must emphasize to the committee that this is an extremely conservative estimate. FDA always claims that randomized clinical trials provide the best data. If you apply the risk levels seen in the two Merck clinical trials, VIGOR and APPROVe, you obtain a more

realistic and likely range of estimates for the number of excess cases.

This estimate ranges from 88,000 to 139,000 Americans. Of these, 30 to 40 percent probably died. For the survivors, their lives were changed forever. This range does not depend at all on the data from our Kaiser-FDA study. Indeed, Dr. Eric Topol at the Cleveland Clinic recently estimated 160,000 cases in an article that was published in the New England Journal of Medicine.

So how many people is 100,000? We are talking about many lives, not just numbers. Senator Grassley, 100,000 would represent 5 percent of the population of the State of Iowa, and would represent 67 percent of the citizens of Des Moines. We are talking about many lives.

Now, imagine that we were talking about jetliners. If there were an average of 150 to 200 people on an aircraft, this range of 88,000 to 139,000 would be the rough equivalent of 500 to 900 aircraft dropping from the sky. This translates to two to four aircraft every week, week in, week out, for the past 5 years.

If you were confronted by this situation, what would be your reaction? What would you want to know and what would you do about it?

What does history teach us? You can see in the figure that is part of my testimony that, in 1938, Congress enacted the Food, Drug and Cosmetic Act, basically creating the FDA in response to the deaths of about 100 children caused by elixir of sulfanilamide. In 1962, Congress enacted the Kefauver-Harris Amendments in response to the thalidomide disaster in Europe which affected 5,000 to 10,000 infants.

Today in 2004, we are faced with what may be the single greatest drug safety catastrophe in the history of this country. I strongly believe that this should have been, and largely could have been, avoided. But it was not, and over 100,000 Americans have paid dearly for this failure. In my opinion, the FDA has let the American people down.

Now, why was the question of Vioxx and heart attack important to me? Well, one, Vioxx would undoubtedly be used by millions of people, and that is a very large number to expose if there is a serious drug risk.

Two, heart attack is a fairly common problem. It is a common event. Given the commonness of the event and the large number of people who would be using it, even a small increase in the risk due to Vioxx could mean that tens of thousands of Americans might be seriously harmed or killed by the drug.

If these three factors were present, I knew that we had all the ingredients needed to guarantee a national disaster. The first two factors were established realities. It came down to the third factor. That is, what was the level of risk with Vioxx at both the low and the high dose?

I worked with Kaiser Permanente in California to perform a large study which was carefully done, and took us nearly 3 years to complete. In early August of this year, we assembled a poster describing some of our findings.

We concluded that the high-dose Vioxx significantly increased the risk of heart attacks and sudden deaths, and that the high dose should not be prescribed, or used by patients.

This is exactly the finding that VIGOR had, high dose increases the risk of heart attack. We found the same thing. This conclusion triggered an explosive response from the Office of New Drugs, which approved Vioxx in the first place, and was responsible for regulating it post-marketing.

The response from senior management in my office, the Office of Drug Safety, was equally stressful. I was pressured to change my conclusions and recommendations. One Drug Safety manager recommended that I should be barred from presenting the poster at the meeting, and also noted that Merck needed to know our study results. So, I guess Merck needed to know the results, but the public did not.

An e-mail from the director for the entire Office of New Drugs was revealing. He suggested that since the FDA was not contemplating a warning against the use of high-dose Vioxx, my conclusions should be changed.

CDER and the Office of New Drugs have repeatedly expressed the view that the Office of Drug Safety should not reach any conclusions or make any recommendations that would contradict what the Office of New Drugs wants to do, or is doing.

Even more revealing, a mere 6 weeks before Merck pulled Vioxx from the market, the Center for Drugs, the Office of New Drugs, and the Office of Drug Safety Management did not believe that there was an outstanding safety concern with Vioxx. So while they think that there is nothing going on, two to four jumbo jetliners are dropping from the sky every week.

There were two other revelatory milestones. In mid-August, despite our study results showing an increased risk of heart attack with Vioxx, and despite the results of other studies published in the literature, FDA approved Vioxx for use in children with rheumatoid arthritis.

Then, on September 22 at a meeting attended by senior managers from the Office of New Drugs and the Office of Drug Safety, no one thought that there was a safety issue with Vioxx that needed to be dealt with.

At this meeting, the reviewing office director responsible for Vioxx asked why I had even thought about studying Vioxx and heart attacks in the first place because FDA had made its labeling change and nothing more needed to be done.

At this meeting, a senior manager from my office labeled our Vioxx study a "scientific rumor." Eight days later, Merck pulled Vioxx from the market and jetliners stopped dropping from the sky.

Finally, we wrote a manuscript for publication in a peer-reviewed medical journal. Senior managers in the Office of Drug Safety have not granted clearance, even though it was accepted for publication after rigorous peer review by that journal.

Until it is cleared, our data and conclusions will not see the light of day in the scientific forum they deserve, and serious students of drug safety and drug regulation will be denied the opportunity to consider and openly debate the issues we raised in that paper.

My experience with Vioxx is typical of how CDER responds to serious drug safety issues in general. It is similar to what Dr. Mosholder went through earlier this year when he reached his conclusion that most SSRI antidepressants should not be used by children.

The Office of New Drugs and the Office of Drug Safety and Management, together, suppressed his report and he was blocked from presenting at an FDA Advisory Committee meeting. He was subsequently proven to be right about SSRI risk.

There are many other examples where CDER and its Office of New Drugs proved to be extremely resistant to full and open disclosure of safety information, especially when it called into question an existing regulatory position.

In these situations, the New Drug Reviewing Division that approved the drug in the first place, and that regards it as one might regard their own child, typically proves to be the single greatest obstacle to effectively dealing with a serious drug safety issue.

The second greatest obstacle is often the senior management within the Office of Drug Safety, who either actively or tacitly go along with what the Office of New Drugs wants.

Vioxx is a terrible tragedy and a profound regulatory failure. I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless.

It is important that this committee and the American people understand that what happened with Vioxx is really a symptom of something far more dangerous to the safety of the American people. Simply put, FDA and the Center for Drug Evaluation and Research are broken.

The organizational structure within CDER is entirely geared towards the review and approval of new drugs. When a serious safety issue arises post-marketing, the immediate reaction of the reviewing divisions is almost always one of denial, rejection, and heat. They approved the drug, so there cannot possibly be anything wrong with it.

The same group that approved the drug is also responsible for taking regulatory action against it. This is an inherent conflict of interest. At the same time, the Office of Drug Safety has no regulatory power and must first convince the New Drug Reviewing Division that a problem exists before anything beneficial can be done to help the public.

Often, the New Drug Reviewing Division is the single greatest obstacle to protecting the public against safety risks, and a close second, in my opinion, is the Office of Drug Safety management, that sees its mission as pleasing the Office of New Drugs.

The corporate culture within CDER is also a barrier to effectively protecting the American people from unnecessary harm due to prescription and over-the-counter drugs. The culture is dominated by a world view that believes only randomized clinical trials provide useful and actionable information, and that post-marketing safety is an after-thought.

This culture views the pharmaceutical industry that it is supposed to regulate as its client. It over-values the benefits of the

drugs that it approves, and it seriously undervalues, disregards, and disrespects drug safety.

Finally, the scientific standards that CDER applies to drug safety guarantee that unsafe and deadly drugs will remain on the U.S. market. When it comes to safety, the Office of New Drugs' paradigm of 95 percent certainty prevails.

Under this paradigm, a drug is safe until you can show that, with 95 percent or greater certainty, it is not safe. That is an incredibly high, almost insurmountable barrier to overcome. It is the equivalent of beyond a shadow of a doubt.

And here is an added kicker: in order to demonstrate a safety problem with 95 percent certainty, extremely large studies would be needed. Guess what? Those studies usually are not done, or they cannot be done.

If the weather man says there is an 80 percent chance of rain, most people would bring an umbrella. Using CDER's standard, you would not bring an umbrella until the weatherman said there is a 95 percent or greater chance.

I have a second analogy. Imagine that you have a pistol with a barrel having 100 chambers. Now, randomly place 95 bullets into those chambers. The gun represents a drug, and the bullets represent the probability, the certainty, of a serious drug safety problem.

Using CDER's standard, only when you have 95 bullets or more in the gun would CDER conclude that the gun is loaded, that is, that there is a drug safety problem with that drug.

Now remove five bullets from the chamber. Now we only have 90 bullets. Because there is only a 90-percent chance that when I pull the trigger a bullet will fire, CDER would conclude that the gun is not loaded, that is, the drug is safe.

A more rational and patient-protective standard is required when dealing with safety. I thank you very much.

[The prepared statement of Dr. Graham appears in the appendix.]

The CHAIRMAN. Thank you, Dr. Graham. Now, Dr. Psaty?

STATEMENT OF BRUCE M. PSATY, M.D., PROFESSOR, MEDICINE AND EPIDEMIOLOGY, UNIVERSITY OF WASHINGTON, CARDIOVASCULAR HEALTH RESEARCH UNIT, SEATTLE, WA

Dr. PSATY. Mr. Chairman and members of the committee, thank you for the opportunity to testify about the cardiovascular risks associated with Vioxx.

My name is Bruce Psaty. I am a practicing general internist and cardiovascular disease epidemiologist, with expertise in pharmacoepidemiology and drug safety. I have no financial interest in this matter.

Epidemiology is the study of patterns and causes of disease in human populations. One important goal is to identify treatments or approaches that can prevent disease. My comments today are directed toward the prevention of future Vioxx-like problems.

In order to make informed decisions, patients and physicians must have information about both the benefits and the risks of drug therapy. This duty to obtain and provide risk/benefit informa-

tion devolves to all who work in medicine, including the pharmaceutical industry.

In November of 1996—and I draw your attention to Exhibit 3—Merck scientists hypothesized that patients taking Vioxx would have higher rates of heart disease than those taking an aspirin-like comparison.

By April of 1998, Merck scientists knew that Vioxx not only lacks the anti-platelet effects of aspirin, but it also disables one of the blood vessel's main defenses against the clumping of platelets.

On the basis of this biologic evidence, it would be reasonable to hypothesize that, compared to placebo, Vioxx treatment might increase the risk of heart attack and stroke.

For Vioxx to be used safely in millions of patients, the potential cardiovascular risks need to be defined clearly. Merck conducted a number of small, short-term clinical trials of Vioxx. By the time of approval in May, 1999, only 371 and 381 patients had received doses of 12.5 or 25 milligrams for 1 year or more.

These studies were not adequate to evaluate the effects of Vioxx on the occurrence of heart attack and stroke. The FDA medical officer aware of the mechanisms by which Vioxx might increase the risk of heart attack—and one of the Senators turned your attention to the same quotation—observed that in the 6-week studies, thromboembolic events, such as heart attack and stroke, are more frequent in patients receiving Vioxx than placebo.

Especially in view of the known biologic effects of the COX-2 inhibitors on platelets, this three-fold increase in the risk represents a basis for concern.

The VIGOR trial included adults with rheumatoid arthritis. About 8,000 patients were randomized to receive Vioxx or naproxen. Compared with naproxen patients, Vioxx patients had lower rates of GI events, but higher rates of cardiovascular events.

For the outcome of heart attack, the rate was 5 times higher in Vioxx patients than in naproxen patients. In 1,000 patients who were "eligible for VIGOR," who met the eligibility criteria for the trial, followed for 1 year, Vioxx treatment would likely be associated with 24 fewer GI events, about eight of them serious or complicated, but six more heart attacks in this low-risk population that was admitted to the VIGOR trial.

These findings, the GI benefit and the cardiovascular harm, present patients and physicians, regulators and industry, with a difficult choice. Although GI events are potentially serious, they are not usually fatal and recovery is usually complete.

About 25 percent of heart attacks are fatal. For persons who survive a heart attack or stroke, the quality of life and the duration of survival are usually compromised.

On the basis of VIGOR, some physicians did not think the benefits of Vioxx outweighed the risks. The Pharmacy and Therapeutics Committee of Group Health Cooperative, the health plan where I conduct many of my studies, chose not to add Vioxx to their formulary.

If the VIGOR safety results known in December, 1999 had been available to the FDA 7 months earlier—7 months earlier—it is possible that Vioxx might not have been approved in May, 1999, at

least not without additional studies. So, we are talking about a window of months and not years, I think.

Because VIGOR and many other Vioxx trials excluded patients with recently diagnosed cardiovascular disease and patients taking aspirin, Vioxx was not adequately studied in the large numbers of high-risk patients who would eventually take it. In one post-marketing study, 42 percent of the Vioxx users had a history of some major form of cardiovascular disease.

Among the naproxen users in this study, the heart attack rate is about 8 times higher than the rate for naproxen patients who were eligible for VIGOR. In other words, in the patients who would eventually use these medications, it is conceivable that Vioxx might cause more heart attacks than the number of GI events prevented.

In February, 2001, the FDA reviewed the VIGOR results, but revisions to the "Precautions" sections of the Vioxx label were delayed until April of 2002. No black box warning about adverse cardiovascular events, the most prominent warning, was added to Vioxx.

In contrast, black box warnings about the increased risk of cardiovascular events were added to estrogens and progestins after the NIH-funded Women's Health Initiative results had been published. The public health rationale for these two different approaches remains unclear.

Several post-marketing studies of Vioxx were conducted. In Dr. Graham's study, users of Vioxx were compared with users of Celebrex. Vioxx, at doses of 25 milligrams or less, was associated with a 50 percent increase in the risk of heart attack; doses of greater than 25 milligrams were associated with a 375 percent increase in the risk of heart attack.

These risk estimates are consistent with the findings from the randomized trials, VIGOR and APPROVe. And let me talk about APPROVe for a minute. In the APPROVe trial, patients aged 40 years or older with benign tumors in the large intestine were randomly assigned to receive Vioxx, 25 milligrams daily, or placebo.

Compared with placebo, Vioxx patients had a two-fold higher risk of heart attack or stroke. On the basis of these data, Merck withdrew Vioxx in September of 2004.

Senator BREAUX. I am sorry. I hate to interrupt. Can you tell me, after how long of a period?

Dr. PSATY. I am sorry. I did not hear you.

Senator BREAUX. I was wondering. You said they had increased spiking of the potential for cardiovascular events.

Dr. PSATY. Right.

Senator BREAUX. After how long of a period of taking it?

Dr. PSATY. Well, the life tables suggest it occurs after 18 months. Basically, Merck lacked information to know when the risk occurred. You cannot say with confidence, given the available data, even with APPROVe, when the risk occurred. It is just, we lack information.

On the basis of these data, Merck withdrew Vioxx from the market. The failure to conduct large, long-term randomized trials in a more timely fashion permitted millions of Americans to use a drug that, in APPROVe, doubles the risk of heart attack or stroke. Tens

of thousands of patients may have had adverse events attributable to Vioxx.

Recommendations for the prevention of Vioxx-like problems:

(1) Large, long-term trials to assure patient safety—

Medicines for common chronic conditions have large potential markets, with the result that even small increases in the risk of adverse events can affect tens of thousands of people.

Medicines that will be used by large numbers of Americans for long periods of time are best evaluated in large, long-term clinical trials that are started as early as possible in the approval process. This approach, used for the statin drugs, has benefitted not only patients and physicians, but also the pharmaceutical industry.

(2) Evaluation of medicines in patients who are likely to use them and may be especially vulnerable to adverse effects—

Initially, Merck excluded patients recently diagnosed with cardiovascular disease and patients taking aspirin. This approach maximized the possibility of finding a GI benefit and minimized the possibility of uncovering evidence of cardiovascular harm.

For the high-risk patients, it was not clear whether Vioxx was, at the time of approval, safe and effective for its intended use.

(3) Improvements in post-marketing surveillance—

The FDA should re-orient priorities and devote more attention and resources to patient safety. Specific, proactive post-marketing trials or studies should be designed, conducted, and completed in a timely fashion. Moreover, with the development of new post-marketing surveillance systems and approaches, an almost on-line assessment of risk may be possible in the near future.

(4) Independent Center for Drug Safety and conditional approval of new medications—

To implement the improvements in post-marketing surveillance, the FDA needs a new Independent Center for Drug Safety that can pursue potential signals or biologic hypotheses.

A system of conditional approvals for new medications or the regular re-review of all medications, which actually takes place in Europe, would provide the FDA the authority and the opportunity to insist on timely revisions to labels, to assure that post-marketing commitments have been completed, and to compel new post-marketing commitments when they may be indicated.

Finally, to balance the interests of patients and industry, decisions about label changes, new studies, suspension of sales, or withdrawals of drugs might be best made by the new Independent Center for Drug Safety.

Thank you.

The CHAIRMAN. Thank you very much, Dr. Psaty.

[The prepared statement of Dr. Psaty appears in the appendix.]

The CHAIRMAN. Now we go to Dr. Singh, by teleconference.

STATEMENT OF GURKIPAL SINGH, M.D., ADJUNCT CLINICAL PROFESSOR OF MEDICINE, DIVISION OF GASTROENTEROLOGY AND HEPATOLOGY, DEPARTMENT OF MEDICINE, STANFORD UNIVERSITY SCHOOL OF MEDICINE, STANFORD, CA

Dr. SINGH. Chairman Grassley, Senator Baucus, Senators, ladies and gentlemen, thank you for inviting me to testify before the Senate Finance Committee.

I apologize for not appearing in person and giving this testimony by video conference. I am not able to travel, because exactly 2 weeks ago today I had a heart attack. Before the plaintiffs' attorneys rush out of this room to call me, no, I was not taking Vioxx. [Laughter.]

The science of the specific COX-2 inhibition is in the medical testimony and I am not going to read it today, to save time. Suffice it to say that the reason for the development of these drugs was safety. A few years ago, my colleagues and I estimated that there are over 103,000 hospitalizations and 16,500 deaths every year from stomach bleeding complications.

These specific COX-2 inhibitors were developed to prevent this. Indeed, in May of 2004, we show data at the Digestive Disease Meeting showing that this was, indeed, happening in the United States.

But today my task is to review the information surrounding the events that happened around the approval and the withdrawal of Vioxx. The Senate Finance Committee supplied me with the supporting documents that are available to you as exhibits, and, yes, I did read every single one of those documents.

I have been asked to comment on this for the specific purpose of identifying the key events that could lead us to recognize these kinds of problems earlier and avoid something like this from happening again.

Before I review the exhibits for you, I wish to reiterate two fundamental principles of medicine. Number one, is *primum, non nocere.* That is Latin for, "first, do no harm."

The second principle is a careful evaluation of risk to benefit ratio for any therapy that we wish to implement. As an example, we as physicians are more willing to accept a more serious side effect, such as a heart attack, in a drug that cures cancer than in one that is used to treat a benign rash.

With that background, let me walk you through the exhibits that you have been provided. By now we know that in November of 1996, Merck scientists were seriously concerned and were actually discussing a potential risk of Vioxx, its association with heart attacks.

At that time, it was not known that Vioxx might itself cause heart attacks. Rather, the discussion focused on the issue that other painkillers, by inhibiting platelets, may protect against heart attacks. Vioxx has no such effect on platelets, and thus may seem to increase the risk of heart attacks in studies comparing it to other painkillers.

This was a very serious concern, ladies and gentlemen, because the entire reason for the development of Vioxx was safety. It is no

more effective than any of a large number of NSAIDs that were already available in the market.

However, if the improved stomach safety of the drug were negated by an increased risk of heart attacks, physicians might not be willing to make such a trade-off. Merck scientists were among the first to recognize this.

At this point in time in 1996, scientists should have started a public discussion about this potential trade-off and they should have designed studies that would have more carefully evaluated the risk-benefit ratio of Vioxx.

Is that what happened? No. It appears from internal Merck e-mails provided to me, and in your exhibit, that in early 1997, Merck scientists were exploring study designs that would, in fact, exclude people who may have had a weak heart so that the heart attack problem would not be evident.

The discussion also focused on the fact that if aspirin were permitted in these trials, there may not be any significant safety advantage of Vioxx on the stomach. As one scientist pointed out, however, if aspirin were excluded, patients on Vioxx might have more heart attacks and this would "kill the drug."

The scientist also pointed out that in the real world, "everyone is on it." Senators, ladies and gentlemen, clinical trials should be designed to test a drug under real-world circumstances, on patients who are most likely to use the drug.

Clinical trials should not be designed to selectively favor one outcome over another by excluding people who would be otherwise limited to those who would take the drug after its approval.

Second, clinical trials should not be designed to put marketing needs in front of patient safety. We need to know how a drug will be used in people who are going to take it, even if it "kills the drug." It is better to kill the drug than kill a patient.

According to documents provided to me by the Senate Finance Committee, there were many, many other internal discussions within Merck on these concerns of heart attack and stomach bleed trade-offs, although the practicing physician did not learn of this until many years later.

In 1998, Dr. Doug Watson presented an analysis of serious heart problems with Vioxx compared to patients enrolled in other Merck studies. This analysis concluded that, indeed, there was the signal of a greater risk of heart attacks with Vioxx compared to people not taking any drug. To the best of my knowledge, these data were never made public.

By 1999, an even more serious problem was emerging. By the time Merck had filed for the approval of Vioxx, there were several small studies evaluating the efficacy and safety of Vioxx in patients with pain and arthritis. But as has been pointed out, these were not sufficient to look at heart attacks.

Nevertheless, in a very careful review of Merck's new drug application, the FDA reviewer, Dr. Villalba, noticed a three-point increase in risks of heart attacks with Vioxx compared to placebo.

Again, I quote what has already been said before. She went on to point out that it was impossible to answer with complete certainty what was going on, since there were not enough numbers.

There was no available data. She said that a larger database would be needed to answer this, and other, safety questions.

Was such a database assembled? Was such a database required to be assembled? What was the urgency in approving a drug without this data? After all, the drug was no more effective than any other available drug. There were nearly 30 such drugs available in the United States.

Another drug, the COX-2 inhibitor, Celebrex, which had no such signals for heart attacks, had already been available in the U.S. market for 6 months prior. Multiple studies, including some that we did, have also shown that a combination of two older drugs were as effective and almost as safe on the stomach as Vioxx, with no heart attack risks.

There was certainly no emergent need to approve Vioxx without further studies if there were lingering safety concerns among the FDA reviewers. The trade-off of heart attacks for the rare instances of stomach bleeds is not a reasonable one. Remember, *primum non nocere,* "first, do no harm."

Ladies and gentlemen, the prescribing physicians of the U.S. remained unaware of any of these data or discussions. The FDA approved Vioxx with a 6-month priority review and we did not learn of the problem until April of 2002, with the new label change.

The VIGOR trial was the first one that talked about the heart attack/stomach bleed trade-off concerns. At the time the results of the VIGOR trial were released, I was actively involved in research and teaching in this area.

The result? A 500 percent increase in the risk of heart attacks with Vioxx stunned me. Clearly, the trade-off of a 500 percent increase in heart attacks for a 50 percent reduction in stomach bleeds did not seem attractive, at least not without the further discussion of data or generation of new data.

Merck's press release on this issue and a brief mention of the heart attack data were not enough for me to continue to educate physicians in my lectures. I asked Merck repeatedly for more data, including information on high blood pressure and heart failure rates.

When I was unable to obtain this data after multiple requests, I added a slide to my presentations that showed a man—representing the missing data—hiding under a blanket.

Up until this point in time, Merck had responded to all of my requests promptly and in a scientific fashion. With VIGOR, suddenly it was as if the company had to think what questions to answer, and what answers to give.

I persisted in my inquiry, and I was warned that if I continued in this fashion there would be serious consequences for me. I was told that Dr. Louis Sherwood, a Merck senior vice president and a former Chief of Medicine at the medical school, had extensive contacts within academia and could make life very difficult for me at Stanford, and outside.

But as a research scientist, I felt that it was unethical for me not to discuss my concerns in public. An open, scientific debate was important. It is only through such an open debate and discussion that we advance science.

Dr. Sherwood called several of my superiors at Stanford to complain. I subsequently learned that this was a persistent pattern of intimidation.

Stanford, too, felt the suppression of scientific discussion was unethical and complained to Mr. Raymond Gilmartin. To Mr. Gilmartin's credit, he took immediate action and the threats stopped immediately.

From then onwards until today, Merck scientists and officials have treated my colleagues and me with necessary and appropriate respect, and have shared all relevant scientific data promptly.

What happened with the label change? The FDA review of VIGOR correctly pointed out that the explanation advanced by the authors, that naproxen reduced the risk of heart attacks, could not explain the 500 percent difference between Vioxx and naproxen. The reviewers also highlighted data from many other studies showing that this was not an isolated finding in VIGOR.

VIGOR data were first made public in May of 2000. It was not until almost 2 years later that the FDA requested a label change. These revisions, as Dr. Psaty pointed out, were added to the "Precautions" section rather than being prominently displayed as a "Warning," as recommended by the FDA's cardiology reviewer.

While the safety data on stomach bleeds was added in a prominent fashion, the heart attack information seemed to support Merck's contention that Vioxx did not increase the risk. But adding statements such as "because of its lack of platelet effects, Vioxx is not a substitute for aspirin for cardiovascular prophylaxis."

Ladies and gentlemen and physicians in the audience, let me ask you. Do you know of a single physician, one physician in the world, who has ever prescribed Vioxx for cardiovascular prophylaxis? What are we talking about here?

Why not also say on the label, because of its lack of anti-tumor effect, Vioxx is not a treatment for brain cancer? Or do not use Vioxx for erectile dysfunction? It does not work like that. Or do not use it for depression. Why confuse the issue?

The favorable data for the Alzheimer's disease studies was included at Merck's insistence, but no unfavorable data, such as from studies 085 or 090, were added.

Even the Alzheimer's disease study data were relatively biased. While the label showed that there was no difference in heart attacks, it did not mention that the mortality rates of patients on Vioxx was almost twice that on placebo. Negotiation with the FDA certainly succeeded for Merck.

The CHAIRMAN. Dr. Singh, how much more time do you need? Because we have gone over your 10 minutes.

Dr. SINGH. I will wind up in 1 more minute.

The CHAIRMAN. Thank you.

Dr. SINGH. More importantly, there were no efforts to design and carry out large safety studies to prove or disprove the link of Vioxx to heart attack. Evidently, decisions were made for marketing reasons and for PR reasons, because the implied message of these studies would not be favorable, therefore the studies were not done. In my opinion, ladies and gentlemen, it is still better to kill a drug than to kill a patient.

Such a failure of the FDA to demand, and Merck to conduct, large, long-term studies subjected millions of people, over 4 years, to a drug whose safety had been questioned by the FDA even before its approval. This is not the proudest chapter in drug approval in the United States.

What can we do to prevent this from happening? First, we must find out what went wrong. A public inquiry should be conducted by an independent group of scientists with free access to all Merck internal documents that should be put in the public domain.

Two, there needs to be a public discussion of the role of FDA in approving drugs and labels. As the delay in the Vioxx label shows, the current process of labeling is one of negotiations. If the "sponsor" does not agree with what the FDA wants, it can continue to stall, or worse.

The FDA approval process needs to be more open and subject to public scrutiny. Once a drug is approved, all the data supporting such approval should be put in the public domain.

On drugs that need further safety data, a system of condition or time-limited approvals should be instituted.

And, ladies and gentlemen, I also suggest that an independent office of drug safety should be established that does not report to the FDA new drug approval section, so that there are no conflicts of interest. Only then will we be able to adhere to the principle of *primum, non nocere,* "first, do no harm."

Thank you very much, ladies and gentlemen.

The CHAIRMAN. Thank you, Dr. Singh.

[The prepared statement of Dr. Singh appears in the appendix.]

The CHAIRMAN. We will begin 5-minute rounds for questioning. It would be my intention to have at least two rounds, so I hope members will stick within the 5 minutes.

I am going to direct my questions to each individual separately, and I am going to start with Dr. Graham. Why did you decide to self-initiate a study on Vioxx? Despite the fact that the study was self-initiated, the FDA did provide financial support for that study, and indeed, even paid your way to France to present your poster and your position on the study.

Dr. GRAHAM. I studied this question because, as I said in my testimony, this is an important issue. VIGOR had raised a very important question, and that was, does Vioxx raise the risk of heart attack?

If Vioxx increased the risk of heart attack and there were going to be tens of millions of Americans using the drug, then you have a situation where you could have tens of thousands of people having a heart attack because they are taking a drug.

That needed to be looked at and additional data needed to be brought to bear because, at least based on the current available evidence, FDA did not seem like it was going to do anything else than what it had done with the labeling.

The CHAIRMAN. Did Merck have access to a study similar to your study that has not been made public? I would refer to Exhibit 46, which is available here in the series of posters.

Dr. GRAHAM. I am familiar with the exhibit. You are referring to the Ingenics study, I believe.

The CHAIRMAN. Yes.

Dr. GRAHAM. Right. Yes, there was a study from Ingenics. Dr. Walker, one of the investigators for the study, is a very well-known and respected epidemiologist. He was the former chair of Epidemiology at Harvard.

The findings from their study were virtually identical to ours. They showed an increase in heart attack risk with Vioxx. Their study design was also similar to ours. My understanding is that Merck had the results from this study at least as early as November of 2003.

The CHAIRMAN. All right.

If the findings of these studies are accurate, how many Vioxx patients had adverse complications due to Vioxx? Could you tell us how many heart attacks and/or how many deaths, generally?

Dr. GRAHAM. Right. Regarding the estimates of excess cases of heart attack and sudden death, we estimate that there were 88,000 to 139,000. That was based on Merck's own clinical trials data, their VIGOR study, and their APPROVe study. Those estimates were not based on looking at the epidemiologic studies. Merck, in many of its press releases, has said that the best data come from clinical trials.

FDA has said the same thing. So, that estimate, 88,000 to 139,000, is what happens when you take the risks from those clinical trials and you project it against the population that got Vioxx over 5 years. You do it on a spread sheet. It is mathematics. There is nothing strange or magical about it. It is just automatic.

Dr. Topol, at the Cleveland Clinic, arrived at very similar numbers. He came up with 160,000. So, he used an approach similar to ours. I do not know what the exact number is. I do know that it is a big number. It is a large number. It is closer to 100,000 than it is to 10,000. It is large. So from that perspective, Vioxx has been a disaster.

As somebody who has spent his entire career working in drug safety and who believes passionately in protecting patients from drug harm—I am not talking about what the new drug side of the house does in improving drugs. I am talking about after it is on the market. What do we do about what we find? This is unparalleled in the history of the United States.

The CHAIRMAN. We know that after the VIGOR study was evaluated, the FDA determined that the Vioxx label had to change to reflect the cardiovascular risks. There are a few things that, in my mind, are interesting about the label change, and I would ask you about them.

It took almost 2 years after the CV risk was known for Merck and the FDA to get the new labels for Vioxx, and even then the cardiovascular risk was not placed in the "Warning" section of the label. During that period, Merck was aggressively marketing Vioxx without any cardiovascular risk information in the label. As a doctor and a scientist who has worked for drug safety for 20 years, is that troubling to you?

Dr. GRAHAM. It is very troubling. I think Dr. Singh identified part of the problem, which I think is this need to negotiate labeling. But just put it in this perspective. You have a drug that is increasing the risk of heart attack five-fold, and Merck is saying we put patient safety first. Yet, it takes them 2 years to get that infor-

mation out to physicians. To me, that is very disturbing. But I think even more disturbing, though, is the fact that it ends up in the "Precautions" section and not in the "Warnings."

As Dr. Psaty pointed out, with the hormone replacement therapy for women, it actually had what is called a boxed warning. Now, a boxed warning is the most severe, serious, however you want to describe it, powerful—I have heard that used for the SSRIs—form of labeling that the FDA can use. It used it for SSRIs in suicidality in antidepressants that was just announced a month ago.

It did not do that here. Had there been a boxed warning on the Vioxx, I believe—and you can ask Dr. Kweder to correct me if I am incorrect—Merck would have been prohibited from direct-to-consumer advertising for Vioxx.

The CHAIRMAN. Senator Baucus? Then I have a corrected version of how people arrived, so it will be Hatch, Breaux, Bunning, Bingaman, Lott, and Snowe, in that order.

Senator BAUCUS. Dr. Graham, who determines the content of labels? Who at FDA, which office?

Dr. GRAHAM. That is dealt with in the Office of New Drugs.

Senator BAUCUS. It is not the Office of Drug Safety?

Dr. GRAHAM. No. Actually, when we try to make recommendations, our own managers try to make us take them out of our reports. If we are "maverick" enough to insist on keeping them in there, we suffer consequences. New Drugs and the reviewing divisions do not want to hear our recommendations, because if we make a recommendation, that puts them on the spot, because now they have to do something. If they do not do it, they have to explain why.

Senator BAUCUS. Listening to all three of you, you seem to suggest, and do suggest, that there would be more independence in the Office of Drug Safety. Is that correct?

Dr. GRAHAM. I think, without it, you will have another Vioxx. It might not be 100,000 people, but I can tell you right now, there are at least five drugs on the market today that I think need to be looked at quite seriously to see whether or not they belong there.

Senator BAUCUS. Dr. Psaty, do you agree with that?

Dr. PSATY. Yes. I think an independent office or center for drug safety is absolutely essential. I also think that drugs should be rereviewed. Companies make commitments for post-marketing studies. There were reports that only about 40 percent of these ever get started or initiated, much less completed or published. That is not adequate to protect the health of the public.

The FDA would have more power to make sure that those post-marketing commitments are done in a timely fashion if the drug came up for re-review instead of having to negotiate in a passive fashion. So, we have advocated for regular re-review. In Europe, they re-review drugs every 5 years.

Senator BAUCUS. Dr. Singh, do you agree, generally?

Dr. SINGH. I agree with that. I would add on something else, too. As Dr. Graham pointed out, the fundamental problem in labeling negotiations is it is a consensus club, and it cannot be a consensus club. The FDA has a lot of data. It is not allowed to use the data and is not allowed to put that data in the public domain.

Let me give you my example. I had a heart attack 2 weeks ago. I am not considering what my next therapies are. As a physician and as an epidemiologist, I am not sure that everything that needs to be known about these medicines and devices is out in the public domain, so I am not sure any more as to whether the FDA and the companies reach a negotiated settlement on this.

Senator BAUCUS. Well, this makes good sense to me, at least on the surface. What is the argument? Is there any legitimate argument against making the office totally independent, giving it regulatory powers so that it is not under the thumb, if you will, of the Office of New Drugs? Is there a legitimate counter argument?

Dr. GRAHAM. I do not believe that there is. For the last 15 years, this has been so obvious to me that this needs to happen. But you would have to talk to the people in New Drugs, because they might have a different view.

Senator BAUCUS. But you talk to them a lot, so you probably have a good idea.

Dr. GRAHAM. Yes. They are going to say, we need to work really closely with these people so that we get the drug approval right. This is basically my view on it. As soon as you start involving people whose responsibility it is to look at the post-marketing safety of a drug, you start dragging them in to start looking at the pre-marketing safety of the drug; you co-opt them.

Now you become part of the approval process. Then when the drug goes on the market and a problem happens, well, we are partly responsible. You have got to have a group that is just insulated from that that can take a second and a fresh look and deal with it. It is kind of like a backstop.

Now, I am trying not to be so critical of the New Drug side of the house, and it sounds like I have been. The fact is, they do a remarkably good job. Most of the drugs that go out there, considering what they do to our bodies, are remarkably safe. That is true.

Every year, however, there are a couple of drugs that are really bad actors, and when you have a bad actor, it takes down a lot of people. Then you have a second class. It is like a pyramid. You have the really bad actors at the top, a couple of those. Then you have another class.

It might be five drugs a year where you have major labeling that needs to be done, or other, major interventions that need to be done to protect patient safety. Those things get forwarded as well. Then everything is sort of really minor. Physicians do not read the labeling. It is pretty established that labeling does not change physician or patient behavior.

Senator BAUCUS. Even the black box label?

Dr. GRAHAM. The black box will catch people's attention. As I pointed out before, I think the most effective thing that the black box would have done is, it would have given prominence to the heart attack risk of Vioxx and it would have stopped direct-to-consumer advertising.

Senator BAUCUS. How are the bad actors found and discovered? Say the Office of New Drugs approves a drug, it is a good drug. Then, uh-oh, lo and behold, it becomes a bad actor, or an almost bad actor.

How is that discovered and what is the best way to discover those?

Dr. GRAHAM. Well, most of the time it is discovered using what we call our adverse event reporting system, the Med-Watch system, which you may be familiar with. It is case reports. Physicians and patients around the country, and health professionals will report cases to FDA of adverse experiences to drugs. And if we get reports in, a lot of reports in on a particular drug with a particular problem, that signals that we have a problem.

Senator BAUCUS. And it is presumably up to the Office of Drug Safety then to take action at that time.

Dr. GRAHAM. Right.

Senator BAUCUS. Start some studies, surveillance, and so forth.

Dr. GRAHAM. Right. That is right. And we do a lot of that.

Senator BAUCUS. Thank you very much.

The CHAIRMAN. Senator Hatch?

Senator HATCH. Well, thank you, Mr. Chairman.

Dr. Psaty, I have been interested in all of this testimony. Dr. Graham is an employee of the FDA and he does represent, or at least is attempting to represent, the views of the Agency.

Dr. GRAHAM. May I correct that? I do not represent the views of the Agency.

Senator HATCH. All right.

Dr. GRAHAM. I think that is pretty clear. [Laughter.]

Senator BREAUX. We are getting that drift.

Senator HATCH. I think you are attempting to try and establish that they ought to listen to your views.

Dr. GRAHAM. Well, that is different.

Senator HATCH. Well, all right. I can understand why the FDA would want to review Dr. Graham's materials, which they have. I think any government agency or private company would want materials written by staff to be analyzed, to be cleared before they are published.

Now, tell me if this is true. Is it not true that FDA requires all employees to get clearance before something is submitted to any publication, including a scientific journal?

Dr. PSATY. You are not asking that of me. I am from the University of Washington.

Senator HATCH. No, no. Dr. Graham. Is that true?

Dr. GRAHAM. They have that policy. But the policy, as Dr. Gawson said to Richard Horton, the editor of the *Lancet,* is ambiguous. There are actually two policies.

Senator HATCH. All right.

Dr. GRAHAM. One of the policies said that there was a 2-week time clock. Another policy said, if it is not cleared, the author can send it out with a disclaimer on it. It is very ambiguous. In my situation, I put it through clearance. I sent repeated e-mails asking people at the end of the time, is there a controlling authority why I cannot submit it to a journal?

What I got back from Dr. Trontel was an e-mail that said, I talked to Jane Axelrad. Jane Axelrad is CDER's head lawyer. What she said was, the best that I could do is to ask if you would hold off on submitting it. They were telling me that it was all right to go ahead and do it. They just did not want to say that.

Senator HATCH. All right.

You also say, Dr. Graham, that your experience with Vioxx is typical of how CDER—or the Center for Drug Evaluation and Research, so everybody understands what that acronym means—responds to serious drug safety issues in general.

Now, Dr. Graham, to me, that is a very serious allegation that you are making. In your testimony, you decline to "bore the committee with a long list of prominent and not-so-prominent safety issues where CDER and its Office of New Drugs proved to be extremely resistant to full and open disclosure of safety information, especially when it called into question an existing regulatory position."

Now, believe me, that type of information would not bore members of this committee. I am curious to review, as somebody who has spent 28 years here trying to understand FDA, trying to help FDA, trying to help the public in general, and trying to make sure that this drug approval process works efficiently and well. But let me just say, I am curious to review the evidence that you have regarding these specific incidents.

I am also anxious to give FDA the opportunity to respond to your allegations. I also want to hear FDA's response to your charge that the FDA "as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless." That is what you have said. Now, your charges are important. I think it is important that we examine them, and important that FDA be given an opportunity to respond, too.

But let me just ask you this. Is it true that one of the co-authors of your paper was a paid consultant of trial lawyers who are suing Merck? That is what I heard. Now, if that is true, I think that would cause serious questions about the neutrality of your findings.

Dr. GRAHAM. Well, all right. A couple of things on that. Dr. Wayne Raye was the last author on our paper, and he has been a paid consultant for Pfizer. When I asked him to join our team, I was not aware of that. And maybe that is my fault for not having asked him.

Senator HATCH. I am not finding fault here.

Dr. GRAHAM. Right. No, no. It is true.

Senator HATCH. My question is, does that not lend some——

Dr. GRAHAM. I do not think it does. If you saw how we did the study, and if you knew Dr. Wayne Raye and you knew how the study was conducted and you saw the safeguards that were built in to protect against bias, the fact that he was a paid consultant to Pfizer or to any other company would have no bearing on the study.

Senator HATCH. Or to the trial lawyers.

Dr. GRAHAM. I wrote the draft of the paper. I wrote the protocol. It got modified, but it was done by a large group of people. We had seven or so authors on it.

Senator HATCH. All right. I will accept that.

Let me ask Dr. Singh, if I could. Dr. Singh, we have enjoyed your testimony and have been very interested in it. But in your testimony, you discussed how you asked Merck numerous times for additional data from the VIGOR trial, and when you got no response,

you added a slide to your presentation with Merck hiding under a blanket.

Now, my understanding is, the data from the VIGOR trial was available during the FDA advisory committee meeting, which was open to the public. Additionally, the data from the VIGOR trial was included in the *New England Journal of Medicine.* So, I am perplexed on why you feel that you did not feel that you did not have access to the data that you needed.

Did you eventually get the data that you requested? It sounds to me like Mr. Gilmartin, the CEO of Merck, did intercede on your behalf. But I wanted to make sure that you got the data, and I could not tell from the testimony what ended up being the outcome there. Could you answer that for me?

Dr. SINGH. Yes, Senator. First of all, in my slide it was not Merck hiding under the blanket, it was data hiding under the blanket.

Senator HATCH. All right.

Dr. SINGH. Number two, VIGOR was publicly released in May of 2000. The *New England Journal of Medicine* publication did not come until November of 2000. During this time, there were millions of people who were taking Vioxx and I told them that I needed to know the answers before the VIGOR trial's publication in the *New England Journal of Medicine.*

The *New England Journal of Medicine* publication, Senator, we are now told was a preliminary publication. At the time that it was published, there was no mention that this was a preliminary publication.

Everyone that I know of, all the scientists I know of, consider it inappropriate to publish an article in the *Journal* and not tell people that it is preliminary, especially since the unfavorable data are not shown in the article. Data on hypertension and congestive heart failure were not available in that publication.

Senator HATCH. All right. Could you answer the part of the question about Mr. Gilmartin?

Dr. SINGH. Yes. Mr. Gilmartin acted promptly. Mr. Gilmartin acted very ethically.

Senator HATCH. And responsibly.

Dr. SINGH. And responsibly, and put a stop to all the intimidation and threats that I was receiving, and made sure that I received the data that I wanted.

Senator HATCH. Thank you. My time is up, Dr. Singh.

The CHAIRMAN. Senator Breaux?

Senator BREAUX. Thank you, Mr. Chairman. I thank the panel of witnesses. You have been very informative.

Dr. Graham, the way I understand it, the Office of Drug Safety really looks at drugs—and I will get this from the FDA—after they are on the market, and the Office of New Drugs is sort of before they get approved and start being marketed. Is that generally correct, the theory behind it?

Dr. GRAHAM. It is. It is, but also the Office of New Drugs that looks at it before it is approved also is responsible, after it is approved, for doing all regulation of the drug. So we look at the safety afterward.

Senator BREAUX. What about the Office of Drug Safety? What do they do?

Dr. GRAHAM. We tell the Office of New Drugs that we think there is a problem, and then they are supposed to decide whether they think that what we are bringing to them requires anything to be done.

Senator BREAUX. I do not think you said that quite correctly. You said you tell the Office of New Drugs?

Dr. GRAHAM. We find a problem.

Senator BREAUX. You tell the Office of Drug Safety that you think there is a problem.

Dr. GRAHAM. No, we are the Office of Drug Safety. We find a problem.

Senator BREAUX. Oh, you are Drug Safety? I apologize.

Dr. GRAHAM. When we find a problem, we have to go to New Drugs and say to them, there is a problem with the drug, something needs to be done. Then they have got to decide whether they want to do anything with it.

Senator BREAUX. I have got that now.

So when you did the study that you worked with Kaiser Permanente on, it was an epidemiological study versus a clinical trial, like in clinical trial #3.

Dr. GRAHAM. Right.

Senator BREAUX. First, you did that after the drug had been approved by FDA?

Dr. GRAHAM. It was done after approval, and we started it after we saw the VIGOR results.

Senator BREAUX. And the epidemiological study that you did with Kaiser was FDA authorized and approved?

Dr. GRAHAM. Yes. I mean, I work for the Office of Drug Safety. I got permission from my supervisors to do it. I got approval from them to get the funding that we used for the study, so I suppose the answer to your question is yes.

Senator BREAUX. The reason for you conducting that was the VIGOR study, which compared Vioxx with Naprosyn, indicated, in your opinion, a much higher incidence of cardiovascular problems with the use of Vioxx as opposed to those on Naprosyn. I take it at that time, were you aware that Merck was saying that that was because naproxen had a positive effect and you did not believe that, or what?

Dr. GRAHAM. Well, we did not believe it. I think that most serious scientists in the field did not believe it. Naproxen had been on the market for perhaps 20 years, had been used by tens of millions of people, and nobody had ever reported this before.

One other reason why our study was so important, it has to do with dose response. The VIGOR study was done using the very highest doses of Vioxx, but most of the use of Vioxx is with the lower dose. It turns out that maybe 15 or 20 percent of Vioxx use is at the high dose, but 80 or 85 percent of it is at the lower dose.

From a population perspective, from a public health perspective, what I was afraid of is, if the high dose causes heart attacks at a five-fold increased risk, what about the low dose?

What if the low dose increases the risk as well? Then we have a really big problem. Nobody was studying that. To my knowledge,

that was not even a question on the radar screen of the Office of New Drugs.

Senator BREAUX. Was the APPROVe study not looking at Vioxx versus a placebo?

Dr. GRAHAM. Yes. I did not even know about the APPROVe study until Merck released the results simultaneously with the withdrawal of the product.

Senator BREAUX. Well, you are in FDA, Office of New Drugs, and they are conducting a clinical trial with a drug, and you do not know it is being done?

Dr. GRAHAM. Well, I did not know. It is possible my supervisors knew. You would have to ask them. I do not know the answer to that. I can say that neither I, nor anybody on my study team, nor the safety evaluator who was responsible for Vioxx and with whom I worked, knew about that study.

Senator BREAUX. I find it incredible that you would start conducting a major study on Vioxx, an epidemiologic study, and not know that there is an APPROVe study, which is a clinical trial, ongoing. That is a whole other question. I do not understand why not.

But give me the difference between a clinical trial, like in a Stage III trial, versus an epidemiologic study in terms of the content and the effectiveness of an epidemiologic comparison versus a clinical trial. Just explain for the committee, what is the difference?

Dr. GRAHAM. Well, clinical trials are true experiments that are done prospectively. That is, they are planned. You start to expose people. You have a question and you study it.

The patients who are selected into clinical trials are usually highly selected. The way I like to think about it is, think of an envelope with a postage stamp on it. The envelope, all that white part of the envelope, is the population that is going to get the drug when it is on the market. The postage stamp represents the types of patients who get studied in the clinical trials.

What an epidemiologic study tries to do, is look at what is the effect of the drug when it is used across the entire envelope, not just in that small, little postage stamp, patients who are only this old, who are not using aspirin, who do not smoke on Sundays, whatever the entry criteria are.

We are trying to get something that is more representative, but it is observational and it is not randomized so it is viewed as being a less robust, a less precise, more potentially prone to error form of evidence than a clinical trial.

Senator BREAUX. That is because, when you are getting data from Kaiser Permanente, it does not tell you whether the patients are diabetic, whether the patient has had another heart attack, whether they are obese, or does it?

Dr. GRAHAM. Well, we did not know about obesity, but we knew about the other things that you talked about. We were able to collect data on 23 different risk factors for heart attacks, so we had that data. But whether they were obese or not, that, for example, was a piece of information we did not have.

The CHAIRMAN. Senator Bunning?

Senator BUNNING. Thank you, Mr. Chairman.

Dr. Graham, according to your own testimony you have been with the FDA for over 20 years. Is that correct?

Dr. GRAHAM. Yes.

Senator BUNNING. In various capacities at the FDA.

Dr. GRAHAM. That is correct. I started as a staff fellow.

Senator BUNNING. All right.

You said in your testimony that you were pressured to change the conclusions in the study you had done with Kaiser on Vioxx by both the Office of Drug Safety and the Office of New Drugs.

Dr. GRAHAM. Correct.

Senator BUNNING. Did you change your conclusions?

Dr. GRAHAM. I changed them to a fair degree. To me, it was a fair degree. Maybe for the people reading it, it was not. It caused me a lot of mental anguish. In fact, I telephoned four close colleagues that I respect around the country to compare the two wordings, because I was so afraid that the change that I was making might compromise the message that I had.

Senator BUNNING. Why did you change your conclusions?

Dr. GRAHAM. Why? Because I thought that if I did not, there would be no way on earth that that data would see the light of day. That is the honest truth.

Senator BUNNING. Is that because the FDA paid for the study?

Dr. GRAHAM. I am not sure I understand. The reason why I changed things, is because I thought that if I did not, they would not let me go to present the paper and it would just be more trouble down the line.

Senator BUNNING. But the FDA did pay for the study, so you were thinking you were not going to be able to publish your conclusions unless you changed it.

Dr. GRAHAM. Correct.

Senator BUNNING. All right.

Did you complain to anyone about the pressure internally? I am talking about at the FDA.

Dr. GRAHAM. Did I? I complained to lots of colleagues. You can talk to——

Senator BUNNING. No. I am asking a different question now.

Dr. GRAHAM. All right. I do not understand.

Senator BUNNING. I am asking the question, did you complain to anybody at the FDA?

Dr. GRAHAM. I complained to my supervisors. I said to them that I thought that I was being pressured. Later on, I told them that I thought that I had been ambushed when they set up a meeting with them and the Office of New Drugs and they spent an hour basically just criticizing me because my study report was not completed yet, but they knew that the study report was going to be available on September 30.

So on September 22, I am in this room with three people from the Office of New Drugs and my two supervisors from the Office of Drug Safety, and they are all complaining at me because my study report is not done yet.

They already knew that it was going to be done on September 30. I had a meeting 2 days later with these people and I told them that I felt that I had been ambushed and that they had not supported me.

Senator BUNNING. Is there anyone specifically at the FDA that handles this kind of complaint?

Dr. GRAHAM. I do not know who one would go to.

Senator BUNNING. No one? It is a structural problem then, you are saying, with the FDA?

Dr. GRAHAM. Well, they have an ombudsman, but I do not think anybody realistically thinks that they are going to get help from that.

Senator BUNNING. How long before Merck got approval of Vioxx from the FDA? How long was their application?

Dr. GRAHAM. You will have to talk to Dr. Kweder about that. I had nothing to do with the pre-approval side of things.

Senator BUNNING. You do not have any idea of whether it was 1 year, 2, 3, 4, 5?

Dr. GRAHAM. I do not know how long that review took.

Senator BUNNING. Do you feel that the FDA proceeded appropriately with concerns raised about the cardiovascular effect of Vioxx?

Dr. GRAHAM. Personally? No.

Senator BUNNING. No.

What steps has the FDA taken to better resolve internal differences of opinions like yours?

Dr. GRAHAM. I am aware of none.

Senator BUNNING. None.

Then you think it was the FDA's problem and the internal workings of the FDA, and the approval process and the follow-up by your specific portion of FDA, because there is a conflict between one side and the other.

Dr. GRAHAM. Correct.

Senator BUNNING. All right.

Dr. Psaty, in your opinion, what should Merck and the FDA have done differently, if anything, to handle this issue?

Dr. PSATY. I have tried to outline that in my recommendations. I think there is a system problem. With the recent emphasis on rapid new drug approvals, which started in 1992 with the first authorization and the reauthorization in 1997, there has been a lot of attention to rapid drug approvals.

There has not been a comparable attention to drug safety. What has happened, is in the United States in the early 1990s, 2 percent of drugs would first appear in the U.S. market. The FDA had a terrific system, but it was slow. Drugs would not appear here. They would appear in Europe. They would come on the market in Europe. We would see the adverse effects, and Americans would be protected.

With the rapid drug approvals, more than 60 percent of the drugs first appeared on the market in the late 1990s in the United States.

Senator BUNNING. Do you happen to know how long it took to get FDA approval of Vioxx?

Dr. PSATY. I understood it was a 6-month priority review. But, again, I am not an expert. May I just finish my answer, briefly? With 68 percent of the drugs first appearing on the U.S. market now, we need to pay more attention to drug safety, both prior to approval by doing the large clinical trials for patients that are

going to be exposed, the millions of patients that are going to be exposed, and to pay more attention to drug safety. We have a new situation now than we did in 1990.

Senator BUNNING. In other words, we do not have a test market.

Dr. PSATY. We are the test market.

Senator BUNNING. That is what I mean. We used to test them in other places. Thank you.

Thank you, Mr. Chairman.

The CHAIRMAN. Yes. You bet.

Senator Bingaman?

Senator BINGAMAN. Thank you, Mr. Chairman.

Dr. Graham, you said some complimentary things about the Office of New Drugs about their generally doing a good job in checking drugs before they are released. Then you said, however, there are five drugs currently out there that need to be looked at very seriously. Is that accurate?

Dr. GRAHAM. Yes, that is what I said.

Senator BINGAMAN. Will you tell us what five need to be looked at?

Dr. GRAHAM. Cybutramine, Meridia. It is a weight loss drug. I think that that needs to be carefully looked at because it only works if you take it for a long time, but nobody stays on it for more than a month, just about, because they cannot tolerate the side effects.

So they get the side effects, they get the risks of raised blood pressure and stroke, and they do not stay on it long enough to lose the weight that is going to make a difference. So to me, I question, what is the utility of that drug?

Actually, we had done a study 2 years ago in which we pointed this out, and our management made us take that conclusion out of it. We were forced to take out of it, this observation erases the utility of the continued marketing of this drug. That got taken out of that report. So, cybutramine is one.

Another one is Crestor. It is a cholesterol-lowering drug. It is the only cholesterol-lowering drug—there are a bunch of them out there, and some of you may be on one of them—that causes acute renal failure.

It also has a higher risk of causing a very severe type of muscle injury called rabdomyelysis, which, by the way, I and colleagues in our Office of Drug Safety have just completed a big study on and it is going to be published in the *Journal of the American Medical Association* soon.

I think that Accutane is another drug that represents, in my view, a 20-year failure, regulatory failure, by FDA. Let me tell you the story on Accutane. It is used to treat severe nodular cystic acne. That is a disorder that is relatively uncommon. It happens 5 times more in men than it does in women.

Well, the way the drug is used, it is used equally in men and women. If a woman takes the drug and becomes pregnant while she is on it, she has a 20- or 25-percent risk of having a child with a birth defect.

Well, what did FDA do about this? When the drug was first approved it did not recommend contraception. Then it said, oh, we are

getting reports of children with birth defects, so they recommended that, but it did nothing to stop the expansive use of the drug.

What happened in 1989 is, FDA was under so much pressure, it instituted this thing called the Pregnancy Prevention Program. The Pregnancy Prevention Program was supposed to eliminate pregnancy exposure to Accutane. Well, during that time the use of Accutane went up almost 250 percent in women of child-bearing age over the 10 years of that program. To me, that is a tragedy.

It came to an advisory committee meeting in 2000. The advisory committee said, this drug needs to have a restricted distribution system. Well, that was something I had recommended 10 years previously, but it was nice to see that history finally caught up with reality.

FDA then said, all right, we are going to do it. There was an abrupt about-face. I do not know what happened, I do not know why it happened, but FDA backed off from that and instituted another risk management system that they called SMART. Well, SMART was not very smart. In my view, SMART was dumb, but it had this neat little gimmick.

The gimmick was, we put a little yellow sticker on a prescription and if the dermatologist signs the prescription, that guarantees that the woman is not pregnant, that she has had a pregnancy test, that she has severe cystic acne, and that she is on two forms of contraception. We are not even going to check to see if those other things are really true, we are just going to trust the doctor because he signed a sticker.

Well, we found out eventually that, well, a doctor signed a sticker, but those things were not being done. So, that is where we are. We just lost time and time and time again.

Another one would be, I would be looking at Bextra very, very closely. That is a cousin of Celebrex, a cousin of Vioxx. I think that there is some disturbing evidence on that drug as well.

The fifth drug is Serevent. It is a drug that is used to treat asthma, and it has the unfortunate property—I believe, at least—that it increases the risk of somebody who has asthma of dying because of their asthma. Sorry for the long answer.

Senator BINGAMAN. No. I appreciate it.

Let me ask about Bextra. Dr. Furberg has done some analysis of Bextra, I believe, and he is on the FDA Advisory Committee. There has been some suggestion that he should not be part of any review of Bextra because he is suffering from an "intellectual conflict of interest."

Dr. GRAHAM. When I saw that, first I had to laugh, and then I was just mortified. If you knew Dr. Furberg, you would know that he is probably the single most eminently qualified person that FDA has access to to sit on that committee and render judgment about the safety of Bextra. The man has no financial conflict of interests. FDA has this amazing conflict of interest policy.

You can come in, get money from Merck, get money from Pfizer, and what FDA will say is, well, since you are getting money from everybody, you do not have a conflict. Or they can say, you are getting money from Merck, you are getting money from Pfizer, you are not getting it from both.

But they will say, we have determined that the nature of the conflict will not interfere with your ability to render an impartial decision. So, they have ways of waiving these conflicts of interest that are meaningful all the time.

Then you come along with somebody who, for 20 years, worked in the National Institutes of Health, he headed a large study section on doing cardiovascular clinical trials, he is one of the country's leading experts on heart attacks and epidemiology and the clinical trials of heart attacks.

Then he goes to Wake Forest University. He establishes one of the best epidemiology programs in the country. This is a man who is not taking any money from any drug company. Well, he looks at a paper that gets published on Bextra. I read the paper too, and it is atrocious, what you can do with statistics.

When Curt looked at it, he said, this is garbage, and he re-analyzed the data that were presented in that table and he said, you re-analyze these data correctly and you will see that there is a problem with Bextra.

So, being a man who is based on evidence, who is an evidence-based scientist, what he said was, the evidence suggests there is a problem. So he is a scientist. It is kind of a double standard. The fact that he is a scientist, he looks at the evidence, and he says the evidence suggests there is a problem.

Curt did not say Bextra needs to come off the market, I am certain. I know Curt Furberg very, very well. I am certain that, if he was presented with evidence that said otherwise and he believed that it was convincing, that it was well-done evidence, that he would change his conclusion.

That is not a permanent conclusion, that is a conclusion based on the evidence as it stands at the moment, at the time. FDA's reaction, in my view, is just one more example of their trying to game the whole system.

Senator BINGAMAN. Thank you very much, Mr. Chairman.

The CHAIRMAN. We will do a second round, and last round of this panel so we can move on.

Dr. Graham, some rumors have been circulating that you have another agenda in mind by your testimony here today. Is there any truth to the allegation that you will be leaving the FDA to make your fortune as an expert witness on drug safety?

Dr. GRAHAM. Oh, golly. I am sure FDA wishes that I would. [Laughter.] Anybody who knows me for more than, like, 5 minutes, knows that that is a ridiculous question and the answer is no. If I wanted to go and make my "fortune" as an expert witness, I could have done it years ago.

There was plenty of money to be made with Fen-Phen, and I was at the very heart of that. There was plenty of money to be made on Rezulin. It was my research that eventually got it off the market. I could have been involved.

That long list that I gave you? Dollar signs with each one of those. That is not what I am about. That is not what my career is about. That is not what I see myself as doing. I enjoy doing post-marketing safety.

The CHAIRMAN. Dr. Psaty, Merck has tried to explain the result of the VIGOR trial by claiming that naproxen prevented heart at-

tacks. First, I present the question to you, is there a credible explanation? Second, I would like you to comment on Exhibit 17, which is presented here on a poster.

Dr. PSATY. All right. Thank you. It is just not a credible scientific explanation. Compared to naproxen, Vioxx increased the risks of heart attack by about 500 percent. When Merck first considered the issue, they hypothesized that the absence of an aspirin-like effect would increase the risk by 33 percent.

There are no clinical trials evaluating naproxen on heart attack risk. The observational studies suggest that naproxen has about half the benefit of aspirin, so it would be about a 10 percent difference.

The best available evidence suggests that Vioxx was primarily responsible for the 500-percent increase in risk, and if naproxen had the full anti-platelet effect of aspirin, Vioxx would be expected to increase the risk by about 380 percent. That is almost identical to the results in Dr. Graham's study for the high-dose Vioxx.

The CHAIRMAN. Does that include your comment on Exhibit 17?

Dr. PSATY. Well, Exhibit 17 is information from a consultant for Merck that says basically the same thing that I just did.

The CHAIRMAN. I think you have said enough.

Dr. PSATY. All right.

The CHAIRMAN. If you, as a scientist, knew what the Merck scientists knew in 1998, what would you have done to evaluate Vioxx?

Dr. PSATY. Well, the biologic mechanisms that were known in 1998 suggested two things. One, the possibility of a GI benefit, and two, the possibility of cardiovascular harm.

In order to understand the public health consequences of widespread use of Vioxx, I would have recommended a complete, symmetrical, and fair evaluation of the hypothesized GI benefits and risks. Heart disease is more common and serious. In an effort to improve GI safety, it would be important not to create a whole new set of adverse events.

The CHAIRMAN. What was the problem with the design of the Vioxx study?

Dr. PSATY. Well, there were a number of Vioxx studies. Consistently, the early Vioxx studies, right through the VIGOR trial, were designed to maximize the ability or the chance of finding a GI benefit and minimize the chance of finding cardiovascular harm.

The attentions to risks and benefits were not symmetrical. These features include short studies, small studies, the exclusion of patients at high risk, the inclusion of venous thromboembolism as a thromboembolic event.

This does not make good medical/scientific sense. Fundamentally, they chose not to ask the question about cardiovascular risks, but the lack of evidence about a drug is not evidence that the drug is safe.

The CHAIRMAN. Dr. Singh, I would like to refer you to Exhibit 2, the memo that you referred to in your testimony which was prepared by Merck in 1996. Would you state in your own words the value of that memo and why it is important to the situation here with Vioxx?

Dr. SINGH. Chairman Grassley, that shows that in 1996, Merck was fully aware of a potential heart attack trade-off with Vioxx.

The CHAIRMAN. All right.

Dr. SINGH. This is the point in time when they should have started studies, as Dr. Psaty pointed out, in a symmetrical fashion, and what I talked about in my testimony, so that the public and the scientists could weigh the risks and the benefits of naproxen.

Instead, what happened after that was that there was an attempt—and a successful attempt, at that—in designing studies that maximized the benefits of the drug, but that would tend to camouflage and hide any controversial problems that might occur. This went on systematically.

The approved drug had claims for patient safety. Mr. Chairman, it was not a safety study. It had never been designed for safety. It was designed to extend the indication of Vioxx into another area so that more Vioxx would be sold. That we found out about heart attacks in the trials is a very fortunate bit of coincidence for the American public.

So what this letter points out, is that the company was aware in 1996, 8 years ago, of what the problems were, or what the problems would be. The company needed to explore this to find out if the drug was all right. It was a drug for pain, and you cannot take these kinds of risks.

The CHAIRMAN. And a yes or no answer, and I think it is a continuation of just what you said. But to sum up, there were numerous red flags, both before and after the marketing of Vioxx that would raise questions, legitimate questions about its safety.

Dr. SINGH. Yes.

The CHAIRMAN. Senator Baucus?

Senator BAUCUS. Dr. Graham, how much is enough? What I am getting at is, clearly we want to study new drugs for safety, comprehensively, thoroughly to make sure that they are efficacious, they are safe, and all that.

But how does the FDA, or how should the FDA, design studies or approve studies to know when enough is enough, particularly for longer effects? I understand with Vioxx, there is maybe a cut-off prior to 18 months, then after 18 months. So, just give us a rule of thumb.

Dr. GRAHAM. Well, I do not think there is a rule of thumb, but I think there are maybe some guiding principles. Dr. Psaty has alluded to them already.

If you have a drug that is going to be used by large numbers of people on a chronic basis, I think you are obligated to do really large studies and follow them for a reasonably long period of time. What that "reasonably" is, I do not know. I can tell you, it is not a month, it is not 2 months, it is not 6 months. A year might not be enough.

With Vioxx, for example, the idea would be, arthritis is a chronic condition, so you might be on this drug for 5, 10, 20 years. Diabetes is kind of similar, where it is a chronic disease and you have this drug where you know you are going to have to take it day in and day out. There are other conditions where maybe you are taking it for a much shorter term duration of use.

Those situations, short of clinical trials, are appropriate. I think that you have got to try to strike a balance, because there is this

issue of, well, how big can the study be? How much does it cost? How long can you do it?

You might say, well, we have done the best we can pre-marketing, and then what you have to do is rely on really good post-marketing to catch something if it is a problem.

Senator BAUCUS. Do you think the FDA is doing a pretty good job there in designing the studies or is the problem that they are not following the results of the studies?

Dr. GRAHAM. I am not familiar with all the different reviews.

Senator BAUCUS. Right. Generally.

Dr. GRAHAM. Well, in general, they probably do a good job. I would say that with Vioxx, though, they did a terrible job. They did a terrible job because, exactly what Dr. Psaty described.

The studies that were done removed, excluded the patients who were at highest risk for heart attack and who would make up a large portion of the people who would get the drug afterwards. So it is kind of like, we studied the postage stamp.

The postage stamp has people who are not at risk of heart attack, who are not taking aspirin. Now what we are going to do, is we are going to make a bundle of money selling it to all those other people, and many of those do have it.

Senator BAUCUS. Now, kind of following up a little bit on Senator Breaux's question, do you think the FDA should be aware of all internal clinical trials?

Dr. GRAHAM. Oh, definitely.

Senator BAUCUS. And it sounded like, at least, your office was not aware of the APPROVe study.

Dr. GRAHAM. No, no. But I would imagine that the new drugs area, the Office of New Drugs who do the new drug reviews, approve it, and regulate it, that they were aware.

Senator BAUCUS. All right.

Should all of those studies be made public?

Dr. GRAHAM. Oh, I definitely think that there has been a lot of controversy about that. But I think that when a study starts, that that should be posted somewhere so the people know the study has started, and when the results are completed, that those results should be available as well.

Senator BAUCUS. And that is not the case today?

Dr. GRAHAM. It is not the case today.

Senator BAUCUS. Why is it not?

Dr. GRAHAM. There is probably a host of reasons. It is something that is being written about extensively in major medical journals around the world. I know from FDA's perspective, they will consider much of this information to be proprietary, so they will say that they cannot.

But maybe there is some other way of making that information available. Because what Dr. Singh was talking about is a very dangerous problem. It is only the positive studies, only the studies that show what the company wants are the ones that get published.

Senator BAUCUS. Right.

Dr. GRAHAM. All the other studies get buried. I am not saying anything evil there. I am just sort of saying that when you are looking, as a physician, at the body of evidence, it is truncated. You only see the good stuff.

You do not see the stuff that shows, well, the drug did not work here, or it caused these problems. You need all of the information to sort of come to a better, fuller appreciation of whether a drug works or not and what its benefits are. That is not pointing fingers at anybody. That is just sort of a global problem.

Senator BAUCUS. But you cannot think of a legitimate reason for not making studies public?

Dr. GRAHAM. No, I cannot.

Senator BAUCUS. The proprietary question is a question, but you believe there is a way to deal with that so that can be resolved.

Dr. GRAHAM. I think scientific evidence is scientific evidence. I do not need to know the chemical structure, the manufacturing processes, or all that other stuff that might be proprietary. All I want to know is what the studies were, what the types of patients were that were studied, and what the results were that were found.

Senator BAUCUS. I see you, Dr. Psaty, nodding your head in agreement. One other question here. My time is a bit short. What about, should our country be doing comparative analysis of drugs and making that information public?

Dr. GRAHAM. I personally think that that is the way to go. I think that there is lots of resistance on the part of industry from doing that, and you would have to talk to Dr. Kweder about what FDA's official view on that is. But I think, from a public health perspective, from a health effectiveness/cost effectiveness perspective, that that is definitely the way to go.

If you have got five different drugs and two of them are clearly superior to the other three and they are all supposed to do the same thing, why be paying money for the ones that do not work as well, and why have patients using drugs that do not work as well?

Senator BAUCUS. Just one very quick question. I know that part of the solution here is monitoring results. That is, physicians, when they are prescribing a drug, should monitor their patient, and do monitor the patient, and so forth. Sometimes I wonder, there are there just so many drugs, it is hard for physicians to keep up to date on effective drugs.

Dr. GRAHAM. It is. Right.

Senator BAUCUS. Is it, or is it not?

Dr. GRAHAM. No, I think that is right.

Senator BAUCUS. Is that rising to a level where something has got to be done about that, or not?

Dr. GRAHAM. Well, I do not know what you could do about that. I think it is definitely a problem. Most physicians probably carry in their head the 10 or 20 drugs that they use for most things that they are going to see most of the time, and then if something else comes up they call a colleague who has more experience with that.

The other place where I think they end up getting a lot of their drug information, though, is from the drug representatives from industry. So, I think that a lot of physician education about medicines comes through the industries, symposia, and things like that that are offered.

Senator BAUCUS. Thank you very much.

The CHAIRMAN. Senator Hatch?

Senator HATCH. Well, thank you, Mr. Chairman.

I think all of you have made some constructive suggestions on how to improve the drug approval process and strengthen drug safety, especially where you state that the data supporting drug approval should be made available to the public.

Now, many of us believing that opening up those studies for public scrutiny and evaluation is important, and I am interested, especially you, Dr. Psaty, and you, Dr. Singh, in your perspective on the FDA's five-step plan to strengthen the FDA's drug safety program.

Now, I think, as I view it, your goals are in step with the goals of the FDA. If I am wrong on that, I would like to have you inform me where I am wrong.

Dr. PSATY. I do not work with the FDA and I do not know what their five-step program is.

Senator HATCH. All right.

Dr. PSATY. So, it is difficult for me to comment on it.

Senator HATCH. All right.

Dr. Singh, are you familiar with that five-step plan as well?

Dr. SINGH. I do not know the details of that. I have read about it in the press. But if the program does, indeed, figure out a way of putting data in the public domain, that is very important. If we scientists reviewed all the studies that were done on Vioxx and what was happening, we would have made our own independent judgment. We just did not know. That is problem number one.

Senator HATCH. All right.

I just want to ask one other question. That is, is it not true that all drugs, approved drugs, have a certain level of risk? I would just like to ask the three of you, what, in your opinion, is an acceptable level of risk by scientific standards? I would just like you to tell us that in more detail than we have had today.

Dr. Psaty?

Dr. PSATY. Well, I review grant proposals for the NIH. I am on one of the study sections. What I would have required of a Vioxx trial, is a symmetrical evaluation of the risks and the benefits. The studies designed by Merck were not studies that would help inform the public about the risks and benefits.

I referred in my testimony to the idea that if the VIGOR trial results had been available—they were available to the DSMB in December of 1999—7 months earlier, if they had moved that large, long-term trial up—and this is a drug used by many people for long periods of time—by a few months, it is possible the FDA never would have put Vioxx on the market. Now, I do not know that for a fact.

I know that I, as a physician, chose not to use Vioxx after the VIGOR came out. The Pharmacy and Therapeutics Committee of Group Health Cooperative, where I do many of my studies, looked at the VIGOR trial results and said, we do not want our patients on this drug.

Senator HATCH. Anybody else care to comment?

Dr. SINGH. Let me add on to that testimony of Dr. Psaty's by saying that it is very important to consider the risk/benefit ratio. Senators, you have got to make sure, what is the drug being used for, and what is the result we are getting? If it is a drug that is going to cure my cancer, absolutely, I will accept some risk of heart attack.

If it is a drug for pain, and there are 30 other medications available that, combined with a stomach-protecting agent, will give me the same efficacy and the same safety, why do I need to subject my patients to an increased risk of heart attack? Why would I trade a five-fold increase in heart attacks for half of the risk of GI complications? So this question should be answered for individual drugs.

It is the risk/benefit ratio that needs to determine how much study needs to be done, how long the study needs to be done, and what is the value of the drug over and above what is already available to the American public.

Senator HATCH. Well, thank you. Thank you all. I appreciate your testimony.

The CHAIRMAN. I am going to call on Senator Breaux, and then I am going to step out for a minute. So when Senator Breaux is done, then would you just pick up, Senator Bingaman?

Senator BREAUX. Thank you, Mr. Chairman.

Dr. Singh, this is Senator John Breaux. Were you referring to the memo where apparently Merck was indicating that they did not want to combine low doses of aspirin with the testing of Vioxx? Is that what you were referring to?

Dr. SINGH. Yes. This is the November, 1999 memo written by Dr. Tom Mosliner that was the first one that I knew of where there was a discussion about the trade-off of stomach bleeds and heart attacks. Then subsequently in February of 1997, there were many e-mails that discussed, how can we design studies so that this heart attack risk is not evident to the public.

Senator BREAUX. Were they saying that in the studies we ought to have some amount of aspirin combined with the taking of Vioxx so that we would not get a negative CV, cardiovascular, indication?

Dr. SINGH. Right. They were talking about that. Then they were saying if we did that, the combination of aspirin and Vioxx, it would probably be no safer than a drug like naproxen, and therefore you would not see any GI safety benefit, and therefore you would kill the drug.

The whole question here is, it appears that the advantage on the GI side would be negated by what is happening on the heart attack side, and if you try to remove the heart attack difference by adding aspirin, then the GI advantage would disappear.

Senator BREAUX. All right.

Dr. SINGH. Even if you add aspirin to Vioxx, the heart attack risk still remains. That is what the APPROVe trial shows, so there is probably a direct effect of Vioxx in causing heart attacks. But at that point in time in November of 1996, they did not know that. They only knew that there was a strong reason to believe there is a trade-off between heart attacks and stomach safety.

Senator BREAUX. Let me ask whoever can answer the question. The VIGOR study and the APPROVe study. Really, none of these studies were designed to test Vioxx's cardiovascular connections. I think that APPROVe was for colon polyps, principally, and VIGOR was comparing Vioxx with Naprosyn with regard to GI, or gastrointestinal, problems.

So, the question I have, in general, is when a drug comes out, do you have to design a study to compare the use of that drug with

all types of potential problems that are out there? I am afraid, if we had to do that, we would probably never get any drugs ever approved.

Dr. SINGH. If I might respond. No, sir. That was not the case. Here in this particular case, there was a theoretical reason. There was a physiological reason why this would be happening. We knew the biology of why this should be happening in 1996.

Then in 1997, 1998, and 1999, there were multiple small studies that showed that this was, indeed, happening. By 2000, we had a large study that proved conclusively that this was happening, and was happening at a five-fold level.

Senator BREAUX. Which study was that?

Dr. SINGH. That was the VIGOR study.

Senator BREAUX. I am familiar with it.

Dr. SINGH. The VIGOR study established it. At that point in time, there was a whole series of evidences that something needs to be done, a large clinical trial to look at the safety of this drug needed to be done.

Senator BREAUX. Why do you disagree with, apparently, Merck's conclusion on the VIGOR study, that the negative implications for Vioxx were because of the positive thrust of what naproxen did for people who were taking it at the same time, and therefore it didn't indicate that Vioxx was a problem, but rather that naproxen had a very positive effect on reducing cardiovascular problems? Why do you disagree with that?

Dr. SINGH. For multiple reasons, Senator. Dr. Psaty already pointed out some of them. Number one, naproxen cannot be better than aspirin because aspirin inhibits platelets permanently, naproxen would only eliminate temporarily.

Aspirin itself is only about 20, 30, 35 percent effective. That is exactly what Merck was predicting, also as shown by the Mosliner memo.

Senator BREAUX. I want to hear from Dr. Psaty, too. But your premise is that Merck was incorrect because naproxen could only have had a relatively minor positive effect on preventing heart attacks?

Dr. SINGH. That is exactly correct. And there were multiple other studies that were at least placebo that also continued to show the difference between Vioxx and the placebo risks.

Senator BREAUX. Thank you.

Dr. Psaty, what is your comment?

Dr. PSATY. I agree. There are two different issues.

Senator BREAUX. Agree with what?

Dr. PSATY. With Dr. Singh.

Senator BREAUX. All right.

Dr. PSATY. The naproxen explanation offered by Merck is not a credible explanation for the findings in the VIGOR trial. When Merck put out a press release called "The Cardiovascular Safety of Vioxx," the FDA criticized it for not——

Senator BREAUX. They sent them a warning letter.

Dr. PSATY. They sent them a warning letter and called that explanation "simply incomprehensible," the idea that Vioxx was safe and that naproxen explained it.

Senator BREAUX. I understand that.

Can anybody help me understand—and this will be my last question, Mr. Chairman—back in 1999, at the time of the FDA approval of Vioxx, what FDA was saying when I quoted in my opening statement that FDA said at that time when they had approved Vioxx, they said, all right, use it? It is safe and it is effective.

There is a little thing that never goes on a label, where they said there is a theoretical concern that patients treated with this COX-2 selective inhibitor may be at a higher risk for cardiovascular problems. With the data we have, it is impossible to answer with certainty whether these events are increased with people taking it. We need to have a larger database.

If I had had that, I would say, time out. We need a lot more data before we approve it. But FDA had approved it at that point. Yet, they were saying, we do not have enough data to know if there is a connection between the taking of the product and cardiovascular heart attacks.

Dr. PSATY. I agree. We did not know at that point whether it would prevent ulcers, and that is why the VIGOR trial was developed. So the argument here for this particular drug, is that the evaluation about whether it prevented ulcers and may have caused heart attacks was important to ask fully. They said they needed a more complete database, and I think that medical officer was correct.

Senator BREAUX. In your or Dr. Singh's opinion, do either of you think they should have approved the drug when they said that statement about not knowing the potential effects on cardiovascular problems?

Dr. SINGH. In my opinion, when they said with the data available it was impossible to answer with complete certainty and that a large base is needed, this is the point when they should have asked for, requested, and obtained a larger database. They should have asked for, and forced, Merck to do the larger studies.

Senator BREAUX. Before approving.

Dr. SINGH. Before approving the drug. Yes.

Senator BREAUX. All right.

Dr. SINGH. There were other safe drugs available for the patients.

Senator BREAUX. I have got you.

Dr. PSATY. The optimal approach would have been to start that earlier in the process. They have been negotiating with the FDA about the trials to be done earlier. These issues were hypothesized earlier on, and that work should have started earlier.

Senator BREAUX. We are Monday morning quarterbacking now, after these other tests are done, and somebody sees, after 3 years, the APPROVe study or the VIGOR study. I mean, those things have been going on for a long time. It is easy to say, Monday morning, well, we should have studied from the very beginning, does it have an impact on cardiovascular problems.

Dr. PSATY. The mean duration of enrollment in the VIGOR trial was only 8 months.

Senator BREAUX. How long before we got the results of the VIGOR study? How long did it go on?

Dr. PSATY. It was known to the DSMB in December of 1999.

Senator BREAUX. Well, it had to have been at least a year and a half because it did not start causing problems until after it had been used a year and a half, right?

Dr. SINGH. Oh, no. That is not true.

Dr. PSATY. No. That is the APPROVe trial.

Senator BREAUX. Oh. VIGOR was with the placebo.

Dr. PSATY. The mean follow-up with the patients was 8 months.

Senator BREAUX. All right.

Dr. SINGH. And also, Senator, there are other studies that showed that the risk is there even before 18 months. The VIGOR trial itself, the risk begins to appear at about 6 weeks. So I do not think that one can say that you can use the drug safely up until 18 months and nothing is going to happen. I do not think that is true at all.

Senator BREAUX. All right. I am sorry.

Jeff?

Senator BINGAMAN. Let me just ask a few additional questions.

Dr. Graham, could I ask you a follow-up? You cited five drugs that you think need to be looked at very seriously.

Dr. GRAHAM. Right.

Senator BINGAMAN. What concrete action would you recommend be taken with regard to each of the five? Do we need to do more studies? Do we need to take them off the market? Do we need to put big labels on the bottles? What do you recommend as concrete steps?

Dr. GRAHAM. All right. First, I hesitated to mention those drugs because I do not want to be accused of affecting the stock price of any particular company.

Senator BREAUX. You did. [Laughter.] Let me assure you.

Dr. GRAHAM. But I was compelled under testimony here.

The second thing is, I have not fully evaluated all of these drugs currently to tell you exactly, but I will give you a quick run-down of what I think.

With Meridia, I think, seriously, we have to consider whether there is just a need for the product in the first place. It has to do with, what is a reasonable balance of benefit to risk? I do not think that Meridia passes that test. Actually, the medical officer who reviewed this drug apparently recommended against approval at first.

Crestor. I think that an intense amount of work needs to be done to look to evaluate, in a serious fashion, the occurrence of renal failure and rabdomyelysis with the drug. We have got three other major statins on the market, the three market leaders, that do a fine job of lowering cholesterol.

I think two of the three have been shown to actually prevent heart attacks and stroke, and none of them cause renal failure. I personally doubt, and maybe Dr. Kweder can explain, what the advantage of Crestor is from a lipid lowering perspective that would sort of counterbalance that. So, I have a problem with that.

Accutane. I think what you need, immediately, is a restricted distribution system. I have a lot of recommendations on that, and they have been written time and time again.

For Bextra, I think that we are in the same situation we are with Vioxx in terms of needing to have good studies on cardiovascular risk. I do not think that we have them.

And with Serevent, Serevent is an example of, in my view, I told you before about the gun analogy and the 90 bullets. Well, before Serevent was approved in the United States, it had 90 bullets in the chamber for respiratory death. It was a large study that had been done in the United Kingdom.

It showed that, with 90 percent certainty, Serevent was causing an increased risk of asthma deaths. But it was not at 95 percent, it was at 90 percent. So, FDA approved the drug and called it safe and effective.

Then, based, actually, on work that I did about 10 or 12 years ago, FDA told GlaxoSmithKline—I think at the time it may have been Burroughs-Welcome—to do a very large, simple, randomized clinical trial to study whether or not Serevent increased the risk of asthma deaths.

Well, that study got canceled about a year, year and a half ago. It was very peculiar. The data are published on one of the FDA websites. When you analyze that data, there is a statistically significant increase in serious asthma complications in the Sereventtreated group.

But because it was done at an interim look—this is getting technical. Because of some technical, statistical rules, that conventional level of statistical significance, where at that point we had, like, 97 percent certainty, was not certain enough because they had planned to peek at the data early.

What they did, is they canceled the study. There is a letter from the Data Safety Monitoring Board, which I encourage you to request FDA to get a copy of. The Data Safety Monitoring Board says something such as, the data are trending in a bad direction for Serevent, but the recruitment into the study is so low, it would basically be almost impossible to study this drug long enough to get a definitive answer.

So, here is an example. We have this drug before it goes on the market. There are 90 bullets in the chamber. FDA approves it. Then we go out and we got all these case reports. Before, the question was asked, how do we find out about things? We got case reports of people dying, clutching their Serevent inhaler. It is asthma medicine that you inhale. They were found dead clutching the Serevent inhaler.

The question was, does Serevent increase asthma deaths? Well, we went out, and the company went out, to do the study, and the data are trending in the same way. But Serevent is still on the market.

So to me, that gets to, when it comes to safety, what is the appropriate standard? I do not think that 95 percent certainty protects Americans. What it does, is it protects the drug.

Senator BINGAMAN. Thank you very much.

I guess my time is up, Mr. Chairman. Thank you very much.

The CHAIRMAN. We are done with this panel. We may not be done with you entirely, but for today, we thank you very much for coming and thank you for your service to the people of this country by your testimony.

Dr. GRAHAM. Thank you.

The CHAIRMAN. Thank you also, Dr. Singh.

Dr. SINGH. You are welcome.

The CHAIRMAN. You bet.

Our next panel is Dr. Sandra Kweder, Acting Director of FDA's Office of New Drugs. I thank her for appearing before our committee today. It is an important role as the representative for Dr. Crawford, the Acting Commissioner, to testify about what is going wrong and what is going right at the FDA.

I know she will testify today about the initiatives that FDA has put into place to fix the problems within the FDA's Center for Drug Evaluation and Research. I expect that the FDA will continue to address the committee's concerns and take action to improve the situation, and I welcome you, Dr. Kweder. You also are entitled to 10 minutes.

STATEMENT OF SANDRA L. KWEDER, M.D., ACTING DIRECTOR, OFFICE OF NEW DRUGS, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION, WASHINGTON, DC

Dr. KWEDER. Thank you, sir. I am Sandra Kweder. I am a Captain in the U.S. Public Health Service, and I am the Deputy Director of the Office of New Drugs in the Center for Drug Evaluation and Research.

By way of training, I am a graduate of the Uniformed Services University of Health Science School of Medicine. I trained in internal medicine and am board certified from Walter Reed Army Medical Center.

I did graduate work at the University of North Carolina in public health, and I completed a fellowship at Brown University in the care of medically ill pregnant women.

I have been at FDA since 1998, and I have worked in many capacities at the Agency as a reviewer of new drugs, and, as a manager of reviewers of new drugs, I was the Acting Director of what is now the Office of Drug Safety for 2 years, from 1993 to 1995, and have subsequently been pretty much in the Office of New Drugs.

I also am happy to have the opportunity to see the effects on the ground of what we do at FDA. I am an Associate Professor of Medicine at Uniformed Services University, I attend at the Navy Hospital, seeing patients, teaching students and medical residents on a weekly basis.

Modern drugs provide unmistakable health benefits, and as a society we are increasingly reliant on medicines to take care of our ills, our aches and pains, and to prevent disease. At FDA, we grant approval to drugs after a sponsor demonstrates that they are safe and effective.

However, as you have already stated, all drugs do pose risks. These risks are often identified in clinical trials and are listed on a product's label. Unless the benefit of a new drug outweighs its known risk for an intended population, FDA will not approve the drug.

Experience has shown us, though, that the full magnitude of some potential risks does not always emerge during clinical trials conducted before approval. To address this, FDA has a strong drug safety program to assess adverse events. I think the recent events relating to Vioxx illustrate the need for such a program.

FDA approved Vioxx in May of 1999 for the reduction of signs and symptoms of osteoarthritis, the common arthritis that most of us get if we live long enough, as well as for acute pain in adults. Acute pain would be something like toothaches or muscle strain, something very short-term. Also, for the treatment of primary dysmenorrhea, which is also known as menstrual cramps.

As with many other drugs, an FDA Advisory Committee considered all of the data that were part of the review of this product. At the time, we were aware of some test tube data suggesting that there might be a potential for an increased cardiovascular risk associated with the drug related to its effect on platelets.

As a result of that knowledge—and this has already been referred to—we conducted an intensive and extensive review of the database that had come in to us for this drug. There was in that database a relatively clear suggestion of GI benefit in protecting the GI tract. It was not strong enough that we would allow the company to make such a claim, but the data were far better than we had expected.

The cardiovascular risk was examined with a fine-toothed comb. The company provided a database of 5,000 patients. That is quite a large database for any drug. The duration of study, the duration of exposure in many of the patients, exceeded international standards for clinical trials of new drugs.

At the time, Vioxx and other drugs in this class—Celebrex was under review slightly before Vioxx—held out tremendous hope for reducing the substantial morbidity and mortality associated with GI bleeding and ulcers from this class of drugs, non-steroidal anti-inflammatories. I believe Dr. Singh went into that in a fair amount of detail.

After Vioxx was approved, the company went about doing continued studies of Vioxx to look at clinically meaningful GI effects, such as on the development of stomach ulcers and bleeding. In any of those studies, if there were heart attacks, they would be pretty hard to hide.

Merck's study, known as VIGOR, that has been discussed extensively today, was a large, 8,000-patient study evaluating the GI safety of Vioxx compared to naproxen.

Again, we knew that that study was ongoing before the drug was approved. It was the largest study of the drug that had been conducted, and we expected that it would provide us with a large body of general safety data, in addition to whatever it told us about the GI effects.

Senator HATCH. The people studied took 50 milligrams?

Dr. KWEDER. That is correct, sir.

Senator HATCH. And the normal dosage would be 12 to 25 milligrams.

Dr. KWEDER. Exactly. Most people take 12.5 milligrams or 25 milligrams, particularly for the indications that we had approved,

although there would be some people who would need a higher dose, particularly large people.

The VIGOR study was designed to address the 50 milligram dose of Vioxx because we wanted to be sure that if there was an increased rate of stomach bleeding, we would see it. If the 50 milligram dose proved to be safer than naproxen, we could be very comfortable that the lower doses were safer as well.

Senator HATCH. Excuse me. But the point is, you would have a much greater tendency with the 50 milligram dose to have difficulties than you would with the 12.5 or 25 milligrams.

Dr. KWEDER. We would expect. So what we understand about the GI safety and toxicity of this class of drugs, is that for the most part, they are what we call dose-related. The more drug you take, the higher your risk of one of those events. So, that was the rationale for the higher dose.

The results of the VIGOR study were the first indication of a clinical indication of an increase in cardiovascular risk. We were very concerned about this risk and, because of that, we took the study and our full review of the data to an expert advisory committee, the Arthritis Advisory Committee, that we also supplemented with two members of our Cardiology Advisory Committee. We asked them to assess the benefits and risks that were evident based on the VIGOR study and in the context of the previous data that they had reviewed for the NDA.

In response to the recommendations of the advisory committee, the Agency then took a number of important steps. First, the advisory committee recommended that we review all ongoing studies to ensure that they were fully designed to be able to assess cardiovascular end points in the clinical trials. We did that.

In particular, we reviewed ongoing studies that had any data available to determine whether safety data could tell us anything more about this cardiovascular risk, particularly at the lower doses.

What we had available at the time or shortly thereafter were two ongoing studies to prevent Alzheimer's disease in relatively elderly patients, comparing Vioxx to placebo. There was no suggestion of cardiovascular risk in those data.

Shortly after the advisory committee meeting, the company provided us with an additional database from another study of osteoarthritis. In this one, low-dose aspirin was included. There were comparisons of Vioxx to naproxen in 6,000 patients.

The study was only 3 months long in osteoarthritis patients, but, nonetheless, this same comparison as was in VIGOR in a very large database, but at a lower dose, had very, very few cardiovascular events and did not support that we could extrapolate the findings from VIGOR down to lower doses of Vioxx.

Nonetheless, we remained concerned and we worked with our Office of Drug Safety to determine whether any of the databases, through cooperative agreements, which are a grants-like process that we have with outside research groups, could be utilized to try to do some kind of epidemiology study to help us address this issue more broadly.

That resulted in the study with Kaiser Permanente that Dr. Graham has described to you today. The initial study was well dis-

cussed and the initial study team in the Agency did include reviewers from the Arthritis Review Group in the Office of New Drugs.

The third thing we did was we modified the Vioxx label to reflect cardiovascular risk. We pursued that label change vigorously. In the period after the 2002 labeling changes, we did not sit back. The FDA continued to monitor and review adverse event reports from Vioxx.

We worked extremely closely with our colleagues in the Office of Drug Safety to make label changes where new signals were coming up in the adverse event database, and we continued to monitor the literature, and every study that came out related to Vioxx in the medical literature.

It was on August 11, 2004 that Dr. Graham's poster was submitted as a draft for review to a number of scientists in the Agency in the Office of Drug Safety and the Office of New Drugs.

That poster summarized the epidemiology study conducted by the Office of Drug Safety with Kaiser, and reported findings, from what we could see in the poster, that did not appear to be different from previous studies.

Dr. Graham did present his poster on August 24, and on September 30 he submitted his draft study report to the Office of Drug Safety management for full review.

On the 28th of September, as you know, Merck met with FDA officials. They had called us the day before to advise us of their decision to remove Vioxx from the market voluntarily.

The data that they shared with us at the meeting demonstrated an increase in cardiovascular and stroke risk starting after 18 months of treatment on 25 milligrams of Vioxx compared to placebo.

This was the first demonstration of a difference between Vioxx and placebo, and the robustness of the data from a placebo controlled trial cannot be over-emphasized in this case. The data supported the previous signal in the VIGOR trial and some, but not all, of previous epidemiology studies.

On the broader issue of drug safety, I want to highlight the Agency's recent announcement of a five-step plan to strengthen our safety program. First, we welcome the opportunity to work with and sponsor an Institute of Medicine study on our drug safety system.

We have had evaluations of the drug safety system in the past, but they have never been by a group as robust and highly regarded as the Institute of Medicine. We understand that there are concerns by the members of the Congress and by the public about how sound our system is, and we look forward to change if that is what is deemed needed.

Second, the Center for Drugs will implement a new formal program to address differences of professional opinion. We already have many avenues for addressing those. Disagreement is part of science. It is what we do. If we did not have disagreement, I think we would be in much worse shape than could ever be imagined.

However, we will implement the system in a more formal manner to absolutely ensure that scientists who do not believe they are being heard have an extra measure to ensure that.

Third, CDER will conduct a national search to fill the position of the Director of the Office of Drug Safety, which has been vacant for over a year.

Fourth, we plan to conduct workshops and meetings utilizing our advisory committee system and beyond to bring complex drug safety and risk management issues into a public forum before the time we are faced with a regulatory decision. This is to make sure that the public and practicing medical community are aware of what our concerns are in an ongoing manner.

Finally, FDA will publish three guidances to help pharmaceutical firms manage drug risks, establishing expectations for what the standards are for adequate safety assessment and risk management before and after marketing.

In summary, FDA worked to inform public health professionals of what was known regarding the cardiovascular risk of Vioxx and to pursue the further definitive investigations to better define, qualify and quantify the risk.

FDA also reviewed and remained current on new data as it became available and continued to seek such data. Indeed, the recent study findings disclosed by Merck leading to their decision to withdraw Vioxx from the market were triggered by FDA's vigilance in requiring these long-term outcome trials to address our concerns.

Detecting, assessing, managing, and communicating the risks and benefits of drugs are highly complex and demanding tasks. Medicines that receive FDA approval are among the safest in the world, and the measures we are taking will strengthen this quality, as well as, we hope, consumer confidence in FDA's protection of the public health.

Once again, thank you for the opportunity to testify on this important issue. I am happy to take your questions.

[The prepared statement of Dr. Kweder appears in the appendix.]

The CHAIRMAN. Before I begin my questions, I would like to reiterate what I have repeatedly stated in writing and had verbally communicated to your Agency. Namely, that this committee takes its responsibility to protect witnesses, and particularly government witnesses, very seriously. That holds particularly true for Dr. Graham. I just want to be sure that you understand that. All right?

Dr. KWEDER. Senator Grassley, we take that very seriously.

The CHAIRMAN. Also, I have received assurances that you are speaking on behalf of the FDA today and that there is no question about that being your capacity.

Dr. KWEDER. Absolutely.

The CHAIRMAN. On February 23, 2004, Bob Temple, Director of the Office of Medical Policy, wrote a letter to Novartis, which has been identified as Poster Exhibit 54. When I read this, it sounded to me like the FDA and the drug company needed to come to a meeting of minds before the FDA takes any action. That is just a statement on my part.

I refer you to Poster Exhibit 29. Can you explain why the FDA permitted Merck to place the cardiovascular risk of Vioxx in the "Precaution" section of the label rather than the "Warning" section, or why it was not put in a black box, as the FDA did on the cardiovascular risks for estrogen after the women's health trials? After

all, the exhibit points out that Dr. Targum was recommending that.

Dr. KWEDER. Excuse me, sir. Do you want me to address Dr. Temple's letter as well or just Dr. Targum's?

The CHAIRMAN. Well, you can address both of them.

Dr. KWEDER. All right. Dr. Temple's letter, as I recall, was in response to a specific issue raised by a company—Novartis, I guess—regarding a publication in the *New England Journal of Medicine.*

Their concern, as I recall it, was that when something does get published, the company will receive many questions about the data and whether they were aware of it, not just the FDA. So this was a concern, that the company had not been aware of it. We discussed at length with them whether or not we could, as a courtesy, provide information concurrent with publication.

As for Dr. Targum's review, yes. Actually, one of the things that we routinely do when we have any questions about a potential cardiovascular concern, or if it is a skin concern, our reviewers are very good at seeking input from other clinical experts around the center and across the Agency to help address specific safety issues.

In this case, what I have before me is consultative review of, I believe—I am looking to see what she reviewed. The VIGOR data, given the date, February of 2001. Let me just check. This is the 50 milligram dose, the cardiovascular safety of 50 milligrams in rheumatoid arthritis that would have been the VIGOR trial.

Dr. Targum was asked to look solely at the cardiovascular data. Her conclusion was that there seemed to be a concern based on the 50 milligram dose, but she, too, could not come to any conclusion about how this applied broadly.

Dr. Targum recommended that the information be included in the label, and that further studies of the drug try to address this issue. Those were exactly what was done.

The specifics of whether or not something goes in a precaution or a warning is very difficult to address. In fact, in our proposed physician and labeling rule which we are about to finalize, the Agency is in the process of collapsing those two sections into one, because historically, both from what the regulations tell us as well as from a practical perspective, determining what goes in which section is not particularly helpful.

When we sought to change the labeling for Vioxx based on the VIGOR trial, our goal was to ensure that the information was accurate and provided enough data, enough perspective to clinicians, so that they could understand what we were concerned about and what that was based upon. I believe that the revised labeling for Vioxx did just that.

The CHAIRMAN. The next exhibit, Number 60, is an e-mail dated October 7, 2004, which included the meeting minutes for a teleconference between Merck and the FDA at which the status of the Vioxx withdrawal was discussed, among other matters.

I would refer you specifically to the "Actions" item on page 2. Number 6 on that list says, "Merck will critique the Graham paper in a teleconference with the Agency."

Now, is it common practice for the FDA to permit a drug company to critique an unpublished FDA study of that company's drugs?

Dr. KWEDER. Well, first of all, I do not think I have the right exhibit here. I am looking at an e-mail from Diane Lewey to Ned Bronstein. I do not think that is the right exhibit.

The CHAIRMAN. Number 60, page 6. It says, "Merck will critique the Graham paper in a teleconference with the Agency." Well, we will come back to that.

Dr. KWEDER. All right. Thank you.

The CHAIRMAN. I will go to Senator Baucus now, then I will come back to you on that issue.

Dr. KWEDER. All right. That would be fine. I would like to see it.

Senator BAUCUS. Dr. Kweder, do you agree with Dr. Graham that the five drugs he mentioned pose a significant safety risk to Americans?

Dr. KWEDER. No, I do not.

Senator BAUCUS. Why is that?

Dr. KWEDER. I believe that all drugs pose some safety risk, and that some drugs pose a greater risk than others. But there is no magic formula for deciding what drug is the biggest risk of all. If there were a magic formula, our jobs would be very much easier.

Dr. Graham has raised concerns about drugs that we have had much discussion and activity over in the Agency, and there were many more drugs about which we have much discussion and much activity over in the Agency.

Senator BAUCUS. Are those five drugs more suspicious than others?

Dr. KWEDER. That is clearly Dr. Graham's opinion.

Senator BAUCUS. In your opinion?

Dr. KWEDER. I do not have reason to believe that that set of five drugs is specifically more concerning than any other drugs that we review.

Senator BAUCUS. Do you want to explain that in a little more detail, compared with other drugs you are looking at?

Dr. KWEDER. Well, there are thousands of drugs on the market. It is very difficult to try and compare one drug to another. One, it is a mistake to try to assume that they are equal. Every drug has risks and benefits, and it is important not to get so focused on the risks that one forgets to look at the benefits. In evaluating any individual medication, our job is to do just that.

Senator BAUCUS. Why are consumer groups targeting these five drugs? What do they know that you do not know, or what do you know that they do not know?

Dr. KWEDER. I was not aware that consumer groups were specifically targeting all of these five drugs.

Senator BAUCUS. If not most of them. Are you aware that consumer groups are targeting any of them?

Dr. KWEDER. Yes, I am.

Senator BAUCUS. Which ones?

Dr. KWEDER. I am aware that there has been a great deal of interest by Public Citizen in Crestor recently. That is something that we are in the process of, and have been in an ongoing manner, evaluating very, very closely. I believe we have a Citizen's petition regarding that.

Senator BAUCUS. When will you conclude your results?

Dr. KWEDER. I am not aware of a set date. I am sorry. I can get that answer for you.

Senator BAUCUS. What about, not only Dr. Graham, but all the previous witnesses have a very significant problem with the independence of drug safety with respect to the New Drug Office, saying that basically it is your office which tends to preempt or prevent Drug Safety from doing its work.

Dr. KWEDER. Sir, that is not the FDA I know. We work extremely closely with our colleagues in the Office of Drug Safety. There was a drug safety reviewer on Vioxx, for example, that worked on a daily basis, combing through adverse event reports and working with the New Drug Review Division on this drug, just like we have for every drug.

Senator BAUCUS. Well, how is it then that Dr. Singh, Dr. Psaty, in addition to Dr. Graham, someone within the FDA, two not within the FDA, have that same view?

Dr. KWEDER. It is not clear to me how Dr. Singh or Dr. Psaty would have specific information about the day-to-day operations of the Agency.

Senator BAUCUS. But you heard that. You were here.

Dr. KWEDER. Yes, I did hear them. The sources of that information are not clear to me. I have worked at the Agency both in Drug Safety and in New Drug Review for many years. There are always, always tensions between scientists. We have tensions between scientists even within the Office of New Drugs.

Senator BAUCUS. That is obvious, Dr. Kweder. But the real question is whether the tension is inappropriate, that is, whether one office, trying to do its work, is being told what to do, if you will, by the other office, say, the New Drug Office, in this case. When you have got three different people, three different perspectives, it certainly raises that question.

Dr. KWEDER. Well, in the Agency the authority for actually making the regulatory decisions, the final regulatory decisions, does rest within the Office of New Drugs.

Senator BAUCUS. Maybe the safety question should not. Why should there not be a post-review operation with independence that is separate from New Drugs? It stands to reason, just psychologically, if someone comes up and says, uh-oh, a new drug, you made a mistake.

The psychological reaction of New Drugs is going to be, oh, gee, you are challenging my earlier decision. That is going to tend to compromise that operation's judgment.

As was mentioned earlier by one of the witnesses, Europeans have a 5-year post-approval review. Why should we not have a post-approval operation that is clearly independent from the New Drug?

Dr. KWEDER. Senator, those are excellent questions. Those are exactly the kind of things that we hope the Institute of Medicine will address.

Senator BAUCUS. I am asking you. I am asking, what is your personal opinion? I am not going to punt this down the road, some new study, some new study. You have been there a long time now. What is your personal view?

Dr. KWEDER. My personal view is that our system works very well.

Senator BAUCUS. No. I would like you to address the questions I asked, please.

Dr. KWEDER. All right. Let me make sure. I thought I did. My personal view on, why should we not have an independent Office of Drug Safety?

Senator BAUCUS. Correct. Correct.

Dr. KWEDER. I do not have any objections, sir, to an independent Office of Drug Safety.

Senator BAUCUS. Do you think that is a good idea?

Dr. KWEDER. I think it is an idea worth looking carefully at, how it would operate, what kind of resources it would take. Absolutely, it is worth looking at.

Senator BAUCUS. And the reason is?

Dr. KWEDER. And the reason is, because there is clearly concern by some members of the public, by members of this committee, that somehow the system is not working as well as it could without that independence. If that is a concern, we need to assess that.

Senator BAUCUS. I appreciate that. Thank you.

The CHAIRMAN. Senator Hatch?

Senator HATCH. Dr. Kweder, were you given any opportunity by the committee or committee staff to review any of the exhibits today before the hearing?

Dr. KWEDER. No, sir.

Senator HATCH. All right. I just wanted to know.

Now, there is a press report in today's paper which talks about the FDA lowering its standards for approving drugs, and how FDA has developed cozy relationships with drug manufacturers.

I would just kind of like to hear your views on that allegation, because that has not been my experience, but that is the report in the newspaper today.

Dr. KWEDER. Thank you for asking that question, sir. It is very interesting that that should come out today, because several years ago the Director of the Center for Drugs actually specifically requested an Inspector General report of our system of drug review because there were concerns, with the Prescription Drug User Fee Act, that FDA had developed too much of a cozy relationship with industry.

The evidence for people who had that concern at the time, the evidence that was cited, was the fact that there were more drug withdrawals, at least numerically, in the late 1990s, in that period of time after user fees than there had been prior to user fees. So, consequently, the conclusion was that it must then be that we were approving new drugs too quickly, causing us to miss things, and ultimately require them to come off the market.

The Inspector General's report actually looked at that and confirmed what we had already put forward, which was that the actual rate of drug withdrawals, the number of drug withdrawals compared to the number approved, was exactly the same and steady over decades and decades, at 2.7 percent.

So these new allegations or these new concerns are interesting, but I would point out that it certainly cannot be both ways. We cannot have fewer drug withdrawals being a reflection of a cozy re-

lationship with industry and too many drug withdrawals as evidence of same.

Senator HATCH. My experience has been that a lot of industry is complaining. They complain continuously that it takes too long, there is too much review, too much red tape, too much bureaucracy. That is what I have heard for all of my 28 years in the U.S. Senate. Whether that is accurate or not, that has been my experience.

Dr. KWEDER. Well, we certainly hear it, too.

Senator HATCH. You hear it, too. Well, I want your opinion on the statistics that Dr. Graham gave the committee regarding heart attacks and deaths caused by Vioxx. Could you give us your opinion on that?

Dr. KWEDER. Well, I am not prepared today to go into a detailed statistical analysis. But let me say that, first of all, these are not real deaths. The rate of deaths in the VIGOR trial, in the naproxen and the Vioxx arms, were equal.

So the data on deaths, as Dr. Graham himself said, is something you figure out on a spread sheet. They are a mathematical model that is put together with a number of assumptions along the way. We do utilize some mathematical models to help guide how we study drugs and, to a certain extent, make some decisions about them. But one has to be extremely cautious.

Also, keep in mind that what seems to have been lost in a lot of the discussion of Vioxx, is that this drug remained the only nonsteroidal anti-inflammatory that had a clear-cut GI safety benefit. It is the only one. Celebrex, despite multiple clinical trials, has never been shown to have that effect, and neither has Bextra.

So you cannot just look at the cardiovascular risks of this drug. One has to look at the full spectrum of risks and potential benefits.

Senator HATCH. Let me just ask you one other question. My time is just about up. How seriously did FDA take the concerns about the cardiovascular risks associated with Vioxx during the drug approval process, and once it was approved and put in the marketplace?

Dr. KWEDER. We took it extremely seriously. Dr. Villalba's review was quoted regarding our concern and our interest in combing through the data to detect any evidence of a cardiovascular risk. We also raised this issue and shared all of the data that were available to us through her review with our arthritis drugs advisory committee before approving the drug.

Senator HATCH. Maybe I misconstrued, but I kind of got from your earlier statement that you really did not realize the problem until after Mr. Gilmartin took Vioxx off the market. When they finally did that final study, the minute that was done, he took it out of the market.

Dr. KWEDER. We did not realize the problem at the usual dose of the drug. After VIGOR, we did require the company to change their label and recommend that the high dose of Vioxx not be used for longer than 5 days.

The issue remained, how those data applied to the vast majority of people who were using this medicine at the lower doses. It was the APPROVe study, the one that led to the market withdrawal, that ultimately gave the answer to that.

Senator HATCH. Is there any evidence, as far as the FDA is concerned and you are concerned, that Merck acted improperly prior to the removal or pulling of the drug from the marketplace or that they acted pursuant to the scientific data that was accumulated?

Dr. KWEDER. Senator Hatch, I have not seen any data to suggest that. I am not aware of any.

Senator HATCH. So what you are saying here is, when their own VIGOR program finally showed that 50 milligrams could be a problem, they pulled the drug off the market. Am I wrong?

Dr. KWEDER. No. Sorry. When the 50 milligram dose did show a problem, they worked, with our encouragement, to ensure that they had studies in place to address the issue of the lower doses as well as the issue of all this confounding about naproxen.

One of those studies was the APPROVe study. It was not an arthritis study, but we knew that that study, and many others that were ongoing, would hopefully contribute to assessing the question.

Senator HATCH. I am sorry, Mr. Chairman, but this is important. I guess what I am asking is, do you feel that Merck acted inappropriately during this process or that they acted responsibly once they realized what the problem was?

Dr. KWEDER. I believe that Merck acted responsibly once the problem was recognized.

Senator HATCH. That is all I wanted to know. Thank you, Mr. Chairman.

The CHAIRMAN. You did not answer his question about, during the process, do you think Merck acted responsibly. I think you asked about, during the process as well as the final action.

Senator HATCH. Well, that would be fine. I mean, the whole process.

Dr. KWEDER. The whole process. Yes.

The CHAIRMAN. Yes. But, I mean, you are talking about 7 or 8 years that there have been some red flags.

Dr. KWEDER. Yes. That is right. It is a long time. Yes. Yes. I believe that Merck acted responsibly. I will say that it did take a very long time, much longer than usual, to make that change to the labeling for the drug.

Senator HATCH. That was unusual?

Dr. KWEDER. Yes, that was unusual. Normally it is just several months, at the most.

Senator HATCH. All right.

Dr. KWEDER. However, during that period of time we were also collecting additional data from Merck. Merck was in the process of collecting additional data from ongoing studies to try and bring more information, to try and assess how to address that. Yes.

Senator HATCH. And Merck was cooperative throughout that process?

Dr. KWEDER. Yes.

Senator HATCH. All right. That is what I wanted to know.

The CHAIRMAN. Senator Breaux?

Senator BREAUX. Thank you, Mr. Chairman.

Thank you very much, Dr. Kweder. Let me start off by saying, I think I have indicated in my opening statement that I think that the Food and Drug Administration, the FDA, is the finest in the

world in terms of approving pharmaceutical products for the people who are consumers of those products.

I think no other country comes close, which has always been one of my concerns about importing drugs which we could not certify here as to how they were approved, handled, or managed in other countries.

Some may argue that there was sort of a rush to approval for Vioxx. How long did it take from the time they submitted the application for FDA to approve Vioxx?

Dr. KWEDER. It was a 6-month review. It was a priority review, as had been Celebrex.

Senator BREAUX. And why were they priority reviews, since there were other anti-arthritic types of products already out there and doing a pretty good job, and a lot of pain relievers, which I have probably taken all of them for various tennis injuries? So, why was there a priority to approve Vioxx?

Dr. KWEDER. The general standard for a priority review is applied when something is considered to have the potential to provide a clinical or therapeutic advantage.

In the case of Celebrex and Vioxx, it was hoped and expected that these drugs would provide an important GI safety advantage. We of course could not know that until we reviewed the data, but that was the general expectation based on what we knew about the drugs at the time.

Senator BREAUX. But the VIGOR study, which I take it was looking at the GI problems, potential problems, of Vioxx, was not completed until after the FDA had already approved Vioxx for the less adverse effects on GI problems.

Dr. KWEDER. That is right.

Senator BREAUX. I mean, how is that possible?

Dr. KWEDER. I can explain that. Yes. It is quite possible. The VIGOR study was started before the application was approved and was not part of the original NDA database.

The data in the NDA did suggest pretty clearly that the drug was likely to have a better GI safety profile, for lack of a better term. The way that had been studied was—and this sounds very gross—was by doing endoscopy studies.

There were some patients—not all of them—in the clinical trials who agreed to participate in studies that would do a look down into the stomach at the beginning of the study and periodically throughout the study looking for any evidence of ulcers. In the original studies that came to the NDA, the company clearly showed that there were many fewer ulcers in patients taking Vioxx compared to naproxen.

What we told them, however—and we told them as soon as we had some indication of what the database in the NDA was going to be—was that that would not be enough to make a claim about a safer GI safety profile, because lots of ulcers, nothing really happens with. Lots of ulcers do not have symptoms, they do not have pain.

Senator BREAUX. I mean, it was enough of a reason to give it priority status in the review process, the early indications of less GI problems?

Dr. KWEDER. Yes. We had not reviewed the data. We knew that they had some data. We did not know how strong. What we would call clinical outcomes data, or the actual occurrence of bleeding from ulcers, of hospitalizations related to ulcers, from stomach obstruction, those kinds of things. We had not reviewed that.

But we agreed to look at it in the NDA, and we told them that if those data were not supportive, that we would not be able to give them the claim for GI safety. Nonetheless, because the potential was there—and this is usual—we would give it a priority review.

Senator BREAUX. All right.

Explain to me, in 1999 when FDA approved Vioxx basically as an arthritic drug, not for lessening of an effect of GI problems—not you, but FDA as an Agency—talked about this theoretical concern that you could have a higher risk for thromboembolic cardiovascular adverse experiences, heart attacks, and that you needed a larger database to answer this, and other safety comparison questions.

Dr. KWEDER. Yes.

Senator BREAUX. I mean, for a lay person—I am one—if I knew that FDA had approved this drug for my use, but there were a couple of paragraphs back at FDA that said that it may cause heart attacks, possibly, but we do not have enough data, and more data is needed, that is one thing on this side.

Then on the other side, I have the FDA imprimatur for approval for use. I mean, if I knew both of those things, I do not think I would have taken it. It would have scared the hell out of me.

But you have an FDA imprimatur of approval for safety and effectiveness that the company has been given by our government, and yet there were some very strong—I do not know who wrote this. Do you know?

Dr. KWEDER. Who wrote that? Yes, I do. She is sitting right here.

Senator BREAUX. Well, bless you for writing it, because you kind of got it right back in 1999. So, how do we balance that? FDA says, this person over here who is a scientist is telling me that we need a larger database to answer this, and other safety comparison questions, *i.e.,* does it cause a greater risk of heart attacks. Yet, you approved it at the same time. How can that possibly be?

Dr. KWEDER. Two things. First, it is not unusual, when a drug goes on the market, to have ongoing concerns about a particular aspect of its safety, because we have learned from experience that clinical trials do not uncover many events for a variety of reasons. So, that is not an unusual circumstance.

We did know at the time that there were many studies ongoing with the drug. First, we had a very large safety database for this drug, much larger than we have for most drugs. That was quite reassuring. We also knew that we were likely to, over the course of time, be able to have additional data to bring to the table. But in a 5,000-patient database, not seeing evidence to show that there was a risk is pretty reassuring.

Senator BREAUX. So at that time there was a theoretical concern.

Dr. KWEDER. Yes. Exactly.

Senator BREAUX. But there was not an evidentiary concern.

Dr. KWEDER. Exactly. Exactly.

Senator BREAUX. Now, having said that, because the studies that followed that expression of concern about cardiovascular problems, the FDA, to my knowledge, did not order, suggest, request, or require that there be additional clinical trials testing Vioxx for the purpose of whether it caused cardiovascular problems.

The other study that was ongoing, the VIGOR study, was not looking at that. They were looking at GI concerns. The APPROVe study was looking at colon polyps. I mean, did FDA ever follow up on that suggestion that more data was needed on this question by requiring a test of any type?

Dr. KWEDER. Two things. First, any one of those studies would be quite informative in assessing cardiovascular risk. As I mentioned, it is hard to miss heart attack or a stroke in a clinical trial.

Second, in thinking about how one would address this, the kinds of studies that were ongoing, there is no one way to get an answer. But in thinking about other ways that one might put together a clinical trial to assess cardiovascular risk, there were not very many options.

Senator BREAUX. Well, Dr. Graham said he did it with Kaiser Permanente.

Dr. KWEDER. What the Kaiser study was, was an observational epidemiology study. From our perspective, what the Kaiser study showed, was actually it confirmed the results of the VIGOR trial and also raised some questions about other non-steroidals on the market that we have not really considered in the past.

The risk assessment from the Kaiser study for the lower dose, the 25 milligram dose of Vioxx, is similar to that in the same study of the usual doses of naproxen and diclofenac, something that we had not considered before. So, an epidemiology study, once VIGOR came out, we hoped might be helpful, but did not expect it to provide a definitive answer.

Senator BREAUX. Thank you, Mr. Chairman. Thank you, Doctor.

The CHAIRMAN. Thank you. Let me restate the question, because I think we have the right citation now, or you have got the right document in front of you.

This is Exhibit 60, and it is an e-mail dated October 7, 2004, including meeting minutes for a teleconference between Merck and the FDA, at which the status of the Vioxx withdrawal was discussed, among other matters.

I refer specifically to the "Action" item on page 2. Number 6 on that list says, "Merck will critique the Graham paper in a teleconference with the Agency."

Is it common practice for the FDA to permit a drug company to critique an unpublished FDA study of that company's drug?

Dr. KWEDER. I was not involved in this. I think that Merck certainly, undoubtedly, would have more information than anyone about a particular drug and be quite familiar with all of the studies in great detail that had been done on the drug. Their assessment, the scientific assessment of a particular study, would be something that would be of interest.

The CHAIRMAN. All right. Here is what I think I will have you do. I will have you submit in writing the answer to that question.

Dr. KWEDER. That would be helpful. Thank you. I had not seen this prior to today.

[The response appears in the appendix.]

The CHAIRMAN. Senator Baucus?

Senator BAUCUS. Yes. Dr. Kweder, I would just like to ask you about your view on the provisions in a bill here in Congress called S. 11, a tort reform bill. That legislation, among other things, provides that a pharmaceutical company is shielded from punitive damages with respect to any drug that has FDA approval. In view of what has happened with Vioxx, a drug that had approval, but now there are a lot of problems, in view of the general point that there probably will be other drugs in the future that have problems post-approval, is it your view or is it the administration's view that those people who are injured or damaged from those drugs that have FDA approval should be subject to a shield if the FDA has approved the drugs? That is the provision in that legislation.

Dr. KWEDER. Senator, I am not aware of the specifics of the legislation. I would be happy to get you an Agency response to that.

Senator BAUCUS. I appreciate that.

But I am asking you your general view again on the subject. It is just pretty simple. You do not have to know the specifics. It is very simple.

It says that if FDA approves a drug, that any subsequent personal injury suit on behalf of a person injured by a drug that is approved by the FDA is shielded from any punitive damages. It provides a shield. Basically, it says if the FDA approves it, that is it. You get very limited damages. It is a $250,000 limit of non-economic damages, even if the drug causes all kinds of problems after approval. Does that make sense to you?

Dr. KWEDER. It does not make sense to me.

Senator BAUCUS. Would that also be the administration's position?

Dr. KWEDER. Let me make sure what I am saying. I cannot speak to the administration. You asked me my personal opinion.

Senator BAUCUS. I asked your personal view.

Dr. KWEDER. I guess you would call it preemptive damages.

Senator BAUCUS. That is right. That is preemptive action that shields if the FDA approves, even though there may be subsequent problems.

Dr. KWEDER. I think it is a slippery slope.

Senator BAUCUS. Are you changing from your first response? You said you did not think it was a good idea

Dr. KWEDER. Well, I am unsure. What I am saying is, I do not think my first response was clear, sir. I think that it is a slippery slope to start granting preemption for things that are in labels.

Senator BAUCUS. All right.

What about publicizing or giving public access to all trials?

Dr. KWEDER. I think the more information people have, the better.

Senator BAUCUS. It should be public?

Dr. KWEDER. Absolutely.

Senator BAUCUS. So any trials that a company conducts, that should be public information, the good trials as well as the trials that indicate problems?

Dr. KWEDER. As a clinician, yes, I do. I am not sure that I speak for the Agency on that point.

Senator BAUCUS. I understand. I understand. I appreciate that. Why is that not the case today?

Dr. KWEDER. I think there is a long history behind that. That certainly is not something I am a student of, but it has been well recognized for decades in the medical literature that, even when submitted for publication, studies with negative results, studies that do not show anything, do not get published, or studies that put drugs in a bad light, even the journals themselves tend not to accept them for publication.

There have been a number of prestigious journals that have actually published studies of exactly this phenomenon. So, I think it is more complicated than commercial confidential information. I think it has to do with what is interesting to people, to readers.

Senator BAUCUS. But does FDA have a role here? That is, to somehow take actions that require those studies to be published, the negative as well as the positive?

Dr. KWEDER. Yes. To my knowledge, we are in the process of discussions with a number of groups about how to improve access to positive and negative clinical trial data.

Sometimes, for example, one of the things we often do, is once a drug is approved, the record on that drug and all the clinical trials that are in the application reviews are in the public domain and accessible—not conveniently so, I have to say.

The freedom of information process is pretty cumbersome, although we increasingly post those reviews on the web. That is not the case for drugs that are not approved, although what we do find encouraging is that when we have taken those drugs to review at public advisory committee meetings and made sure to share all the data, those data are then in the public domain and can be shared.

Senator BAUCUS. Should some Agency somewhere, maybe FDA, not pursue a comparative analysis of effectiveness of drugs in the same category, the same class?

Dr. KWEDER. We encourage companies all the time to do comparative analyses.

Senator BAUCUS. But I mean independent, public comparative analysis.

Dr. KWEDER. I think that would be a great idea.

Senator BAUCUS. Thank you. I have another question, which I have forgotten. But I appreciate very much your testimony. Thank you.

The CHAIRMAN. Thank you.

Senator Hatch, do you have any more questions?

Senator HATCH. No. We want to thank you for being here.

The CHAIRMAN. And I thank you.

Senator BAUCUS. I have one other question. I apologize.

Dr. KWEDER. All right, sir.

Senator BAUCUS. What have you learned from all this, from just kind of thinking about all of this?

Dr. KWEDER. From Vioxx?

Senator BAUCUS. Yes.

Dr. KWEDER. I think from Vioxx, and even from the recent SSRI experience, I think that has really brought home to us the challenge that we face as an Agency in communicating to the public.

I work with people who are among the most committed scientists in the world. You heard from Dr. Graham today; they are not in it for the money. They are in this business because they really care about public health and are absolutely vigilant about it.

Our struggle is, as the public becomes increasingly knowledgeable about medicines, they want to hear from us more. They want to hear what we think before we come to a regulatory decision. They do not just want to know that we gave something a thumbs up or a thumbs down. They want to know what we were worried about, what we are thinking about as the drug is on the market. We are committed to doing a better job of that.

Senator BAUCUS. So, basically you are saying that one thing you have learned from all of this, is FDA has to work a little harder to get more information and specific reasons why the FDA has reached certain conclusions.

Dr. KWEDER. Yes. Yes.

Senator BAUCUS. I appreciate that very much. Thank you.

The CHAIRMAN. Thank you very much.

We now have Mr. Gilmartin to come. Mr. Raymond Gilmartin is chairman, president and chief executive officer of Merck & Co., the maker of Vioxx. He has been the CEO of Merck for the past 10 years. Mr. Gilmartin also serves as president of the International Federation of Pharmaceutical Manufacturers Association.

We look forward to your testimony, and thank you for your patience while you heard all of the other questions, as well as testimony.

Would you proceed? You have 10 minutes as well.

STATEMENT OF RAYMOND V. GILMARTIN, CHAIRMAN, PRESIDENT AND CHIEF EXECUTIVE OFFICER, MERCK & CO., WHITEHOUSE STATION, NJ

Mr. GILMARTIN. Mr. Chairman, Senator Baucus, Senator Hatch, on behalf of the 60,000 men and women of Merck, I am pleased to have the chance to come before you to tell you more about who we are and what we stand for.

On the afternoon of September 24, Dr. Peter Kim, president of Merck Research Laboratories, called to alert me to information he had received just that morning from the independent external board of physicians and scientists monitoring the safety of patients in our APPROVe trial of Vioxx.

He told me that there was an increased risk of confirmed cardiovascular events beginning after 18 months of continuous, daily treatment in patients taking Vioxx compared to those taking placebo in that trial.

That call triggered a series of events that led, within 4 days of that call, to Merck contacting the FDA to tell them that we were going to withdraw Vioxx from the market.

Our decision to voluntarily withdraw Vioxx was difficult in several ways. Many patients counted on Vioxx, and we believed it would have been possible for Merck to continue to market Vioxx with labeling that would incorporate the new data.

Vioxx was the only non-steroidal anti-inflammatory medicine, or NSAID, that was demonstrated to provide pain relief similar to high-dose NSAIDs, and proven to reduce the risk of developing de-

bilitating gastrointestinal side effects compared to those on NSAIDs.

This is an important benefit for many who suffer from the pain of arthritis and other conditions. An estimated 15,000 Americans die each year from gastrointestinal bleeding associated with NSAID use.

On another level, however, our decision to withdraw Vioxx was easy. Given the availability of alternative therapies and the questions raised by the data, withdrawing Vioxx was consistent with an ethic that has driven Merck's actions and decisions for more than 100 years: Merck puts patients first.

I would like to make three points clear at the outset. First, the Food and Drug Administration approved Vioxx only after Merck had extensively studied the medicine and found it to be safe and effective. Merck continued to extensively study Vioxx after it was approved for marketing to gain more clinical information about the medicine.

Second, we have promptly disclosed the results of numerous Merck-sponsored studies to the FDA, physicians, the scientific community, and the public, and participated in a balanced scientific discussion of its risks and benefits.

Third, until APPROVe, the combined data from randomized controlled clinical trials showed no difference in confirmed cardiovascular event rates between Vioxx and placebo, and Vioxx and NSAIDs other than naproxen.

When data from the APPROVe study became available, Merck acted quickly to withdraw the medicine from the market. Mr. Chairman, as you know, no medicine is absolutely safe. All medicines have side effects.

To determine both its risks and benefits, Merck extensively studied Vioxx before seeking the regulatory approval to market it, and we continued to conduct studies after the FDA approved Vioxx.

I have provided with this statement a timeline of our research and development process to aid in the committee's understanding of the events. Our original drug application to the FDA for Vioxx included data on more than 5,000 patients with osteoarthritis. Clinical trials compared the effects of Vioxx to other non-naproxen NSAIDs and to placebo, and included data on patients who had been on Vioxx for more than 1 year.

In these studies, there was no difference in the rate of cardiovascular events between Vioxx and placebo, or between Vioxx and non-naproxen NSAIDs.

Prior to the FDA's approval of Vioxx, we initiated a study known as VIGOR. That study was designed to compare the gastrointestinal safety profile of Vioxx with naproxen. We chose naproxen for this study instead of placebo because we intended to test Vioxx in patients with rheumatoid arthritis. It would not have been ethical or practical to subject people suffering from arthritic pain to a placebo for a long time.

We learned the preliminary results from VIGOR in March, 2000. In the trial, there was a higher cardiovascular event rate in patients taking Vioxx than naproxen. These data were of concern to us. It is important to note that, because the VIGOR study compared two drugs, Vioxx and naproxen, and not Vioxx and placebo,

it was not possible to make a determination based on the VIGOR study alone whether naproxen was having a beneficial cardiovascular effect or whether Vioxx was having a detrimental cardiovascular effect.

To help us evaluate the meaning of the VIGOR study, Merck took the step of looking into data from two trials we had already initiated in which patients with memory impairment, or Alzheimer's, were given Vioxx or placebo. We found there was no difference in cardiovascular event rates in these two trials.

These data, our earliest clinical data, and a pharmacological study that showed that naproxen had a strong anti-platelet effect similar to aspirin, when it is taken regularly, twice a day as it was in VIGOR, led us to conclude that the best explanation for the difference in VIGOR was the effect of naproxen.

We also recognized the value and interest in obtaining additional cardiovascular safety data on Vioxx. After deliberation with outside advisers, Merck developed and discussed with the FDA a plan to prospectively analyze the cardiovascular event rates from three large placebo-controlled studies, two of which were already under way.

It was information from one of those long-term trials, the APPROVe study, that led to Merck's decision to withdraw Vioxx.

In all the debate since we withdrew Vioxx, one important point should not be lost. Merck has promptly disclosed the results of Merck-sponsored studies of Vioxx to the FDA, to physicians, to the scientific community, and to the media. By doing so, we fostered, both internally and externally, a robust scientific discussion of the risks and benefits of Vioxx.

In March of 2000, when we received the results of the VIGOR study, we promptly issued a news release providing its conclusions, and we submitted its results to the FDA.

The cardiovascular results of VIGOR were widely reported and discussed at the time. We submitted the initial VIGOR results to the *New England Journal of Medicine* for publication and presented the data at a major scientific meeting.

We also worked diligently with the FDA to review the data and develop revised prescribing information. This revised prescribing information included the cardiovascular data from VIGOR and a cardiovascular precaution.

Since the time of our release of the VIGOR study data, there has been a healthy scientific discussion of the safety of Vioxx and other COX-2 inhibitors. This discussion has occurred within Merck's laboratories and at external scientific forums.

Merck supported that discussion. However, when researchers published articles or gave speeches that presented misleading or inaccurate information about Vioxx, Merck sought to set the record straight about a medicine that provided significant benefits to patients.

We are confident that a careful and complete examination of Merck's conduct shows that, at all times, we acted responsibly and in a manner consistent with Merck's commitment to patient safety and to our rigorous adherence to scientific investigation, openness, and integrity.

In light of the history of our detailed examination of the cardiovascular safety of Vioxx, Dr. Kim's September 24th call to me was unexpected. Our clinical data had shown no difference between Vioxx and placebo.

Mr. Chairman, Merck believed wholeheartedly in Vioxx. I believed wholeheartedly in Vioxx. In fact, my wife was taking Vioxx, using Vioxx, up until the day we withdrew it from the market.

Much has been made of epidemiological studies conducted over the past few years about Vioxx, and two points are worth noting about these studies.

First, because of the design limitations inherent in epidemiological studies, their results must be interpreted with caution. For example, years of epidemiological studies on hormone replacement therapy appeared to indicate it was heart- and cancer-protective. In fact, recent well-controlled clinical studies have proven the opposite.

Second, the epidemiological data were inconsistent. I have included with this statement a timeline of epidemiological studies involving Vioxx or other NSAIDs that illustrates this point.

While epidemiological studies have an important role to play, given their inherent limitations, when both epidemiological studies and randomized controlled clinical studies are available, the randomized controlled clinical trials are the most persuasive evidence.

Prior to APPROVe, there was no demonstrated increased risk of cardiovascular events for patients taking Vioxx compared to taking placebo or NSAIDs other than naproxen in randomized controlled clinical trials.

We only found an increased risk of cardiovascular events because Merck continued to study Vioxx for a long time period. In fact, Vioxx and aspirin are the only two NSAIDs for which there was significant, publicly available long-term safety data. When Dr. Kim contacted me to describe the APPROVe trial findings, Merck acted.

In conclusion, Mr. Chairman, throughout Merck's history it has been our rigorous adherence to scientific investigation, openness, and integrity that has enabled us to bring new medicines to people who need them. I am proud that we have followed that same rigorous scientific process at every step of the way with Vioxx.

Mr. Chairman, at this point I would be pleased to answer the questions that you or the committee may have.

[The prepared statement of Mr. Gilmartin appears in the appendix.]

The CHAIRMAN. I am going to start with Senator Hatch because he has another meeting he has to go to.

Senator HATCH. Mr. Gilmartin, some of this you have answered, but just to make it more clear, if you could answer these briefly. When did Merck first realize that there were increased cardiovascular events associated with Vioxx? What type of follow-up action did you take after discovering this trend? Did Dr. Graham's study play a role in your company's decision to withdraw Vioxx from the marketplace?

Mr. GILMARTIN. Dr. Graham's study played no role in our decision to withdraw Vioxx.

Senator HATCH. All right.

Mr. GILMARTIN. The first definitive data we had that demonstrated that there was a higher risk of cardiovascular events of Vioxx against placebo was when we got the call on September 23rd in the evening, and the data on September 24th, the morning. That is the first time that there was a demonstrated risk in a randomized controlled clinical trial.

Senator HATCH. That is this year, you mean?

Mr. GILMARTIN. That is this year. That led us to act immediately to withdraw the drug from the market.

Now, during this period of time, in terms of the VIGOR study, when we basically had the finding, not only did we reduce serious GI events by over 50 percent, naproxen had a lower rate of cardiovascular events than Vioxx did.

That caused us immediately to start to look at what was going on. Was it the case that naproxen had a lower rate of events, did Vioxx have a higher rate of events, or was it chance?

So what we did, since we did not have any placebo data in that trial, we then went to the two Alzheimer's trials that we had under way, two large trials, and unblinded them for safety data. In those two trials, which are elderly patients at higher risk, we saw no difference between Vioxx and placebo.

From that point, in terms of also looking at the aspirin-like effects of naproxen, we concluded that the weight of the evidence was that naproxen had a lower rate. That was our conclusion then and that is our conclusion today.

Senator HATCH. All right. Now, Mr. Gilmartin, you heard the witnesses on the first two panels. They all argued that your company knew that there was an increased cardiovascular risk for Vioxx even before the drug was approved by FDA, but they say your company ignored the warning signs. Do you have any further comment?

Mr. GILMARTIN. Well, the discussions that they referred to in 1996 about the design of trials was well before there was even a theoretical speculation that there could be a cardiovascular risk with the COX-2 class. There was just not even a theory at that point that that would be possible.

So, those discussions reflected more the expectation that NSAIDs would have a cardio-protective effect. That was the belief at the time, not that Vioxx would have higher risk.

Senator HATCH. All right.

In your VIGOR study, what led your scientists to believe that naproxen had a cardio-protective effect when there was no scientific evidence to support this assumption?

Mr. GILMARTIN. Well, the following. First of all, in a pharmacological study, that naproxen does have an aspirin-like effect if taken twice a day as it was in the VIGOR study. In addition to that, an aspirin-like effect with people at a higher risk of cardiovascular events and so on, such as people with rheumatoid arthritis, that effect would be even greater.

Also, there are two other NSAIDs in which there had been clinical trials done that were similar to naproxen that showed that there was a cardio-protective effect. So, therefore, taking altogether the weight of the evidence, and also given the fact that we had the placebo data, there was no difference between Vioxx and placebo,

we concluded at that point that the weight of the evidence was that naproxen lowered the rate of cardiovascular events.

Senator HATCH. And VIGOR, which was the Vioxx gastrointestinal outcomes research.

Mr. GILMARTIN. Yes.

Senator HATCH. That is what that means.

Mr. GILMARTIN. Right.

Senator HATCH. You actually gave people Vioxx, 50 milligrams, once daily.

Mr. GILMARTIN. That is correct. It was the highest dose, twice the usual dose of 25 milligrams.

Senator HATCH. Twice the recommended product dose.

Mr. GILMARTIN. Right.

Senator HATCH. And that was compared to a common therapeutic dose of naproxen of 500 milligrams twice a day.

Mr. GILMARTIN. Correct.

Senator HATCH. All right.

Now, Mr. Gilmartin, one last question. I am sure if I do not ask it, one of the others will. In the *New York Times* today was an article. Are you familiar with that article that appeared today in the *New York Times?*

Mr. GILMARTIN. Yes.

Senator HATCH. All right.

Could you please talk about the study that is mentioned in today's *New York Times* and what it indicated about the cardiovascular risk of taking Vioxx?

Mr. GILMARTIN. Well, I have not seen the results of that study. That is still basically, I believe, under analysis. Well, I guess actually it has probably completed its analysis. I believe that it has just been submitted for publication.

Senator HATCH. I see. So were you aware of this study before?

Mr. GILMARTIN. Only in general terms. But until these studies are submitted for publication, it is not usual to publish them.

Senator HATCH. If I could just ask one more, Mr. Chairman.

The CHAIRMAN. Yes. Go ahead.

Senator HATCH. My experience is, having watched this industry for years and years, is that Merck is not only a great company, but is a company that has always been concerned with safety and efficacy, and has complied with FDA rules and regulations throughout the lifetime of the company, but particularly your tenure.

The fact of the matter is, there are many drugs that have adverse reporting from time to time in various aspects, and this is something that has to always be sorted out over time.

From what I see, you acted responsibly, and that is what the FDA, Dr. Kweder, said. You acted responsibly once you, as the chief executive officer, knew or saw what should be done.

I just want to compliment you for that, and having known you for a long time, I know that you would never countenance having a drug that was non-efficacious in the marketplace if you knew better.

So, this is a very difficult time for you, I know, but I want to compliment you for doing what you did as soon as you knew what to do, and just tell you that I have appreciated your testimony here today.

Mr. GILMARTIN. Well, thank you very much, Senator. I just might say that it is not only myself in the company that is committed to patient safety, but it extends throughout the entire company.

Senator HATCH. I am aware of that.

Mr. GILMARTIN. That is why we relentlessly pursued additional studies. We monitored this drug for cardiovascular safety. Whenever we found out data, whether unfavorable or favorable, we disclosed it to the public promptly. We continue to study the drug in order to find the answer.

Senator HATCH. One last question. As I see it, Vioxx even has some other not contemplated benefits that you have been discovering, including prostate and some other aspects as well. So, this is a drug that still deserves much further evaluation as to whether it can be fully efficacious or not.

Mr. GILMARTIN. Right. I think, unfortunately at this point, once we had identified that it had a known cardiovascular risk against placebo that began, as we said earlier, only after 18 months of continuous use that the trends started to depart, once we have made the decision to voluntarily withdraw the drug from the market, basically we ended all other trials as well.

Senator HATCH. So that is it, no matter whether it has some further efficacy or not.

Mr. GILMARTIN. Yes.

Senator HATCH. All right. Thank you.

Thank you, Mr. Chairman. Thank you, Senator Baucus, for allowing me to go first.

The CHAIRMAN. Mr. Gilmartin, you probably do not know me very well. I want to state, in perspective over several years, so it is unrelated to what I am saying now to Vioxx and your company, or even the FDA.

What we are about here is trying to make sure that the agencies of government that are set up, in this particular instance to protect the public, but I could be saying this about any agency of government, if they are doing what their job is.

And particularly what bothers me about the Agency that we have before us today, but I could say the same thing about any agency, and it is fairly consistent throughout government and a constant concern of mine, is that things that should be transparent in government are not, or when there are efforts on the part of government to keep information suppressed, or people that are doing what they think ought to be done, their job requires them to do, to not let that information out.

And it is really more disturbing in this particular instance because of the scientific process that we all understand over decades, where scientists do their work and scientists know that that work is going to be subject to peer review, and that they ought to be able to substantiate that before other scientists.

In the case of FDA, we have seen twice in 1 year, back in February, with the antidepressants causing suicide for young people. We saw a scientist there in FDA that was suppressed and his work kind of covered up, whatever you want to call it. In that particular instance, they were actually going to tell him what he could say and not say, as an example.

Or in the case of Dr. Graham here is another example. The scientific process itself will answer all the questions that need to be answered. There is no scientist I know that is afraid to put their work to that sort of test.

So it may sound to you, over the last month or two, that we are only concerned about your company and Vioxx. We are talking about a process of government here, and particularly efforts to keep things from other people.

I happen to believe that sunshine in government is the best disinfectant, so I spend a great deal of my time in the Senate of the United States trying to just make government work.

I want to thank you for coming and thank you for taking a strong step of recalling Vioxx. I appreciate the cooperation that you and Merck have shown the committee as we have gone down this road.

I have some questions now that will indicate that, even regardless of what you have said, or even the removal of your drug from the market, are matters that are still troubling to me.

I am going to start with this question. I only have three or four questions, so I am not going to harangue at you the rest of the afternoon.

Dr. Topol, of the Cleveland Clinic, has estimated the number of heart attacks caused by Vioxx to be about 160,000. While Dr. Graham testified today that nearly 100,000 excess cases of heart attacks and about 30 to 40 percent of those patients probably died, Merck has objected to some of the estimates of the number of heart attacks and strokes associated with Vioxx.

What is Merck's estimate of the number of persons who were harmed or died by Vioxx, given the known cardiac risk?

Mr. GILMARTIN. Well, the first thing I should say, is that heart attacks and strokes occur generally throughout the population from a number of risk factors, so the first thing is that, because a person is taking Vioxx does not mean that Vioxx caused a heart attack or stroke.

Second, in the study, the APPROVe study, in which we showed that there was a difference in the risk of cardiovascular events, it did not begin until after 18 months of continuous use, and only then did the trend start to depart.

Furthermore, the FDA said in their press release, which they issued on the same day that we withdrew the drug voluntarily, was that the risk for any one individual of a heart attack or stroke was very small. So, therefore, there is no way to make any reliable estimates.

The CHAIRMAN. All right. That is perfectly all right, if that is what you feel, you cannot give an estimate. But without your own estimate, how can you object, or Merck object, to other published estimates?

Mr. GILMARTIN. Because all those estimates are just speculation. There is not a way, looking at these databases, to arrive at those kinds of estimates.

The CHAIRMAN. Is it not true that Merck sponsored another study, an observational study, under a contract with a company by the name of Ingenics, which found that patients taking Vioxx were at a 35 percent higher risk of having an acute cardiac event like

a heart attack or angina, and that Merck knew about this risk as early as November, 2003?

I would refer you to the Poster Exhibits 46 and 61. Is that a fact? I would like to have you say yes or no, whether or not that is a fact. Why is the study not on your list of epidemiological studies?

Mr. GILMARTIN. I cannot say yes or no because I do not know what the results of that study are. I would say that the reason that it is not on our list of epidemiological studies is because it was just recently submitted for publication.

It is our policy that, for any study that we have, whether favorable or unfavorable, it is put into the public domain. That has been our policy and that has been our practice. This study, apparently, now is submitted for publication and will also be in the public domain.

The CHAIRMAN. All right.

Let me get back to it, because I used the date of November, 2003. The study people themselves said that your company was aware of this back in November of 2003. So, now you are answering to me, no, you do not know anything about it.

Mr. GILMARTIN. Well, I am saying I do not know what the results of that study are. I am aware of the fact there was a study under way. I became aware of that, as a matter of fact, as a result of the lead-up to these hearings. There were a number of studies that we do, and at the time that we had the results of these studies, we promptly disclosed them.

After the data have been fully analyzed we submit them for publication, we put them out into scientific forums to encourage healthy debate. You had indicated earlier, Mr. Chairman, the importance of scientific debate. We have contributed to that. We have encouraged that. This study, when it is published, will also contribute to that debate as well.

The CHAIRMAN. All right. This is my last question. In your testimony, you said that the placebo control APPROVe trial convinced Merck to take Vioxx off the market. If, as you say, Merck was so concerned about the safety of Vioxx, why did Merck not insist on the label that would notify Vioxx patients of the cardiovascular risks rather than allow patients to be in the dark until April of 2002, 2 years after the risk was known?

Mr. GILMARTIN. After the VIGOR study, there was data about cardiovascular risk. There was a cardiovascular precaution, but that was based on, again, trial against naproxen.

Against all other data that we had up until just a few weeks ago from the APPROVe trial, we had a large database of over 28,000 patients comparing Vioxx against placebo, comparing Vioxx against other non-naproxen NSAIDs, in which we saw no difference in the risk of cardiovascular events between Vioxx, placebo, and those other NSAIDs.

Furthermore, remarkably, for the first 18 months of the APPROVe trial in this placebo controlled trial, there was also no difference. If we had ended that trial early, at less than 18 months, we would not have seen a difference in the risk of cardiovascular events.

It was only after 18 months that they started to see the trend diverge, and at a point, once it reached the statistical significance,

once it was apparent it was statistically significant, we acted quickly and removed it from the market.

I will say that a trial like APPROVe is monitored by outside investigators and we do not have access to that data. So, it is monitored by an external safety monitoring board, and when they met and looked at the data, that is when they called us on September 23rd. They sent us the data on September 24th. The following Thursday morning, we announced the voluntary withdrawal of the drug.

The CHAIRMAN. Senator Baucus?

Senator BAUCUS. Thank you, Mr. Chairman.

Mr. Gilmartin, are there any internal studies, trials, whatnot that Merck conducts that it does not make public?

Mr. GILMARTIN. No. It has been our policy that all the trials that are associated with the development of a drug, and with all the post-marketing studies, those studies have always been published.

There are earlier pilot studies that are really earlier studies to see whether or not we can even advance with the drug that really have no meaning because those studies may never lead to a drug.

Senator BAUCUS. Do you ever discuss those others, the smaller ones, with the FDA?

Mr. GILMARTIN. Well, in the case of Vioxx, those smaller studies were part of the development of the drug. Those studies were shared with the FDA. They were part of the new drug approval filing. They were also discussed in medical symposiums as well, and they were also published.

Senator BAUCUS. To the best of your knowledge, do other companies, other pharmaceuticals, have the same practice?

Mr. GILMARTIN. I really cannot comment on that, Senator. I would really need more specific information.

Senator BAUCUS. Should the FDA then require it, or Congress require it, the appropriate body require it, that all those studies be public and timely?

Mr. GILMARTIN. I think that the industry has moved forward voluntarily to publish study results. They have established a website. And then, therefore, whether or not there should be legislation to that effect, I think, depends on what the nature of that legislation is.

Senator BAUCUS. Right. But if you think it is a good idea to make that information public, then why should it not just be an automatic requirement?

Mr. GILMARTIN. Well, it depends on what the requirement looks like, so it is in the details. Let me just say, clearly, there is no issue with the principle at all. It is a principle that we have followed rigorously throughout our history.

We also have voluntarily taken the step of putting the trials that we are starting, trials that are involved in the development of the drug or trials for post-marketing, voluntarily registering those by using *clinicaltrials.gov,* which is the FDA site. So the idea here is, people have an idea what trials are under way.

That site was originally put in place to alert people to trials that were ongoing for life-threatening diseases. We have expanded that so not only is there published information about trials we have done, but also now in the public domain, trials that we are doing.

Senator BAUCUS. All right.

Now, you heard the discussion about making the Office of Drug Safety independent of drug approval. Why should it not be independent?

Mr. GILMARTIN. Well, our experience with the FDA is that they are very data driven, they are very rigorous, and they are very concerned about patient safety. As a result of that, they are a very effective regulator, a very tough regulator.

Senator BAUCUS. But you heard Dr. Graham voice concerns about whether they are tough enough, that is, whether they are protective enough of the public interest.

Mr. GILMARTIN. Well, I can speak from our own experience. Throughout all of Vioxx, and any concerns about that, they were all over the top of that issue, and we shared with them the data that we had.

In terms of specifying a trial to go forward, as the trials go forward to answer the question definitively, we worked closely with them in terms of what we wanted to do through the protocol, and so on.

Senator BAUCUS. I am a little curious why it took so long to change the label, the label that would eventually say that there is a potential cardio problem. That was 2 years. Frankly, I think it was Dr. Kweder who said that ordinarily that would take a matter of months. But for some reason, she implied it was Merck that was dragging its feet.

Mr. GILMARTIN. No. What she said, is the FDA had requested additional data from us and we were complying with that and cooperating with that.

Senator BAUCUS. Well, just give us a feeling of why it would take 2 years. That is a long time.

Mr. GILMARTIN. Well, it depends on the extent of the data. I think this was a finding that was confounding from the standpoint that we had all this placebo data that showed no difference, and no difference against other non-naproxen NSAIDs.

So, I think that there was a very rigorous analysis on both the FDA's part and our part in terms of, how could one interpret this data. That required additional study. We met additional requests. So, that was really the reason for the time frame.

Senator BAUCUS. My understanding is, the only significant placebo study was the APPROVe study, which was done later. There were interim, smaller studies, but the only really significant placebo study was APPROVe, which was concluded later.

Mr. GILMARTIN. It was the only significant long-term study that had extended out. Our other studies had 1 to 2 years in them. Prior to that time, as part of the original submission of 5,000 patients, which is a large database to submit for drug approval, that we had people in that with both cardiovascular risk and without. So, we had placebo data and we had data against non-naproxen NSAIDs as well, and that data did not show any difference in cardiovascular risk.

Furthermore, we expanded that with the Alzheimer's trials that I discussed earlier, which added even more to that database and once again showed no difference in risk. At the point that we were doing the APPROVe trial, we had 28,000 patients.

Senator BAUCUS. Right. But earlier during the discussions with the FDA with respect to the label, not only what the label said but the degree of the warning, it is clear that Merck was aggressively marketing the product, too, marketing Vioxx. Was that not the case?

Mr. GILMARTIN. Well, given all the safety data that we had, and as I say, with 28,000 patients worth of trials, in effect, in which we saw no difference between placebo and no difference between Vioxx and non-naproxen NSAIDs, that is a lot of safety data, and our marketing was appropriate.

Senator BAUCUS. Clearly, the United States has the best pharmaceutical industry in the world that provides wonderful drugs that serve terrific purposes. Whenever we have these kind of general discussions with the pharmaceutical industry, sometimes the discussion moves into the requirement of patent protection, intellectual property protection, because it costs so much to develop a new drug, and so forth, and there are a lot of dead ends. And some of them are not dead ends, but you need the patent protection to get there.

I think there's sufficient patent protection. If you have a different view, I would like to hear that. Why should Congress go further, in effect, shielding pharmaceuticals from any non-economic damages over $250,000 if there is prior FDA approval of a drug? You heard me ask the question earlier.

In this case, and there are many cases down the road—hopefully not too many—there may be some drugs that, even though they are approved, are later withdrawn from the market because certain problems occurred.

Not because of any fault with respect to the initial approval, but just, it turns out that we find out new things as we have new data. Is that not a bad idea to prevent people from pursuing their legitimate rights when they are injured by a drug post-approval?

Mr. GILMARTIN. Well, I think if we look to the vaccine industry as one example here, 30 years ago there were 25 vaccine manufacturers. Today, there are only five.

One of the major reasons why there was a drop-off in the number of vaccine manufacturers and not any new entrants, is for a number of years there were real issues around product liability.

Congress stepped in to resolve that issue with the Vaccine Injury Compensation Act for people who felt that they had been injured by a vaccine—these are just for pediatric vaccines—that they could be compensated for that and that would be the first place that they would go.

That stabilized, to a large extent, the number of vaccine manufacturers. So, given the high risks of drug discovery and the cost of it, and so on, it was clear in the vaccine industry that there was a negative incentive.

Senator BAUCUS. I understand, and I have heard that argument with the vaccine industry. But that is the vaccine industry. We are not talking about vaccines, we are talking about new drugs going to market.

Mr. GILMARTIN. No, that is true.

Senator BAUCUS. They are very different.

Mr. GILMARTIN. That is true. But I think that that was sort of an experience, I think, that we could look to as an analogy, and therefore I think we have to be concerned about the impact of product liability on the pharmaceutical industry.

Senator BAUCUS. Well, I just urge the industry, the major goal is patient safety and product safety.

Mr. GILMARTIN. Absolutely. Absolutely.

Senator BAUCUS. I have significant questions about that kind of additional shield, frankly, as we try to work our way through the correct balance in tort reform.

Mr. GILMARTIN. Exactly.

Senator BAUCUS. What have you learned from all this? I asked that question of Dr. Kweder, and she said that we have got to do a better job communicating more data with more people who are becoming more sophisticated about drug approvals and so forth, because people have higher standards now, as well they should, with more data available. That is what she learned. I am just curious what you have learned through all of this.

Mr. GILMARTIN. Well, I think that is a very appropriate question, and one, certainly, we ask ourselves.

One of the things that we did, of course, was look back in great detail in terms of the actions that we took, what were the facts surrounding our actions at every step of the way.

I think that the take-aways here, which I am pleased to say that I think we met these standards—I know we met these standards—is, first of all, to study the drug extensively, not only for the premarket approval, but also to continue studying the drug as we have done.

The second thing is, it highlights the importance of monitoring the drugs, in this case for cardiovascular events, but other side effects as well.

The third one, which you have touched on about the publication of clinical trial data, prompt disclosure is very important here. That is something else.

Senator BAUCUS. The positive and the negative trials.

Mr. GILMARTIN. The positive and the negative, and probably you could argue, even more importantly, the negative. Because our disclosure, for example, of the VIGOR data, which we received the preliminary results of in March of 2000, we issued a press release that same month, we submitted that data to the FDA, we submitted that data to the *New England Journal of Medicine.*

That was published by November. We presented that in medical forums. As a result of that, we generated a scientific debate where people had different viewpoints about what was happening as a result of the VIGOR results. That also, as a result of that, raised the level of concern of everyone, ourselves, the FDA, and that basically caused a continuation of the study of the drug and a relentless effort to find out what is going on here.

Senator BAUCUS. What about independent comparative drug analysis? Why should the government not set up some independent comparative analysis system?

Mr. GILMARTIN. Right. Well, I think that comparative effectiveness or cost effectiveness, there are basically a lot of organizations, such as the health plans, who are already starting to try to look

for that kind of information. I think as a matter of competitive advantage in the industry, that we are all starting to do more of those trials.

For example, on our cholesterol lowering drug that we have in partnership with Schering-Plough, we have comparative data on effectiveness against a competitor on the label.

Senator BAUCUS. Why should the public not have that data?

Mr. GILMARTIN. Pardon me?

Senator BAUCUS. Why should the public not have that? After all, this is from a consumer point of view.

Mr. GILMARTIN. Oh, absolutely. No, absolutely. I think that should be available to the public as well. I think that is absolutely essential. So what I am saying is, we actually sponsored a symposium in conjunction with AARP to bring together experts to talk about how one might go about doing that.

Senator BAUCUS. But there is a provision in the last Medicare bill which provided a certain amount, $25 million, $50 million, something like that, to pay for—I have forgotten whether it was FDA, or where it was—comparative analysis. Is that a good idea?

Mr. GILMARTIN. I think it is a good idea to have those kinds of outcomes. I think we have to be careful about how we approach getting there.

Senator BAUCUS. But the general principle is, independent, comparative analysis makes sense.

Mr. GILMARTIN. Well, comparative analyses that can come about from the fact that we compete against one another as well within the industry.

Senator BAUCUS. I think you know what I am saying here. I just hope the pharmaceutical industry does not stand in the way, but actually vigorously embraces something like that, because I think that will help the American confidence in the drugs that they are taking, and frankly I think it will help the pharmaceutical industry, because, as you know, industry now does not enjoy the most wonderful reputation that you would like to have.

Mr. GILMARTIN. As you know, in terms of our actions as a company, in terms of engaging, in terms of trying to achieve these kinds of solutions, not only in the interest of patient safety, but also access to medicines, is something that I think you can count on us to be very active in helping on that.

Senator BAUCUS. I appreciate that. Thank you.

The CHAIRMAN. Senator Breaux?

Senator BREAUX. Thank you, Mr. Chairman.

Mr. Gilmartin, you will have the pleasure, probably, of being the last person I will ever ask questions of as a member of Congress over 32 years. This is it.

Mr. GILMARTIN. Even under the circumstances, it is a privilege.

Senator BREAUX. Let me ask you sort of a side question here. You and Senator Baucus were talking about the vaccination companies having a fund that would be gone to in case of potential liabilities as being a good thing. It certainly has not helped the availability of vaccinations, even though they have that protection.

Mr. GILMARTIN. Well, I think what has happened, is that it has stabilized the industry. It only covers pediatric vaccines. So, there are other factors that I think are important to consider as well.

The Institute of Medicine did a study of, why are there not more vaccine manufacturers? Why are there not a lot more new entrants? One of the factors that they pointed to is the fact that the government purchases more than 50 percent of the vaccines.

Senator BREAUX. The government controls the price.

Mr. GILMARTIN. And controls the price. And so that is a factor as well. So, there are multiple factors here. But it is unfortunate that we do not have the same kind of entrepreneurial and scientific activity going on in vaccines that we do in pharmaceuticals because it is new science.

Senator BREAUX. That is a good point.

Were there ever any clinical studies done on Vioxx vis-a-vis the potential for cardiovascular incidences?

Mr. GILMARTIN. The answer is yes. The APPROVe trial, plus the two other trials that we added to it, one for the prevention of prostate cancer and the other to assess how we can improve the survival rate of patients who had been treated for colo-rectal cancer, these three trials, taken together, represented about 24,000 patients.

They were pre-specified not only for those benefits, but also to look for cardiovascular risk. We worked with the FDA on a protocol to be able to answer that question. So, these were the large placebo controlled trials that were designed to definitively answer the question whether or not there was an increased risk of cardiovascular events with Vioxx compared to placebo.

The difficulty that we were able to overcome, was that the trials have to be ethical, and here there was a potential benefit. Second, in this case, you wanted to be timely. So we took a trial, APPROVe, that was under way, enrolling patients, and actually a second trial that had started up by the time we finished the protocol.

So, therefore, the trial, which is a 3-year trial, started in February of 2000, a month before the preliminary data from VIGOR became available. It takes over a year to enroll patients in a trial of this size.

It was a 3-year study. It was 8 weeks before the end of that 3 years when we got the call from the outside investigators that they saw an increased risk of cardiovascular events. So, from the time we started the trial to the time that we had the answer, it was probably about the shortest possible time we could have had that answer.

Senator BREAUX. Now, the VIGOR study, which was Vioxx versus naproxen. I do not understand how Merck could have concluded in the press release that was released in 2001 confirming a favorable cardiovascular safety profile of Vioxx.

It seems to me that, looking at the VIGOR study, you are looking at something that showed as much as a 5 times increase in the risk of cardiovascular problems for the group taking Vioxx as opposed to the group taking naproxen. Then Merck says this somehow proves that Vioxx has a favorable safety profile.

Mr. GILMARTIN. The favorable safety profile referred to the entire profile of the drug, which included its impact on GI events.

Senator BREAUX. Oh, no. But the headline says, "Favorable Cardiovascular Safety Profile." That is the headline.

Mr. GILMARTIN. Well, that is also because we had data against placebo and we had data against other naproxen NSAIDs. Now, the FDA sent us a letter on that press release.

Senator BREAUX. They went crazy.

Mr. GILMARTIN. And we, in working with them over the press release and in terms of responding to descriptions of the drug that were inaccurate, after the exchanges of information and so on, they did not ask us to take any action specific to that press release and the matter was closed.

In part of that warning letter, there were two other instances that they objected to, which is not a critique of our overall marketing practices, but basically there was a speaker who they felt was not balanced and we stopped using that speaker.

He was using unauthorized slides, and also two sales representatives at two meetings that they felt were not giving balanced information. On those, we took action to notify physicians who may have heard those presentations, but there was no action on the press release.

Senator BREAUX. This warning letter is part of the record, and it is a strong letter. The second paragraph directly talks about you having engaged in a promotional campaign for Vioxx that minimizes the potentially serious cardiovascular findings. They ordered you to do some very specific things with regard to those promotional materials.

Mr. GILMARTIN. That is correct. So, we took that very seriously. Those letters are strongly worded, in general, and we took actions with regard to the speaker. We took actions with regard to correcting the situation with the sales representatives.

The corrective action, as I said, was that the speaker had been using unauthorized slides. We stopped using that speaker. We sent letters to the physicians that may have been exposed either to those sales representatives or to the physician, but there was no action requested or required on the press release.

Senator BREAUX. I do not know who wrote that press release, but, boy, I would have a serious talk with them.

The statement by FDA when Vioxx was approved in 1999 talking about their theoretical concern about the possible cardiovascular problems and saying that with available data it is impossible to answer with complete certainty, a larger database will be needed to answer this, and other safety comparison questions.

What does Merck do when it gets something like that as part of the approval process? Do they say, all right, let us go out and conduct some more clinical trials based exactly on that concern, or do you not do anything with it?

Mr. GILMARTIN. We do large clinical trials and actually monitor them, and set up the monitoring process to address that concern. In fact, just some background here about publishing data, is that it was a study that we funded and also had Merck authors that contributed to the theoretical possibility, based on the analysis that was done, that COX-2s could have a pro-thrombotic effect.

So that study, which had Merck authors on it, was submitted to the FDA as part of our new drug application. That study was also published and that study was also discussed in scientific forums.

So, once again, basically searching and looking to find any issues with the drug, even with issues that could be seen as negative to us, publishing that data, and encouraging that scientific debate. Because of that, we also set up a cardiovascular monitoring of all the trials that we were doing.

Even though it is typically asked for in terms of cardiovascular events, we basically exercised real diligence, extra diligence, on top of that to try to find out if there was any issue.

Senator BREAUX. Was that the VIGOR study?

Mr. GILMARTIN. No. The VIGOR study was designed, really, to determine whether or not we were going to have a reduction in the risk of GI events. But the VIGOR study was monitored closely by an outside board for cardiovascular events.

Senator BREAUX. Was it an external group that raised the concerns about the VIGOR study or was it the APPROVe study? Let me see. The external monitoring board.

Mr. GILMARTIN. Yes.

Senator BREAUX. In 2004, September of this year.

Mr. GILMARTIN. Yes. The way these studies are done is, you have as part of the studies an External Safety Monitoring Board that looks at and monitors the safety data in the study. They are independent of us and we do not have access to the data.

So it was a representative of this board that called us on the evening of September 23rd and sent us the data on the morning of September 24th, which is the first time we had seen the safety data.

This is the way that these trials are carried out. Once having had that data and analyzing it to ensure ourselves that the signal was there, that is when we moved very quickly to voluntarily withdraw the drug.

Senator BREAUX. All right.

Let me just get a final question, or just a comment. There are some who argue that, well, all of these clinical trials are bought and paid for, conducted, and structured by the drug companies. Therefore, that is an unfair advantage to FDA, that the government should do it. They should have their contractors. I know Merck does not do the studies itself, necessarily. You contract with universities and outside groups to do the clinical trials.

Mr. GILMARTIN. Right. Right.

Senator BREAUX. But can you comment on the argument that some would make, that pharmaceutical companies have such a vested interest, they should not be in control of the clinical trials and the tests leading up to approval by FDA of that particular product?

Mr. GILMARTIN. Well, I believe the system we have now works very well. I think the key, and the reasons why it works—well, first of all, these are scientists of great reputation and ability, so therefore are not likely in any way to compromise their own integrity or ethics or their scientific standing.

Second, the system works in terms of the clinical trials because this data is peer-reviewed. I mean, this has to stand up to scrutiny as to whether or not the trials were done properly. The protocols have to be approved beforehand in terms of, will it really demonstrate what you are trying to demonstrate.

So there is a system in place that is a combination of professionalism, a combination of transparency, and a combination of regulatory process here that makes the system work.

Senator BREAUX. All right. Thank you, Mr. Gilmartin.

The CHAIRMAN. Thank you, Mr. Gilmartin. If you want to stay there, you can. I have got closing, administrative stuff I have got to go through here.

I want to remind everybody that the hearing record will remain open for 10 days so that any committee member wishing to submit remarks or questions for the record——

Senator BAUCUS. Mr. Chairman? If you might, because I do not want people to leave before we honor a valued friend and member, Senator Breaux. This is his last day here, and he has done a heck of a job. [Applause.]

Senator BREAUX. That is it. I am finished. I am out of here. [Laughter.]

The CHAIRMAN. We have a number of documents that were discussed today, but given the time constraints, many other documents must and will be addressed in further questioning to Merck from the committee.

Without objection, I submit for the hearing record the balance of the exhibits prepared for today's hearing. [No response.] Hearing no objection, they are submitted to the record.

[The exhibits appear in the appendix.]

The CHAIRMAN. Thanks to the witnesses for their time and important testimony. I extend my personal appreciation to Dr. Graham for his perseverance. I also appreciate the testimony of Dr. Singh, especially given his health circumstances, and Dr. Psaty. Thanks to Dr. Kweder and Mr. Gilmartin for their testimony.

After today's hearing, we will need to stay committed to addressing the problems that we have come to better understand. The public depends on the FDA, and the FDA needs to take meaningful steps to help restore confidence in its commitment to protecting the public safety instead of protecting the profits of drug companies.

The health and safety of the American public must be FDA's first and only concern, and there is no doubt that the performance of the FDA affects the integrity and effectiveness of programs under the jurisdiction of this committee, like Medicare and Medicaid.

I intend to keep pressing for reforms inside the FDA that result in greater transparency and openness, based on the questions that have been raised by the FDA's Office of Drug Safety. I will be asking the Government Accountability Office, the GAO, to review the interaction of the Office of Drug Safety with the Office of New Drugs.

I am also asking the Government Accountability Office to conduct a broad review of the organization's structure and culture in the Office of Drug Safety. Again, an independent Office of Drug Safety would be a positive change at the FDA.

Finally, I will continue the committee's investigation into what happened with Vioxx. It seems clear to me that there is more to learn about this drug disaster.

Senator BAUCUS. Mr. Chairman, I just want to thank you for holding this hearing. There is a lot of valuable information here. I think it is very much in the public interest. You have got a lot

of people, I think, thinking constructively, and I thank you very much for it. Again, I just want to thank Senator Breaux. I do not know anybody with keener intelligence, looking for compromises and solutions, and also with a great sense of humor.

The CHAIRMAN. I associate myself with your remarks about Senator Breaux, and I appreciate the remarks that you said about the hearing.

Meeting adjourned.

[Whereupon, at 2:30 p.m., the hearing was concluded.]

APPENDIX

ADDITIONAL MATERIAL SUBMITTED FOR THE RECORD

PREPARED STATEMENT OF HON. MAX BAUCUS

Thank you, Mr. Chairman, for holding this hearing. The withdrawal of the pain killer Vioxx from the market has raised serious questions.

Two million patients were taking Vioxx in late September when Merck pulled it due to concerns about the increased risk of heart attacks and strokes. While we do not know the true extent of the risk, tens of thousands of patients potentially could have suffered a heart attack or stroke as a result of the drug.

This hearing is an opportunity to take a hard look at what happened with Vioxx. But this hearing goes beyond Merck and Vioxx. We must think critically about the way we test and evaluate drugs to ensure their safety.

In the weeks since Merck withdrew Vioxx, many questions have been raised. Questions like:

- When did Merck know about the potential dangers of Vioxx?
- Should the company have acted sooner to withdraw the drug?
- Why didn't the FDA detect the risks associated with Vioxx during the initial approval process, or even in the 5 years since approval?
- Does the FDA have sufficient resources, authority and independence to ensure that the drugs it approves are safe?
- And should we be doing more to monitor drug safety after a drug has been approved?

These questions, and many others, must be answered so that medications do not pose a risk to Americans' health. These issues are critical to Medicare and Medicaid beneficiaries. In the 5 years that Vioxx was on the market, Medicaid spent more than $1 billion on the drug. And Medicaid bears the cost of any additional medical care necessary when drugs cause injury.

Furthermore, in just over a year, Medicare will begin covering prescription drugs through the optional Part D benefit. We need to be certain that beneficiaries of the new program are not exposed to potentially harmful medications.

I am concerned that what happened with Vioxx may have been due, in part, to insufficient emphasis on complete, rigorous, and expansive clinical trials. Clinical trials focused on drug safety should not stop when the FDA approves a drug. We need to continue testing drugs to thoroughly evaluate the potential risks, not just the benefits.

Clinical trial results should be more transparent. The conduct and reporting of clinical trials are critical to approving a new drug. And we must continue to evaluate and monitor drugs even after they are approved to ensure their safety and effectiveness.

In addition, I have encouraged drug manufacturers to expand the number of patients who participate in clinical trials, including patients in rural areas such as Montana.

I also support greater use of studies that test the comparative effectiveness and safety of drugs in similar therapeutic classes. The Medicare bill that passed last year designated $50 million for these studies. And I have supported raising the level of funding to $75 million. But the current Senate appropriations bill only includes $15 million. We should do more.

Finally, the Vioxx situation raises serious concerns about the broad implications of the medical malpractice reform bill currently being considered by the Congress.

Liability restrictions in this bill apply not just to doctors and hospitals. They also include pharmaceutical and medical product manufacturers, such as Merck. And the legislation creates new protections for products approved by the FDA, like Vioxx.

Given the events we are discussing today, I think the Congress and the public need to take a hard look at this legislation. I hope that today's hearing will shed light on recent events. And I look forward to hearing from our witnesses. Thank you, Mr. Chairman.

PREPARED STATEMENT OF RAYMOND V. GILMARTIN

Mr. Chairman, Senator Baucus, members of the committee, my name is Ray Gilmartin, and I am chairman, president and chief executive officer of Merck & Co. On behalf of the 60,000 men and women of Merck, I am pleased to have the chance to come before you to tell you more about who we are and what we stand for.

On the afternoon of September 24th, Dr. Peter Kim, President of Merck Research Laboratories, called to alert me to information he had received just that morning. The information was from an independent, external board of physicians and scientists monitoring the safety of patients in a major trial on Vioxx. He told me that in the trial we sponsored—known as APPROVe—there was an increased risk of confirmed cardiovascular events beginning after 18 months of continuous daily treatment in patients taking Vioxx compared to those taking placebo.

That call triggered a series of events that led, within 4 days of that call, to Merck contacting the FDA to tell them that we were going to withdraw Vioxx from the market.

The decision that we made to voluntarily withdraw Vioxx was difficult in several ways. Vioxx was the only nonsteroidal anti-inflammatory medicine or NSAID that was demonstrated to provide pain relief similar to high-dose NSAIDs and proven to reduce the risk of developing debilitating gastrointestinal side effects compared to those on NSAIDs. This was an important benefit for many who suffered from the pain of arthritis and other conditions. An estimated 15,000 Americans die each year from gastrointestinal bleeding associated with NSAID use.

Many patients counted on Vioxx to help them when no other medicine would. We believed that it would have been possible for Merck to continue to market Vioxx with labeling that would incorporate the new data.

On another level, however, the decision we made to withdraw Vioxx was easy. Given the availability of alternative therapies and the questions raised by the data, withdrawing Vioxx was consistent with an ethic that has driven Merck actions and decisions for more than 100 years. Merck puts patients first.

I am pleased today to assist the committee in better understanding this decision and the events that led to it. I would like to make three points clear at the outset.

First, the Food and Drug Administration approved Vioxx only after Merck had extensively studied the medicine and found it to be safe and effective. Merck continued to extensively study Vioxx after it was approved for marketing to gain more clinical information about the medicine.

Second, over the past 6 years, since the time Merck submitted a New Drug Application for Vioxx to the FDA, we have promptly disclosed the results of numerous Merck-sponsored studies to the FDA, physicians, the scientific community and the media, and participated in a balanced, scientific discussion of its risks and benefits.

Third, until APPROVe, the combined data from randomized controlled clinical trials showed no difference in confirmed cardiovascular event rates between Vioxx and placebo and Vioxx and NSAIDs other than naproxen. When data from the APPROVe study became available, Merck acted quickly to withdraw the medicine from the market.

In my few minutes, I welcome the chance to review each of these points and welcome your questions.

Merck's actions in response to questions on Vioxx safety

Mr. Chairman, as you know, no medicine is absolutely safe; all medicines have side effects. To determine both its risks and benefits, Merck extensively studied Vioxx before seeking regulatory approval to market it, and we continued to conduct studies after the FDA approved Vioxx.

I have provided, with this statement, a timeline of our Vioxx research and development process to aid in the committee's understanding of the events.

Our original New Drug Application to the FDA for Vioxx included data on more than 5,000 patients with osteoarthritis. The clinical trials compared the effects of Vioxx to other non-naproxen NSAIDs and to placebo, and included data on patients who had been on Vioxx for longer than 1 year. In these studies, there was no difference in the rate of cardiovascular events between Vioxx and placebo, or between Vioxx and non-naproxen NSAIDs.

Prior to the FDA's approval of Vioxx, we had initiated a study known as VIGOR. That study was designed to compare the gastrointestinal safety profile of Vioxx at twice its maximum recommended chronic dose with naproxen.

We chose naproxen for this study instead of placebo because we intended to test Vioxx in patients with rheumatoid arthritis. These are among the patients who we hoped would benefit from taking Vioxx. It would not have been ethical or practical to subject people suffering from arthritis pain to a placebo for a long time.

The preliminary results from the VIGOR trial became available to Merck in March, 2000. In the trial, there was a higher cardiovascular event rate in patients taking Vioxx than naproxen. These data were of concern to us.

It is important to note that, because the VIGOR study compared two drugs—Vioxx and naproxen—and not Vioxx and placebo, it was not possible to make a determination, based on the VIGOR study alone, whether naproxen was having a beneficial cardiovascular effect, or whether Vioxx was having a detrimental cardiovascular effect.

To help us evaluate the meaning of the VIGOR study, Merck took the step of looking into data from two trials we had already initiated in which patients with memory impairment or Alzheimer's were given Vioxx or placebo. We found that there was no difference in cardiovascular event rates in these two trials.

These data, our earlier clinical data, and a pharmacological study that showed that naproxen had strong anti-platelet effects similar to aspirin, when it is taken regularly twice a day, as it was in VIGOR, led us to conclude that the best explanation for the difference in VIGOR was an effect of naproxen.

As Merck continued to monitor the safety of Vioxx, we recognized the value and interest in obtaining additional cardiovascular safety data on Vioxx and discussed how to obtain placebo-controlled data in the population of patients with pain in whom Vioxx was indicated. Among the issues we had to consider was the ethical difficulty in giving placebo, rather than a pain-relief medicine, to patients in pain over a longer period of time.

After deliberations with numerous outside advisers, Merck developed and discussed with the FDA a plan to prospectively analyze the cardiovascular event rates from three, large, placebo-controlled studies, two of which were already underway.

It was preliminary information from one of those long-term trials—the APPROVe study—that led to Merck's decision to withdraw Vioxx.

Merck's disclosure of safety-related information on Vioxx

Merck has promptly disclosed the results of Merck-sponsored studies of Vioxx to the FDA, physicians, the scientific community and the media. By doing so, we fostered—both internally and externally—a robust scientific discussion of the risks and benefits of Vioxx.

In March, 2000, when we received the results of the VIGOR study, we promptly issued a news release providing its conclusions, and we submitted its results to the FDA. The cardiovascular results of VIGOR were widely reported and discussed at the time. Just 2 months later, we submitted the initial VIGOR results to the *New England Journal of Medicine* for publication and presented the data at a major scientific meeting.

We also worked diligently with the FDA to review the data and develop revised prescribing information. This revised prescribing information included the cardiovascular data from VIGOR and a cardiovascular precaution.

Since the time of our release of the VIGOR study data, there has been a healthy scientific discussion of the safety of Vioxx and other COX-2 inhibitors. This discussion has occurred within Merck's laboratories and at external scientific forums.

Merck supported that discussion. However, when researchers published articles or gave speeches that presented misleading or inaccurate information about Vioxx, Merck sought to set the record straight about a medicine that provided significant benefits to patients.

We are confident that a careful and complete examination of Merck's conduct shows that, at all times, we acted responsibly and in a manner consistent with Merck's commitment to patient safety and our rigorous adherence to scientific investigation, openness and integrity.

Merck acted based on data from a placebo-controlled clinical study

In light of the history of our detailed examination of the cardiovascular safety of Vioxx, Dr. Kim's September 24th call to me was unexpected. Our clinical data—from our original application to the FDA seeking approval of Vioxx to that day—had shown no difference between Vioxx and placebo.

Mr. Chairman, Merck believed wholeheartedly in Vioxx. I believed wholeheartedly in Vioxx. In fact, my wife was a user of Vioxx until the day we withdrew it from the marketplace.

Much has been made of epidemiological studies conducted over the past few years about Vioxx.

Two points are worth noting about these studies.

First, because of the design limitations inherent in epidemiological studies, their results must be interpreted with caution. For example, years of epidemiological studies on hormone replacement therapy (HRT) appeared to indicate that HRT was heart and cancer protective. In fact, recent well-controlled clinical studies have proven the opposite.

Second, the epidemiological data were inconsistent. I have included with this statement a timeline of epidemiological studies involving Vioxx or other NSAIDs that illustrate this point.

While epidemiological studies have an important role to play, given their inherent limitations, when both epidemiological studies and randomized controlled clinical studies are available, the randomized controlled clinical trials are the most persuasive evidence.

Prior to APPROVe, there was no demonstrated increased risk of cardiovascular events for patients taking Vioxx compared to patients taking placebo or NSAIDs other than naproxen in randomized controlled clinical trials. And, we only found an increased risk of cardiovascular events because Merck continued to study Vioxx for such a long time period. In fact, Vioxx and aspirin are the only two NSAIDS for which there is significant, publicly available long-term safety data.

When Dr. Kim contacted me to describe the risk, Merck acted.

Conclusion

In conclusion, Mr. Chairman, throughout Merck's history, it has been our rigorous adherence to scientific investigation, openness and integrity that have enabled us to bring new medicines to people who need them.

I am proud that we followed that same rigorous scientific process at every step of the way with Vioxx. Mr. Chairman, I would be pleased to answer the questions that you or the committee might have.

MERCK

VIOXX TIMELINE
Key Dates for VIGOR and Long-term, Placebo-controlled Studies Implemented to Provide Cardiovascular Safety Data

1993	Studies published in which indobufen (Circulation, 1993, 87:162-164) and the non-selective NSAID flurbiprofen (European Heart Journal, 1993, 13, 951-957) are shown to reduce cardiovascular (cv) events.
1998	
April	Results of FitzGerald study first presented. Among the results of the study was the surprising discovery that COX-2 specific inhibitors reduced the urinary excretion of prostacyclin metabolite. Based on these results, it was, for the first time, hypothesized that COX-2 specific inhibitors may alter the balance between prostacyclin and thromboxane and thereby increase the risk of cv events.
	Trial of VIOXX versus placebo in the prevention of Alzheimer's in patients with Mild Cognitive Impairment (MCI) begins.
Nov	Vioxx New Drug Application (NDA) submitted to the U.S. Food & Drug Administration (FDA). The application included data on approximately 5,400 osteoarthritis patients who participated in 8 double-blind, placebo-controlled and active-comparator studies. In these studies, similar rates of investigator-reported thrombotic cardiovascular adverse events were seen with VIOXX, placebo, and comparator NSADs (ibuprofen, diclofenac, or nabumetone).
1999	
Jan	VIOXX Gastrointestinal Outcomes Research[1] (VIGOR) trial initiated.
Feb	First trial of VIOXX versus placebo for the treatment of Alzheimer's disease begins.
April	Public meeting of FDA Advisory Committee on VIOXX NDA.
May	VIOXX approved by the FDA.
Oct	Adenomatous Polyp Prevention On VIOXX[2] (APPROVe) trial protocol finalized.

2000	
Feb	APPROVe trial enrollment begins.
March	Preliminary results from VIGOR become available to Merck.
March	News release on preliminary results of VIGOR issued by Merck.
March	Preliminary VIGOR results submitted to the FDA.
March	Merck unblinded to safety data from two ongoing Alzheimer's studies – one for prevention and one for treatment – that compare VIOXX to placebo. These data show no difference in cardiovascular event rates between VIOXX and placebo.
April	Second trial of VIOXX versus placebo for the treatment of Alzheimer's begins.
May	Preliminary VIGOR data submitted to the *New England Journal of Medicine* for publication.
May	VIGOR presented at Digestive Disease Week.
June	Final VIGOR data submitted to FDA in a Supplemental New Drug Application, which included draft prescribing information.
Nov	The GI and cardiovascular safety findings from VIGOR published in *The New England Journal of Medicine*.
	First VIOXX versus placebo trial in the treatment of Alzheimer's disease ends.
	In preparation for VIGOR Advisory Committee, second interim analysis of safety data from Alzheimer's prevention and treatment trials conducted, again showing no difference in cardiovascular event rates between VIOXX and placebo.
2001	
Feb	Public meeting of FDA Advisory Committee on VIGOR.
May	Second trial of VIOXX versus placebo for treatment Alzheimer's disease stopped.
Oct	Pooled analysis of cardiovascular data from Phase II/III studies published in Circulation. Analysis demonstrated that VIOXX was not associated with excess cardiovascular thrombotic events compared with either placebo or non-naproxen NSAIDs.
Sept	Merck and Oxford University sign letter of intent to conduct the VIOXX in Colorectal Cancer Therapy: definition of Optimal Therapy[3] (VICTOR) trial.
Nov	APPROVe enrollment completed.
2002	
April	U.S. Prescribing Information for VIOXX updated with VIGOR information and data from two placebo-controlled studies
April	First patient is enrolled in VICTOR trial.
June	Pooled analysis of placebo-controlled studies in patients with Alzheimer's and MCI presented at EULAR. The incidence of

serious cardiovascular adverse events in this population was similar on VIOXX and placebo.

2003

March	VIOXX in Prostate cancer (ViP) trial protocol finalized.
April	Trial of VIOXX versus placebo in MCI ends.
June	ViP trial enrollment begins.
	Updated pooled analysis of Alzheimer's treatment and MCI data presented at EULAR. The cardiovascular event rate in patients taking VIOXX 25 mg continued to be similar to the rate in patients taking placebo; mean duration of treatment was 1.2 years in VIOXX group and 1.3 years in placebo group.
Oct	Updated pooled analysis published in the American Heart Journal. Analysis demonstrated that VIOXX was not associated with excess cv thrombotic events compared with either placebo or non-naproxen NSAIDs.

2004

Sept	APPROVe External Data Safety Monitoring Board notifies Merck of its recommendation to end APPROVe trial.
Sept	APPROVe, ViP and VICTOR trials terminated early.
Sept	Merck voluntarily withdraws VIOXX from the market.
Nov	APPROVe trial scheduled to end.

2005

Aug	ViP trial enrollment scheduled to be completed.

2011

Aug	ViP trial scheduled to end.

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1. In VIGOR, Vioxx 50 mg once daily (n=4,047) – a dose twice the highest recommended chronic dose – was compared to a common therapeutic dose of naproxen 500 mg twice daily (n=4,029) in patients with rheumatoid arthritis (median length of participation was nine months). The study assessed the incidence of serious GI events and the most serious, or "complicated," GI events, which included perforations, obstructions or major bleeding (PUB) in the upper GI tract. The study was designed to exclude patients requiring aspirin for cardioprotection.

In VIGOR, Vioxx 50 mg once daily significantly reduced the risk of serious GI events by 54 percent and the risk of complicated GI events by 57 percent compared to naproxen 500 mg twice daily. A total of 56 patients treated with Vioxx experienced a serious GI event compared to 121 patients taking naproxen, and a total of 16 patients receiving Vioxx had a complicated GI event versus 37 patients taking naproxen. In the study, the reduction in risk for serious and complicated GI events with Vioxx was maintained in patients both at high risk for developing a PUB and in patients without risk factors. Such

risk factors include: prior history of a PUB, age of 65 or older, *Helicobacter pylori* infectionor concomitant use of corticosteroids.

In VIGOR, a statistically significant higher incidence of serious cardiovascular thrombotic events was seen in patients receiving Vioxx 50 mg once daily compared to patients treated with naproxen 500 mg twice daily. A total of 45 serious cardiovascular thrombotic events occurred among 4,047 patients taking Vioxx compared to 19 among 4,029 taking naproxen. This was largely due to a difference in the incidence of non-fatal heart attacks: 18 for Vioxx and 4 for naproxen. The number of cardiovascular thrombotic deaths was similar in patients treated with Vioxx (n=7) compared to naproxen (n=6).

2. APPROVe was a multi-center, randomized, placebo-controlled, double-blind study to determine the effect of 156 weeks (3 years) of treatment with rofecoxib on the recurrence of adenomatous polyps of the large bowel in patients with a history of colorectal adenomas. The study included approximately 2600 patients aged 40-96; approximately 62% male. Aspirin was allowed in the study.

In APPROVe there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment for patients taking VIOXX as compared to placebo. Results for the first 18 months of the study did not show an increased risk of confirmed CV events on VIOXX and in this respect, the results are similar to the results of two prior placebo controlled studies described in the current U.S. labeling for VIOXX.

Merck followed the recommendation of the study's External Safety Monitoring Board and terminated this trial on September 30, 2004.

3. VICTOR was a randomized, double-blind, placebo-controlled, international, multicenter study of VIOXX in 7,000 colorectal cancer patients following potentially curative therapy. The primary hypothesis tested in the study was that VIOXX administered for two years will result in greater overall survival compared with placebo. CV events were monitored by the VICTOR trial investigators and Merck as part of the adverse events monitoring conducted as part of the study. The study was stopped on September 30, 2004.

4. ViP was a randomized, double-blind, placebo-controlled, multicenter study to evaluate the effects of VIOXX in decreasing the risk of prostate cancer. The study protocol called for 15,000 male patients, aged = 50 and = 75 years, with a life expectancy of greater than 6 years, with PSA = 2.5 ng/mL and = 10 ng/mL to be enrolled. The primary hypothesis to be tested in the study was that the risk of developing prostate cancer over six years of treatment will be lower in patients treated with VIOXX 25 mg/day than in patients treated with placebo; and that treatment with VIOXX would be generally safe and well tolerated. Cardiovascular adverse events were monitored by an external safety monitoring board as a part of the study. The trial was halted on September 30, 2004.

Forward-Looking Statement

This document contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the cautionary statements in Item 1 of Merck's Form 10-K for the year ended Dec. 31, 2003, and in its periodic reports on Form 10-Q and Form 8-K (if any) which the company incorporates by reference.

MERCK

Timeline of Epidemiological Studies Involving VIOXX or NSAIDs[1]

Jan 2002 — A retrospective cohort study by **Ray et al** is published in *The Lancet*. Objective was to measure the effects of non-aspirin NSAIDs, including naproxen, on risk of serious coronary heart disease (CHD). Study concludes that in a high-risk patient population of people 50 years and older, non-selective non-aspirin NSAIDs neither increased nor decreased risk of serious CHD. Analysis evaluated 6,362 cases from the Tennessee Medicaid program during 181,441 periods of new NSAID use in 128,002 people and the same number of periods of non-use of NSAIDs among 134,642 people.

May 2002 — Three separate case-control studies are published in *Archives of Internal Medicine*. Each showed that use of naproxen reduced the risk of heart attacks. These studies were first presented at the American College of Rheumatology meeting in 2001.

Solomon et al: Objective was to determine whether NSAIDs have a similar effect or whether they differ in their effects on the risk of acute myocardial infarction (AMI). Study concludes that the findings do not support a relationship between the use of NSAIDs as a group and risk of heart attacks. However, use of naproxen was associated with a significant reduction in the risk of AMI (adjusted odds ratio, 0.84; 95% confidence interval, 0.72-0.98; P =.03). Analysis evaluated 4,425 cases from the N.J. Medicare/ Medicaid Program against a control group of 17,700 subjects.

Watson, et al: Objective of the study was to examine the risk of acute thromboembolic cardiovascular events (heart attack, sudden death and stroke) with naproxen use among patients with rheumatoid arthritis. The study concludes that patients with rheumatoid arthritis and a current prescription for naproxen had a reduced risk of acute major thromboembolic CV events relative to those who did not take naproxen in the past year. Analysis evaluated 809 cases from British General Practice Research Database against a control group of 2,285 subjects. Study sponsored by Merck.

Rahme, et al: Objective of the study was to compare the effect of naproxen to other NSAIDs in the prevention of acute myocardial infarction (AMI) in an elderly population. The study concludes that compared to other NSAIDs, concurrent use of naproxen has a protective effect against AMI. Analysis evaluated 4,163 cases from Canadian RAMQ and Med-Echo databases against a control group of 14,160 subjects. Study sponsored by Merck.

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[1] **Editor's Note:** Timeline is not an exhaustive list of every study ever conducted to evaluate the safety of NSAIDs and COX-2 inhibitors; selected studies have been identified to illustrate the wide divergence of results from observational studies.

Oct 2002 A retrospective cohort study by **Ray et al** is published in *The Lancet*. Objective was to assess occurrence of serious coronary heart disease (CHD), specifically acute myocardial infarction (AMI) and cardiac death, in patients taking Vioxx, celecoxib or other NSAIDs. Study concludes use of Vioxx at doses greater than 25 mg could be associated with an increased risk of serious CHD; in contrast, there was no evidence of increased risk among users of Vioxx at doses of 25 mg or less, celecoxib, naproxen or ibuprofen. Analysis evaluated 5,316 events from the Tennessee Medicaid program among 251,046 NSAID users and 202,916 non-users.

Oct 2002 A database cohort analysis by **Levy et al** is presented at the American College of Rheumatology meeting. Objective was to assess the correlation between COX-2 use and heart attacks among persons prescribed a COX-2 inhibitor, ibuprofen, or naproxen for at least 50 consecutive days. Study concludes long-term use of either of the COX-2 inhibitors (Vioxx and celecoxib) separately is not associated with an increase risk of heart attack compared with naproxen or ibuprofen. When users of COX-2 inhibitors were combined, there was an increased risk compared with users of ibuprofen or naproxen combined. Analysis evaluated 645 events from the Kaiser Permanente database among 172,260 subjects.

Feb 2003 A population-based, retrospective cohort study by **Mamdani et al** is published in *Archives of Internal Medicine*. Objective was to compare the rates of acute myocardial infarction (AMI) among elderly patients taking COX-2 inhibitors, naproxen and non-aspirin NSAIDs. Study concludes no increased short-term risk of AMI among users of COX-2 inhibitors and no short-term reduced risk of AMI with naproxen. Analysis evaluated 701 events from administrative health care databases in Ontario among 66,964 users and 100,000 non-users.

Nov 2003 A case-control study by **Kimmel et al** is presented at the American Heart Association annual meeting. Objective was to determine the risk of nonfatal heart attacks in users of COX-2 inhibitors compared with users of non-aspirin NSAIDs. Study concludes there was no increased risk of heart attacks overall from COX-2 inhibitors, or from VIOXX separately and that nonselective, non-aspirin NSAIDs were associated with a reduced risk of heart attack. Analysis evaluated 1,718 cases against 6,800 controls from the Delaware Valley Case-Control Network. Study sponsored by Merck and Pharmacia.

Mar 2004 A population-based analysis by **Whelton et al** is presented at the American College of Cardiology meeting. Objective was to determine the risk of acute myocardial infarction (AMI) or stroke with Vioxx, celecoxib, and non-selective NSAIDs in hypertensive patients. Study concludes Vioxx significantly increases the risk of AMI or stroke compared with non-users of NSAIDS and there was no increased risk among users of celecoxib or non-selective NSAIDs. Analysis evaluated 3,723 users against 1,798 users from a private medical insurance healthcare claims database. Study sponsored by Pfizer.

Mar 2004 A case-control study by **Kimmel et al** is published in the *Journal of the American College of Cardiology*. Objective was to determine the risk of nonfatal heart attacks in users of non-selective, non-aspirin NSAIDs and the interaction between non-aspirin NSAIDs and aspirin. Study concludes non-selective, non-aspirin NSAIDs are associated with a reduced risk of heart attack. Analysis

evaluated 581 events from the Philadelphia community among 4,153 control subjects.

Apr 2004 A case-control study by **Solomon et al** is published in *Circulation*. Objective was to assess the risk of acute myocardial infarction (AMI) among users of Vioxx, celecoxib, and NSAIDs in an elderly population. Study concludes Vioxx all doses combined was associated with a significant increased risk of AMI compared to celecoxib. Non-significant differences were found comparing Vioxx to ibuprofen, naproxen, other NSAIDs and to those not taking NSAIDs. The risk was higher in persons taking greater than 25 mg of Vioxx and during the first 90 days of use but not thereafter. Analysis evaluated 10,895 cases from two state-sponsored pharmaceutical benefits program in the U.S. among 54,475 patients 65 years and older. This study was first presented at the American College of Rheumatology meeting in 2003. Study sponsored by Merck.

May 2004 A population-based retrospective cohort study by **Mamdani et al** is published in *The Lancet*. Objective was to compare the rates of admission for congestive heart failure (CHF) in elderly patients who were given COX-2 inhibitors or non-selective NSAIDs. Study concludes there is a higher risk of admission for CHF in users of Vioxx and non-selective NSAIDs (diclofenac, naproxen and ibuprofen) but not celecoxib in comparison to non-users of NSAIDs. Analysis evaluated 654 events from administrative healthcare databases in Ontario among 45,097 users of NSAIDs/COX-2 inhibitors and 100,000 non users.

June 2004 A cohort study by **Garcia Rodriguez et al** is published in *Circulation*. Objective was to estimate the effect of non-aspirin NSAIDs on the occurrence of AMI and death from CHD. Study concludes there was no risk reduction of NSAIDs on the occurrence of MI. Analysis evaluated 4,975 cases from the General Practice Research Database in the U.K. against a control of 20,000 subjects.

Aug 2004 A case-control study by **Graham et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to determine if NSAID use increases the risk of AMI or sudden cardiac death (SCD) and if the risk is similar among COX-2 selective agents. Study concludes Vioxx use at doses greater than 25 mg increases the risk of AMI and SCD; Vioxx at 25 mg or less had an increased risk compared with celecoxib; and that several other NSAIDs increased the risk of AMI and SCD. Analysis evaluated 8,199 cases from Kaiser Permanente against a control group of 32,796 subjects. Funding provided by FDA.

Aug 2004 A retrospective cohort study by **Rahme et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to assess the rates of hospitalizations for acute myocardial infarction (AMI) in an elderly cohort. 52,029 patients were taking non-selective NSAIDs and 71,543 patients were taking rofecoxib, with 14,056.4 and 37,371.0 person-years of exposure, respectively. Based on the regression model, the adjusted hazard ratios of hospitalizations for MI was 1.03 (0.83-1.27) for rofecoxib vs. ibuprofen/diclofenac. Study concludes there was no difference in the rate of hospitalizations for AMI among Vioxx and the non-selective NSAIDs ibuprofen and diclofenac. Study sponsored by Merck.

Aug 2004 A retrospective cohort study by **Shaya et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to examine the cardiovascular risk of COX-2 inhibitors compared to non-specific NSAIDS in a high risk Medicaid population. Analysis evaluated medical and prescription claims for Maryland Medicaid enrollees, COX-2 users numbered 1208 and non-naproxen NSAID users numbered 5274. Study concludes that COX-2 inhibitors did not increase cardiovascular risk over non-naproxen NSAIDs in a high risk population.

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Forward-Looking Statement

This document contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the cautionary statements in Item 1 of Merck's Form 10-K for the year ended Dec. 31, 2003, and in its periodic reports on Form 10-Q and Form 8-K (if any) which the company incorporates by reference.

RESPONSES TO QUESTIONS FROM SENATOR GRASSLEY

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January 31, 2005

VIA HAND DELIVERY

MERCK
Research Laboratories

The Honorable Charles E. Grassley
Chairman
United States Senate Committee on Finance
135 Hart Senate Office Building
Washington, DC 20510-6200

Re: Request to Merck & Co., Inc.

Dear Chairman Grassley:

In response to your request of December 22, 2004, Merck & Co., Inc. ("Merck") provides the following information and the enclosed documents. Since receiving your letter, Merck has been working diligently to obtain as much responsive information and documentation as possible. Our goal is to provide you with the information and documents requested within the time frame that you stated. However, to the extent we learn responsive information in addition to that stated below, or obtain responsive documents in addition to those enclosed, we will provide that information or documentation to you promptly. As with our previous responses and productions, we request that this letter and the enclosures be treated as confidential.

Request No. 1: On February 11, 2002, Dr. Scolnick wrote an email to Deborah Shapiro, which stated: "It is my understanding that you are the unblinded statistician in our Vigor study. In the last few days we are being pounded by stories like this. As with the key issue with aggrastat when Snappin and i [sic] had to make a decision as soon as you know what the answer is I would like a confidential meeting with you. This situation cannot simply follow the 'book' ways of my knowing. Please let me know when I can talk to you confidentially. I hope your lucky rabbit's foot is as good as it was with mevacor afcaps..." (Hearing exhibit 15).

(a) Please explain in detail what Dr. Scolnick was requesting from Ms. Shapiro in this email and what he was referring to when he said, "[t]his situation cannot simply follow the 'book' ways of my knowing."

(b) State Merck's position on whether any VIGOR protocol(s) or "book ways" were violated or breached during the course of the trial.

(c) Provide for the hearing record a copy of all documents, including but not limited to email communications(s), relating to Dr. Scolnick's request.

Response:

(a) As the full text of Dr. Scolnick's February 11, 2000 email--including the attached news reports--makes clear, Dr. Scolnick was interested in obtaining the gastrointestinal safety

data from the VIGOR trial as soon as possible at the study's conclusion, rather than simply waiting for the results to get to him through the normal internal communications processes. Under the unblinding procedures then in place for the VIGOR study, the first group to be unblinded to the data, after the last patient was out of the study, was to have been only the small group who was expected to be involved in writing up the study results and did not include Dr. Scolnick. In an email response to Dr. Scolnick that same day, Dr. Shapiro replied that patients were still being seen for their final visits in the VIGOR study, and that, until the study was unblinded to the first group on March 9, 2000, she was not permitted under the study protocol to discuss study results with anyone other than the members of the external Data Safety Monitoring Board. Dr. Scolnick then replied by email that he would attend (either in person or remotely) the first meeting at which Merck personnel were unblinded to the data.

(b) The protocol for the initial unblinding of the VIGOR study results proceeded as planned, with the initial group being unblinded and Dr. Scolnick being unblinded later that same day. To Merck's knowledge, there was no unscheduled unblinding of data prior to the scheduled initial unblinding.

(c) The complete email exchange between Dr. Scolnick and Dr. Shapiro is enclosed with this letter, Bates Nos. MRK-AAB0069335—MRK-AAB0069339. There is one reference to an attorney-client communication redacted in Dr. Shapiro's email.

Request No. 2: Mr. Gilmartin testified at the hearing that on the afternoon of September 24, 2004, Dr. Peter Kim called to alert him to information that he had received just that morning from an independent external board of physicians and scientists monitoring the safety of patients in Merck's APPROVe trial of Vioxx.

(a) State for the record whether any Merck employee, other than Merck's unblinded statistician, was aware of any of the cardiovascular adverse events that were discussed during the ESMB closed meeting minutes prior to September 23?

(b) State Merck's position on whether any APPROVe protocol(s) or "book ways" were violated or breached during the course of the trial.

(c) If any APPROVe protocol(s) or "book ways" were violated or breached during the course of the trial, describe in detail the events and person(s) involved and provide the Committee with all documents related to these events that will provide context for the hearing record.

Response:

(a) Dr. Hui Quan, the unblinded statistician, was the only Merck employee with knowledge of the unblinded cardiovascular safety data from APPROVe that were discussed during the ESMB closed meetings prior to September 23, 2004. Merck refers the Committee to the minutes of the External Safety Monitoring Board ("ESMB"), Bates Nos. MRK-S006590—MRK-S006624, for further information.

(b & c) To Merck's knowledge, there were no violations of the unblinding provisions of the APPROVe protocol.

Request No. 3: Identify for the record all members of all safety monitoring boards relating to Vioxx, specifically noting any member(s) who sat on more than one board. Please list the board members alphabetically and the boards on which they sat. In addition, describe each member's affiliation with Merck.

Response:

The voting members of the Data and Safety Monitoring Board ("DSMB") for VIGOR were:

David J. Bjorkman, M.D. – non-Merck employee

James Neaton, M.D. – non-Merck employee

Alan Silman, M.D. – non-Merck employee

Roger Sturrock, M.D. – non-Merck employee

Michael Weinblatt, MD. – non-Merck employee

The voting members of the External Safety Monitoring Board ("ESMB") for APPROVe were:

David J. Bjorkman, M.D. – non-Merck employee

Marvin Konstam, M.D. – non-Merck employee

Richard Logan, M.D. – non-Merck employee

James Neaton, M.D. – non-Merck employee

The ESMB for ViP and the Cardiovascular Outcomes study was to include the same members as APPROVe. Each DSMB or ESMB had a non-voting unblinded statistician reporting to it. The VICTOR study was run by Oxford University, which formed its own ESMB.

Request No. 4: Mr. Gilmartin testified at the hearing that it would not have been ethical or practical to subject people suffering from arthritic pain to a placebo for a long time.

a) State why, for example, a study of Vioxx vs. Tylenol was not feasible and/or ethical?

b) Did Merck ever consider conducting a case control trial, which would examine any new CV patient admitted to the hospital against a comparison group of patients who are admitted for another emergency, for example asthma, and record all the drugs these patients were taking?

Response:

(a) Merck believes that it would not have been feasible to conduct a long-term safety study of Vioxx vs. Tylenol in a population of patients suffering from chronic arthritic pain because Tylenol is not sufficiently effective in treating this type of chronic pain. For instance, arthritis is an inflammatory condition; however, Tylenol is not an anti-inflammatory drug. Merck therefore believed that the drop-out rate among patients in the Tylenol arm who required more effective relief from pain and inflammation would have made it difficult, if not impossible, to obtain meaningful long-term data from such a study.

Instead, in order to obtain additional cardiovascular data, Merck developed a protocol whereby it would prospectively analyze cardiovascular events in three placebo-controlled studies of Vioxx in the treatment and prevention of certain cancers. At the time Merck designed this protocol, the APPROVe study – one of the studies that would be included in the analysis – had been ongoing for over two years and had already been collecting data regarding cardiovascular events. The inclusion of ongoing studies in the analysis was an added advantage to this protocol design because it allowed Merck to obtain data more quickly than if it had to rely solely on newly instituted studies.

(b) Merck both considered and funded several epidemiological studies examining the cardiovascular safety of Vioxx, including both case-control and cohort study protocols. For example, Merck funded the case-control study published by Solomon, et al. in *Circulation*, and

the case control study published by Kimmel, et al. in the *Journal of the American College of Cardiology*. Merck also funded a study by Rahme, et al., which was published in abstract form and presented at the International Conference on Pharmacoepidemiology in August 2004, as well as the study performed by Ingenix, which has been submitted for publication. Copies of these published papers, abstracts, and/or final reports are enclosed, Bates Nos. MRK-S001509—MRK-S001576; MRK-S012988—MRK-S013000. Merck also refers the Committee to its prepared chronology of relevant epidemiological studies at Bates Nos. MRK-S006782—MRK-S006786.

Even well-designed epidemiological studies have inherent limitations in their design, including, among others, the impossibility of controlling for all confounding factors. The results from such studies, therefore, must be interpreted with caution. As a result, when both epidemiological data and data from randomized clinical trials are available, the data from randomized clinical trials provide the most reliable evidence. This is especially true when, as was the case with the epidemiological studies concerning the cardiovascular safety of Vioxx, the results are inconsistent and conflicting. Merck funded numerous randomized clinical trials that provided data regarding the cardiovascular safety profile of Vioxx. Prior to APPROVe -- which was also funded by Merck -- data from randomized clinical trials involving more than 32,000 patients showed similar cardiovascular risk with Vioxx and placebo or NSAIDs other than naproxen.

Request No. 5: Dr. Psaty commented at the hearing that drug companies make commitments for post-marketing studies and that reportedly only about 40 percent of these ever get started, much less completed or published. Has Merck made any commitments for post-marketing studies since January 1, 1999? Please identify all drugs for which Merck made post-marketing study commitments and for each study state when it was initiated, completed and/or published.

Response: Merck has made commitments for numerous post-marketing clinical studies as a condition of approval with respect to many of its medicines and has worked diligently to fulfill those requests. Merck would be willing to discuss with the Committee additional information regarding those commitments. With regard to Vioxx, the FDA agreed to defer the requirement for conducting pediatric studies as part of the initial approval of Vioxx. Merck subsequently completed this requirement by studying Vioxx in patients with juvenile rheumatoid arthritis. Merck submitted a supplemental NDA in December, 2003 that included these studies, and the FDA approved an indication for Vioxx relating to juvenile rheumatoid arthritis in 2004. Merck also made a commitment to study Vioxx for migraine treatment in pediatric patients aged 12 to 17 in connection with Vioxx's approval in 2004 for an indication relating to the acute

treatment of migraines. The study will not be initiated due to Merck's voluntary withdrawal of Vioxx from the market.

Request No. 6: Mr. Gilmartin testified that it was not possible to make a determination based on the VIGOR study alone whether naproxen was having a beneficial cardiovascular effect or whether Vioxx was having a detrimental CV effect.

(a) Describe in detail when and how Mr. Gilmartin was first made aware about Merck's naproxen theory, i.e., the aspirin-like effect of naproxen, which Mr. Gilmartin testified was based on the weight of evidence that naproxen had a lower rate. And explain in detail why "that was [Merck's] conclusion then, and that is [Merck's] conclusion today."

(b) If Merck believed firmly in the naproxen cardioprotective hypothesis, why did it not do any clinical trials to prove or disprove it?

(c) Dr. Psaty testified at the hearing that "the best available evidence suggests that Vioxx was primarily responsible for the 500 percent increase in risk, and if naproxen had the full anti-platelet effect of aspirin, Vioxx would be expected to increase the risk by about 380 percent." After the VIGOR study results came out Merck consulted a number of experts, including Carlo Patrono (hearing exhibit 15, MRK-ABD0001986) who also said naproxen's "cardio-protective" effects were speculative and could not explain the result because even low dose aspirin would not have caused such a large difference in MI rate as was found in VIGOR. Describe in detail who Merck consulted with about naproxen's "cardio-protective" benefit and state the answer Merck received.

Response:

(a) Mr. Gilmartin learned of the naproxen hypothesis in March 2000. At the time of Mr. Gilmartin's testimony, Merck's conclusion that the cardiovascular results of the VIGOR trial were best explained by a cardioprotective effect of naproxen was based on scientific evidence from several sources, a number of which are listed below. First, prior to APPROVe, the data from across Vioxx's clinical development program, including data from two large placebo-controlled randomized clinical trials in Alzheimer's patients, showed similar risk with Vioxx and placebo or non-naproxen NSAIDs. The increased risk was seen only when Vioxx was compared to naproxen. Second, aspirin is believed to have cardioprotective effects because of its inhibition of platelet aggregation. Data from pharmacological studies of naproxen and other NSAIDs showed that naproxen inhibited platelet aggregation in excess of 90% throughout its entire dosing interval. This sustained level of platelet inhibition meant that naproxen, when taken twice a day as it was in the VIGOR study, could have cardioprotective effects. Third, other non-

selective NSAIDs, specifically flurbiprofen and indobufen, had been shown in clinical trials to have cardioprotective effects.

After the VIGOR trial was unblinded, the FDA asked Merck to study a potential thrombotic effect of Vioxx in an animal model of vascular injury, and Merck conducted this study with African Green monkeys. There was no significant effect on clotting after vascular injury seen in monkeys treated with Vioxx, but it took monkeys treated with naproxen a significantly longer time to clot after vascular injury, a result similar to that seen in monkeys treated with aspirin. This further suggested that naproxen had anti-thrombotic properties similar to aspirin.

Data from more recent studies continued to support this conclusion. For example, a recent study by Capone et al. published in *Circulation* confirmed the ability of naproxen to inhibit platelets at a level similar to aspirin. (Bates Nos. MRK-S013001—MRK-S013004.) Also, data from a clinical trial of another COX-2 selective inhibitor, lumaricoxib, shed additional light on this issue. That trial—the TARGET study—was designed to assess GI outcomes but, as a secondary objective, compared lumaricoxib against both ibuprofen and naproxen for cardiovascular morbidity and mortality. When compared against ibuprofen, lumaricoxib did not show a statistically significant difference in the relative risk of cardiovascular events. However, when compared against naproxen, the data, although not statistically significant, suggested that naproxen lowered the rate of cardiovascular events. (Bates Nos. MRK-S013005—MRK-S013014.)

Merck is also aware that, after Mr. Gilmartin testified, there was publicity surrounding cardiovascular events from clinical trials involving other COX-2 selective inhibitors, including one such trial that also involved naproxen at a lower dose than that used in the Merck clinical trials. Because the data have not been made publicly available, Merck has not yet had the opportunity to analyze these data or draw any conclusions from them.

(b) While Merck believed firmly in the naproxen hypothesis, Merck also believed that the most important issue for it to continue to study clinically was the safety of its own medicine, Vioxx. Merck therefore continued to analyze Vioxx's safety, including its cardiovascular safety, primarily through clinical trials, throughout the entire time that Vioxx was on the market.

(c) Merck disagrees with Dr. Psaty's interpretation of the VIGOR results. The confidence intervals around the reduction in cardiovascular events seen in the naproxen arm of the VIGOR study overlap with the risk reduction seen in aspirin trials. Put another way, when the effects of chance are taken into account, the reduction in cardiovascular events seen in the naproxen arm of the VIGOR trial is consistent with the reduction in the cardiovascular events

seen in aspirin trials. Moreover, studies have suggested that aspirin, as well as the NSAIDs flurbiprofen and indobufen, have a larger relative benefit in higher risk patients. The patients in VIGOR all had rheumatoid arthritis which is a recognized high-risk group for experiencing cardiovascular events, and is also a group with high levels of C-reactive protein, a known marker for increased cardiovascular risk.

Merck discussed the VIGOR results with numerous outside scientists and physicians in order to assist in the analysis of the data. These individuals included Dr. Carlo Patrono. As the email cited in this request indicates, Dr. Patrono's initial interpretation of the cardiovascular results of VIGOR was that the disparity in events was due to chance; he did not believe that a cardioprotective effect of naproxen could, on its own, account for the decreased rate of events or that Vioxx increased the rate. Dr. Patrono later came to believe that the results of VIGOR could be explained by a combination of a cardioprotective effect of naproxen and chance. This view is expressed in a review article that he published with Dr. Colin Baigent in 2003 in *Arthritis & Rheumatism*, a copy of which is enclosed, Bates Nos. MRK-S013015—MRK-S013023. Dr. Patrono also participated in the study with Dr. Capone, referenced above, which confirmed that naproxen inhibited platelets at a level similar to aspirin throughout its dosing interval, Bates Nos. MRK-S013001 – MRK-S013004.

As part of its numerous consultations with outside scientists and physicians, Merck held three meetings with outside scientists and physicians in the Fall 2000. The participants are listed in the documents enclosed. Copies of documents relating to those three meetings are enclosed, Bates Nos. MRK-YAD0000001 -- 0000603.

Request No. 7: Dr. Psaty testified at the hearing that if he knew what Merck scientists knew about Vioxx in 1998, he would have recommended a "complete, symmetrical, and fair evaluation of the hypothesized GI benefits and risks." Did Merck conduct such an evaluation or analysis? Please explain in detail why Merck did or did not conduct an evaluation or analysis as Dr. Psaty described on the GI benefit versus the risk of Vioxx.

Request No. 8: Dr. Singh questioned at the hearing why it was efficacious to trade a five-fold increase in heart attacks for half the risk of GI complications. State whether Merck took into account this risk/benefit ratio and describe how Merck's actions adequately reflected this risk/benefit ratio?

Response: In order to respond more fully to both Request Nos. 7 and 8, Merck's response to both Requests is detailed below.

As an initial matter, it is unclear what Dr. Psaty is contending Merck should have done differently. Throughout the development of Vioxx, Merck -- in conjunction with the FDA -- continually evaluated the full safety profile of Vioxx, including its risks and benefits, in a large diverse group of patients. This evaluation was not only performed prior to submitting the NDA to the FDA in November 1998, but was also conducted during the entire time that Vioxx was on the market.

At the time of the NDA submission, Vioxx had been studied in a diverse population that included more than 5,000 patients with osteoarthritis. Moreover, as part of this original NDA submission, Merck provided the FDA with an Integrated Summary of Safety as well as an Integrated Summary of Efficacy that provided a systematic evaluation of the risks and benefits of Vioxx. To assist it in the evaluation of the risk/benefit profile of Vioxx, the FDA convened a public Advisory Committee that examined that issue and recommended the approval of Vioxx. Ultimately, as a result of the weighing of both the benefits and the risks of Vioxx, the FDA approved Vioxx for marketing and approved prescribing information that adequately disclosed its risks and benefits.

With regard to Dr. Singh's characterization of the data concerning Vioxx, it appears as though Dr. Singh is referring to the VIGOR trial. Merck disagrees with Dr. Singh's characterization of these data. As described above, the data from across the clinical development program of Vioxx showed similar cardiovascular risk with Vioxx and placebo or NSAIDs other than naproxen. The increased risk compared to naproxen was best explained by a cardioprotective effect of naproxen. In contrast, Vioxx was clinically proven to reduce the risk of serious and potentially fatal gastrointestinal perforations, ulcers, and bleeds.

Merck disclosed the results of VIGOR to the FDA, the medical community and the press. As part of its supplemental NDA, Merck again provided the FDA with an Integrated Summary of Safety, which evaluated the safety profile of Vioxx, including the VIGOR data. The FDA again convened a public Advisory Committee to examine the new data as part of the process that resulted in an updated label for Vioxx. This label included both the gastrointestinal and cardiovascular data from the VIGOR study, the cardiovascular data from Merck's large placebo-controlled studies in the Alzheimer's Disease program, and a new precaution stating that "caution should be exercised" when using Vioxx "in patients with a medical history of ischemic heart disease." However, the evaluation of the risks and benefits of Vioxx were not confined to those documents or time periods. Instead, Merck continued to study Vioxx and monitor the information it received. Merck continued to weigh the benefits and risks of Vioxx and consistently provided such information to the FDA as part of various submissions such as those described above as well as in the enclosed Safety Update Reports to the Integrated Summaries of

Safety (Bates Nos. MRK-EC.1SUR 000001—MRK-EC.1SUR011669), the Annual Reports to the NDA for Vioxx (Bates Nos. MRK-EC.1AR000001—MRK-EC.1AR006823), Periodic Safety Update Reports (Bates Nos. MRK-EC.1SUR011670—MRK-EC.1SUR020740), Summary Sections of Periodic Adverse Drug Experience Reports (Bates Nos. MRK-ECPAER00001—MRK-ECPAER01549), and the cardiovascular pooled analysis submitted January 8, 2001 (Bates Nos. MRK-I8940064858—MRK-I8940064921) and updated July 12, 2001 (Bates Nos. MRK-01420145847—MRK-01420145961), May 22, 2002 (Bates Nos. MRK-S0420000030—MRK-S0420000072) and March 22, 2004 (Bates Nos. MRK-S013024—MRK-S013095), among other items. These documents provide a more detailed description of Merck's analysis of the benefits and risks of Vioxx.

Request No. 9: Dr. Singh testified that a memo written in 1996 by Dr. Tom Musliner, a Merck scientist, discussed the trade-off of stomach bleeds and heart attacks. He also mentioned a series of internal Merck emails during February 1997, which addressed Vioxx study design questions related to GI benefit versus CV risk, specifically the loss of a GI benefit by adding aspirin to reduce the CV risk. Please explain in detail and provide context to the documents and statements Dr. Singh referred to in his testimony. Provide for the hearing record a copy of all documents, including email communications related to the GI benefit versus CV risk of Vioxx.

Response: Merck strongly disagrees with the characterization of these documents. The 1996 memo written by Dr. Musliner, Bates Nos. MRK-GUE0021986—MRK-GUE0021993, was an analysis of the reduction in cardiovascular events that might occur in a group of patients treated regularly with non-selective NSAIDs. Dr. Musliner specifically states that one of his assumptions in connection with this analysis is that "Patients treated with the selective Cox-2 inhibitor will experience neither a reduction nor an increase in CV events associated with this therapy." In other words, Dr. Musliner was saying that if one compared Vioxx, which was thought to be neutral with respect to cardiovascular events, with certain non-selective NSAIDs, which were assumed based upon limited clinical data to be cardioprotective when taken regularly, then one would see a decrease in the number of cardiovascular events in the patient population taking the non-selective NSAID purely because of the cardioprotective effect of the non-selective NSAID. Dr. Musliner's memorandum has nothing to do with any alleged cardiovascular risk associated with Vioxx.

The 1997 emails concerning the design of a gastrointestinal outcomes study with Vioxx, Bates Nos. MRK-AAD0089672—MRK-AAD0089674, reflect considerations by Merck scientists about whether or not to allow low-dose aspirin in such a study. Low-dose aspirin was known to inhibit COX-1. Allowing it in a gastrointestinal outcomes study could therefore confound the ability to test the hypothesis that a COX-2 selective inhibitor would have an

improved gastrointestinal safety profile compared to a non-selective inhibitor of COX-1 and COX-2. However, Merck scientists also recognized, as discussed in the 1996 memorandum from Dr. Musliner, that patients taking a non-selective NSAID would have a cardioprotective benefit and therefore could have a reduced rate of cardiovascular events. On the other hand, patients taking Vioxx would not have this reduced rate because Merck scientists thought that Vioxx would be neutral on cardiovascular events. This potential difference that might therefore be seen in a trial comparing Vioxx to a non-selective NSAID where no aspirin was allowed could be misinterpreted as an indication that Vioxx increased cardiovascular risk.

Finally, as stated above, the gastrointestinal and cardiovascular safety profile of Vioxx is reflected in Merck's submissions to the FDA discussed in the response to Request Nos. 7 and 8. Please advise whether there are any additional documents you would like for us to produce in response to this request.

Request No. 10: Please state whether any concerns or issues relating to Vioxx were raised by any Merck employee or agent to Merck's Office of Ethics and/or Ombudsman office? In responding to this question, the relevant time period should include both before and after Vioxx was approved by the FDA. Concern(s) relating to Vioxx should include, but are not limited to concern(s) and/or allegations relating to the research, development, marketing, and safety of Vioxx. If concerns were raised, provide for the hearing record a copy of all documents related to the concerns or issues.

Response: Merck is providing along with this letter certain documents related to this Request. These documents provide in summary form the reports regarding the research, development, marketing and safety of Vioxx that are responsive to this Request, along with information concerning the investigation undertaken and the final outcome. Because of privacy concerns, the identity of the person making the report, as well as other persons involved in the investigation, other than the investigator from the Office of Ethics, has been redacted. These documents can be found at Bates Nos. MRK-S013451 – MRK-S013467.

Request No. 11: According to Dr. Eric J. Topol, the Chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic, there were 2 randomized, controlled trials of Vioxx that show statistically significant excess of death, heart attack, and stroke compared with control, which were submitted in Supplement 007 of the Vioxx NDA available in year 2000. Study 090 showed a 760% excess that was statistically significant and VIGOR showed a 190% excess that was statistically significant.

(a) State whether these two trials show independent replication of a cardiovascular risk in 2000.

(b) State whether Merck conducted a statistical analysis of study 090 relating to excess deaths, heart attacks and strokes. Please state yes or no and provide a detailed explanation stating why or why not.

(c) State whether study 090 was published. Please state yes or no and provide a detailed explanation stating why or why not.

Response: To more fully and concisely respond to this Request, Merck's response to all of the subparts is detailed below.

Merck disagrees with Dr. Topol's characterization of the data as outlined in this request. As described more fully above, Merck believed that the disparity in cardiovascular events seen in VIGOR was best explained by a cardioprotective effect of naproxen and did not demonstrate a cardiovascular risk of Vioxx. Study 090 was one of many small studies that Merck conducted as part of Vioxx's clinical development program. In that particular study, Vioxx was compared to placebo and the non-selective NSAID nabumetone. This Request seeks information about deaths, heart attacks and strokes. Merck analyzed these events by using the APTC (Anti-Platelet Trialists' Collaboration) endpoint, which is comprised of unexplained and cardiac deaths, myocardial infarctions and cerebrovascular accidents. Using that endpoint, there were four events in the Vioxx arm of Study 090, zero events in the placebo arm, and one in the nabumetone arm. The number of these events in the Vioxx arm is not statistically significant when compared to the number of events in the placebo arm, nor is the number of events in the Vioxx arm statistically significant when compared to the nabumetone arm. Merck also conducted analyses using the broader endpoint of thromboembolic cardiovascular serious adverse events. Using this endpoint, there were five events in the Vioxx arm of Study 090, zero in the placebo arm, and one in the nabumetone arm. Again, the number of these events in the Vioxx arm is not statistically significant when compared to the number of events in the placebo arm, nor is the number of events in the Vioxx arm statistically significant when compared to the nabumetone arm.

In general, it is not scientifically proper to draw conclusions from small numbers of events that occur in small studies such as Study 090. For example, study 085, another small study identical in design to study 090 comparing Vioxx, placebo and nabumetone showed only one APTC event on Vioxx, zero on placebo, and zero on nabumetone. Moreover, other small studies of Vioxx, such as protocols 033 and 045, have shown fewer events on Vioxx than on comparators, but scientists do not conclude from those studies that Vioxx prevents cardiovascular events. The best way to consider these data is in a pooled analysis with other studies. Merck did that pooled analysis using the APTC endpoint, and it found using data from across clinical trials of Vioxx that there was no increased risk with Vioxx compared to placebo or the non-naproxen NSAIDs ibuprofen, diclofenac and nabumetone. See Bates Nos. MRK-

I8940064858—MRK-I8940064921; MRK-01420145847—MRK-01420145961; MRK-S0420000030—MRK-S0420000072; MRK-S013024—MRK-S013095.

Dr. Topol himself recognized the limitations of drawing any conclusions from small studies like Study 090 when he discussed that study and study 085 in an article published in *JAMA* in August 2001, Bates Nos. MRK-S013096—MRK-S013101. As that article stated:

> Two smaller studies (Study 085 and Study 090) of rofecoxib that both allowed the use of low-dose aspirin did not demonstrate the significant increase in cardiovascular event rate noted in VIGOR. However, these studies had smaller sample sizes, used only 25% of the dose of rofecoxib used in VIGOR, and had few events for meaningful comparison.

Merck completed a Clinical Study Report analyzing the results of Study 090 and included this analysis as part of its submission of the VIGOR supplemental NDA to the FDA. This was also part of the materials presented to the public Advisory Committee that the FDA convened to discuss the sNDA. Bates Nos. MRK-S007061—MRK-S007065.

In addition to the disclosure of the results—including the cardiovascular results described above—to the FDA and the consideration of the cardiovascular results from Study 090 at the public Advisory Committee, these data were included in the pooled analysis of cardiovascular data from Vioxx clinical trials published by Konstam et al. in *Circulation* in October 2001, Bates Nos. MRK-S013102—MRK-S013110. A subset of data (which did not include the non-statistically significant cardiovascular data described above) from Study 090 was also published in abstract form in 2001 as part of a poster presentation at a meeting of the American Geriatric Society. A similar subset of data related to the combined analysis of Study 085 and 090 was presented at the following meetings in 2003: EULAR, Pain in Europe, Osteoarthritis Research Society International, Clinical & Economic Aspects of Osteoporosis and Osteoarthritis, and in 2004 at the American Geriatric Society.

Request No. 12: According to the VIGOR DSMB meeting minutes, dated November 18, 1999 (hearing exhibit 12, MRK-GUE0035229), the DSMB raised the issue of "excess of deaths and cardiovascular adverse experiences" and "increased occurrence of hypertension."

(a) To what extent was Merck aware of cardiovascular adverse experiences? State who was made aware and when.

(b) State whether Merck notified the FDA and what action, if any, was taken by Merck and/or the FDA.

(c) State why was the trial was not unblinded and why the trial was not terminated.

(d) State why the DSMB's concern about "excess of deaths and cardiovascular adverse experiences" was not mentioned in the New England Journal of Medicine report in November 2000.

Response:

(a) Prior to the unblinding of the VIGOR results on March 9, 2000, the Merck unblinded statistician who reported to the Data Safety Monitoring Board, Dr. Deborah Shapiro, was the only Merck employee who was aware of the unblinded VIGOR data.

(b) Merck notified the FDA promptly after learning the VIGOR results for the first time in March 2000. Merck called the FDA with the results on March 22, 2000, and followed up immediately thereafter in writing. Merck took action in several ways after learning the results. First, Merck carefully analyzed the VIGOR data, the data from other clinical studies of Vioxx including data from two large ongoing placebo-controlled Alzheimer's trials, and data from studies of naproxen and other NSAIDs. As described above, this analysis led Merck to the conclusion that the best explanation for the disparity in cardiovascular events seen in VIGOR was a cardioprotective effect of naproxen at the dose used in VIGOR. Second, Merck disclosed the results to the medical community. In addition to the March 22, 2000 disclosure to the FDA, Merck issued a press release describing the results on March 27, 2000 (Bates Nos. MRK-PRL0000114—MRK-PRL0000115), presented the results at a scientific conference in May 2000 (see Bates Nos. MRK-ERN0173851 – MRK-ERN0173852), and submitted the study to the *New England Journal of Medicine* in May 2000. The study was published in the *NEJM* in November 2000. Third, Merck drafted new proposed labeling for Vioxx, which incorporated the VIGOR results, and submitted that labeling to the FDA in June 2000. Following that submission, Merck continued to work with the FDA to analyze these results and continued to provide additional information to the FDA regarding them. Additional actions taken by Merck included the ongoing study of the cardiovascular safety of Vioxx, the design of a protocol to analyze the cardiovascular safety of Vioxx against placebo in a prospective manner, meetings with outside advisors to assist in the interpretation of VIGOR's results, and responding to FDA's requests for more analyses and data to assist in the drafting of the revised labeling for Vioxx. These actions are described in more detail in response to other requests in this letter.

(c) As referenced in the minutes from meetings of the Data Safety Monitoring Board, the DSMB elected not to stop the VIGOR trial because the numbers of cardiovascular events and deaths that they were seeing were small. It appeared to the DSMB that it was possible that the disparity in the numbers of events could be explained by a cardioprotective effect of naproxen. The minutes of the DSMB can be found at Bates Nos. MRK-EC051713—MRK-EC051722. Dr. James Neaton also addressed this question at the February 2001 Advisory Committee meeting. (Tr. at 77-81)

(d) Merck disagrees with the premise of this Request. The rates of cardiovascular events and cardiovascular deaths were discussed several times in the November 2000 *New England Journal of Medicine* article, Bates Nos. MRK-S013111—MRK-S013119. As noted on page 1523 of the article, there was not a significant difference in the rate of cardiovascular deaths in the Vioxx group compared to the naproxen group.

Request No. 13: Mr. Gilmartin testified that Merck promptly disclosed the results of numerous Merck-sponsored studies to the FDA, physicians, the scientific community, and the public, and participated in a balanced discussion of Vioxx's risks and benefits.

(a) Merck first became aware of a heart attack trade-off with Vioxx in 1996. Even if it was a theoretical concern then, why didn't Merck disclose this information to the FDA, physicians, the scientific community, and the public? As more evidence started accumulating through 1997-99, why didn't Merck disclose this information?

(b) Describe in detail what VIGOR data Merck publicly presented in May 2000, including all documents made publicly available, such as poster presentations at meetings and/or conferences.

(c) Mr. Gilmartin testified that Merck submitted the "initial" VIGOR results to the New England Journal of Medicine. However, the November 2000 New England Journal of Medicine publication was only a preliminary publication. Why did Merck not state that it was only a preliminary publication with only "initial" data results?

(d) Is it common practice for Merck to only publish preliminary or "initial" data results?

(e) How many times in the past five years has Merck published only "initial" drug data results without noting it was only "initial" data results?

(f) Why were hypertension and heart failure data not disclosed? Is it appropriate to publish only favorable drug data when unfavorable drug data were available from the same study?

(g) Merck published a Vioxx meta-analysis. Why was the underlying data for the meta-analysis never published? Explain why the Doug Watson analysis done in 1998 was not published?

(h) It appears that Merck does not always "promptly disclose the results of Merck-sponsored studies," because, as Mr. Gilmartin testified, the data must be fully analyzed before Merck submits them for publication. How can Merck say it encourages healthy scientific debate when, for example, the data showing CV risk in VIGOR as well as the Ingenix study results were not promptly and readily available to the scientific community and/or the FDA?

Response:

(a) Merck objects to the characterization of Vioxx having a "heart attack trade off" as stated in the Request. Instead, as discussed above, the hypothesis that Merck was aware of in 1996, which was based upon information in the public domain, was that non-selective NSAIDs, when taken regularly as they would be in a clinical trial, could reduce the rate of cardiovascular events, and that Vioxx, which was a selective COX-2 inhibitor, would not have this effect. That is, Vioxx as a selective COX-2 inhibitor would not be any different than placebo in regard to cardioprotective effect. In 1997, Merck learned of data from a Merck-sponsored study relating to the level of prostacyclin and thromboxane metabolites in the urine of patients given Vioxx and certain non-selective NSAIDs. These data led some scientists to hypothesize that COX-2 selective inhibitors might have the potential to be prothrombotic. Merck disclosed this hypothesis to the FDA when it submitted its NDA in November 1998, Bates Nos. MRK-ECNDA0001—MRK-ECNDA0723, and the study data were submitted to the FDA. This study was published in the *Journal of Pharmacology and Experimental Therapeutics* in 1999, Bates Nos. MRK-S013444 – MRK-S013450, and the article also disclosed the hypothesis. Moreover, prior to submitting the New Drug Application to the FDA, Merck carefully analyzed the cardiovascular event rates in its clinical trials and found no evidence to support the hypothesis.

(b) In May 2000, Merck presented the available VIGOR gastrointestinal and cardiovascular data at the Digestive Disease Week scientific conference. (Bates No. MRK-ERN0173851 – MRK-ERN0173852) Merck had already provided preliminary VIGOR data to the FDA in March 2000, and issued a press release regarding the study results that same month. Merck also submitted the VIGOR study for publication to the *New England Journal of Medicine*

in May 2000, and the study was ultimately published in November 2000. The results of the VIGOR study were widely covered by the media and well known in the medical community, and have continued to be a subject of public scientific debate.

(c, d & e) Merck disagrees with the characterizations contained in this Request. Merck believed that VIGOR was an important study and Merck wanted to disseminate the results of the study to the medical community as quickly as possible. One of the ways Merck sought to do this was through prompt publication in the *New England Journal of Medicine*. The VIGOR study close-out guidelines prespecified a primary analysis based upon reported events as of a certain date which was, in fact, completed prior to and used for the submission to the *New England Journal of Medicine* in May 2000, and for the sNDA submission to the FDA in June 2000. The close-out guidelines also specified that additional data would continue to be collected, analyzed and submitted to FDA. Moreover, the vast majority of the data had been collected and analyzed at the time the study was submitted to the *NEJM*. Only a small number of events remained to be adjudicated by an external adjudication committee. While the final adjudications changed the precise event counts from those available at the time of the submission to the journal in May, the changes were small and did not change interpretation of the results of the trial. Large outcomes trials often provide important, new information to the medical community. Merck believes that it is important to disseminate those data to the medical community promptly through publication in peer-reviewed journals, and has on certain occasions sought to publish such papers based upon the analyses of available data, before all additional data from a study has been collected and analyzed, in order to meet that goal. Where it has done so, Merck has continued to collect and verify those additional data and has, as was done with VIGOR, submitted any further data to the FDA.

(f) Information concerning hypertension were published in the *New England Journal of Medicine*. The article stated that, based on analysis of trial data, there was no association between hypertension and myocardial infarction in VIGOR. Merck also promptly disclosed the hypertension data to the FDA. Moreover, hypertension is a known effect of all NSAIDs, this information was included in Vioxx's label from the time it was first marketed, and the hypertension results of VIGOR were similar to what was contained in the label for the 50mg dose studied in VIGOR.

(g) From the time Merck adopted its cardiovascular standard operating procedure for Vioxx in 1998, Merck planned to analyze the cardiovascular data from its clinical trials through a statistically rigorous pooling of data from Vioxx trials. As is standard practice in the publication of articles in scientific and medical journals, Merck published the data from its pooled analysis in various tables and discussed various analyses of the data in the article. (Konstam, et al, Bates

Nos. MRK-S013102—MRK-S013110.) Portions of these data were published in other journals as well. For example, Reicin et al., published an analysis of the cardiovascular events across the 8 Phase IIb/III osteoarthritis trials of Vioxx. (Reicin, et al., Bates Nos. MRK-S013120—MRK-S013125.) Weir, et al. published a review of the data concerning the cardiovascular safety of Vioxx, which included an updated pooled analysis. (Weir, et al., Bates Nos. MRK-S013126—MRK-S013139.) The much more voluminous tables of data underlying the pooled analysis were submitted to the FDA and updated on several occasions. (Bates Nos. MRK-I8940064858—MRK-I8940064921; MRK-01420145847—MRK-01420145961; MRK-S0420000030—MRK-S0420000072; MRK-S013024—MRK-S013095.)

As part of Merck's response to the Vioxx hypothesis described above in response to Request 13(a), the 1998 Watson analysis looked at blinded cardiovascular data from ongoing trials of Vioxx on a pooled basis across all treatment groups in those trials and compared it to cardiovascular data from the placebo arms of clinical trials of other drugs. The analysis did not detect a signal of an increased cardiovascular risk in its ongoing clinical trials. In light of the fact that this type of analysis has well recognized limitations, is primarily done to help understand event rates observed in blinded trials prior to unblinding the data, and the fact that it showed no signal of an increased risk, Merck did not believe that publication would add meaningfully to the scientific literature at that time. Rather, Merck provided the unblinded results to FDA as part of its NDA for Vioxx and published the unblinded results as described in the preceding paragraph. In addition, as further described above in response to Request 13(a), Merck disclosed the underlying hypothesis to the FDA and published the study in which that hypothesis was set forth in the scientific literature.

(h) Merck disagrees with the premise of this Request. While it is true that data must be analyzed before it is submitted for publication, Merck disagrees that this scientific practice prevents Merck from promptly disclosing the results of its studies. Contrary to the suggestion contained in this Request, Merck promptly disclosed the results from VIGOR once the data were unblinded. As described above, Merck issued a press release concerning the VIGOR results within weeks of first learning about them, disclosed them to the FDA that same month, and promptly presented them at scientific conferences and published them in the *New England Journal of Medicine*. Merck believes that these prompt disclosures did encourage healthy scientific debate about the cardiovascular safety of Vioxx.

With respect to the Ingenix study, Merck disclosed the study to the FDA once the data were final. Merck does not believe that an earlier disclosure of non-final data from this study would have added meaningfully to the ongoing scientific debate about the cardiovascular safety

of Vioxx, in light of the fact that a substantial body of inconsistent epidemiological literature already existed on this topic, as discussed above.

Request No. 14: State why Merck asserts that it takes 18 months for heart attacks and strokes to occur on Vioxx when there are two trials – 090 in 6 weeks and VIGOR with event curve separation by 30 days – showing early risk of heart attack and strokes.

Response: Merck disagrees with this interpretation of VIGOR and Study 090. Merck has stated that the preliminary results of the APPROVe trial show no increased risk on Vioxx compared to placebo for the first 18 months of treatment, and that these results are consistent with prior large placebo-controlled randomized clinical trials of Vioxx. In fact, statistical analysis demonstrates that there is a significant change in relative risk over time in APPROVe. Merck's conclusions as to the best scientific interpretation of the VIGOR study, which did not compare Vioxx to placebo, and Study 090 are described in responses to previous Requests.

Request No. 15: The APPROVe trial was not designed to assess safety. Why do Merck press releases and advertisements continue to say otherwise?

Response: Merck disagrees with the premise of this Request. The APPROVe trial was in fact designed to assess safety. In addition to examining the potential benefit of Vioxx in preventing the recurrence of adenomatous colon polyps, the APPROVe protocol always was designed for the collection of adverse events (including cardiovascular adverse events) occurring during the course of the study, and potential thrombotic cardiovascular events were always subject to adjudication. Moreover, APPROVe was also one of three large placebo-controlled trials included in a combined protocol specifically designed to examine the cardiovascular safety of Vioxx compared to placebo in a pre-specified manner.

Request No. 16: Mr. Gilmartin testified that when researchers published articles or gave speeches that presented misleading or inaccurate information about Vioxx, Merck sought to set the record straight about a medicine that provided significant benefits to patients. Mr. Gilmartin also testified that a careful and complete examination of Merck's conduct shows that at all times Merck acted responsibly and in a manner consistent with Merck's commitment to patient safety and to Merck's rigorous adherence to scientific investigation, openness and integrity. Dr. Singh testified at the hearing to events related to hearing exhibit 26, a letter written by Stanford University to Merck. State in detail the events and circumstances related to the Stanford letter, including an explanation and context for all documents produced to the Committee related to the Stanford letter. Identify for the Committee all documents responsive to this request.

Response: When Dr. James Fries of Stanford wrote to Mr. Gilmartin in January 2001, Merck took Dr. Fries's statements very seriously, and conducted a prompt investigation. Mr. Gilmartin also sent a reply to Dr. Fries, which underscored Merck's commitment to free and open scientific debate. (Bates Nos. MRK-S006814—MRK-S006815.) Please refer generally to Bates Nos. MRK-S006787—MRK-S006820 which are documents sufficient to show Merck's investigation into the allegations made by Dr. Fries.

While Merck respects Dr. Fries as a scientist and educator, his interpretation of Merck's actions was mistaken, and much of his letter was based on hearsay. Dr. Fries's impression that Merck was not disclosing data from VIGOR, either at the American College of Rheumatology or elsewhere, was simply incorrect. Merck's prompt disclosures of the VIGOR data are described above. The communications that Merck had with academics concerning presentations about Vioxx were a proper exercise of Merck's right to defend Vioxx against false claims and unbalanced scientific misrepresentations.

Request No. 17: In the aftermath of the VIGOR study, Mr. Gilmartin testified that after deliberation with outside advisers, Merck developed and discussed with the FDA a plan to: prospectively analyze the CV event rates from three large placebo controlled studies; describe in detail Merck's deliberation with outside advisers and Merck's discussions with FDA about Merck's prospective plan. Explain in detail Merck's deliberations with outside advisers and Merck's actions to prospectively analyze CV event rates in clinical trials. Provide a copy of Merck's regulatory liaison records associated with this plan and all documents related to Merck's deliberation with outside advisers.

Response: As Mr. Gilmartin stated, one of the issues that Merck faced in attempting to prospectively analyze cardiovascular data in placebo-controlled randomized clinical trials with Vioxx was the ethical difficulty of giving a placebo to patients who require pain relief over the course of a long-term trial. Merck discussed this issue with numerous outside scientists and physicians. Ultimately, in order to conduct this analysis, Merck developed a protocol whereby it would prospectively analyze cardiovascular events in three placebo-controlled studies of Vioxx in the treatment and prevention of certain cancers. At the time Merck designed this protocol, the APPROVe study – one of the studies that would be included in the analysis – had been ongoing for over two years. The inclusion of ongoing studies in the analysis was an added advantage to this protocol design because it allowed Merck to obtain data more quickly than if it had to rely solely on newly instituted studies.

Merck refers the Committee to the enclosed communications with the FDA about this protocol, as well as materials related to a meeting of outside scientists and physicians that was held as part of its consultations concerning the design of a prospective cardiovascular analysis.

(Bates Nos. MRK-YAC0000001 -- 001012). Please advise whether there are any additional documents you would like for us to produce in response to this request.

Request No. 18: Merck publicly criticized Dr. Graham's Vioxx study and Mr. Gilmartin testified that Dr. Graham's study played no role in Merck's decision to withdraw Vioxx.

(a) What is the public health rationale for continuing to attack this study when Merck has taken Vioxx off the market?

(b) Why did Merck criticize Dr. Graham's study when the Merck-sponsored Ingenix study had similar findings about CV risk?

(c) Mr. Gilmartin testified at the hearing that while epidemiologic studies have an important role to play, given their inherent limitations, when both epidemiological studies and randomized controlled clinical studies are available, the randomized controlled clinical trials are the most persuasive evidence. Did the Merck-funded Ingenix study play any role in the withdrawal of Vioxx?

(d) State when Mr. Gilmartin first was made aware of the Ingenix study.

(e) Ingenix employees provided the Committee with a time line of events related to the Ingenix study. Describe in detail what Merck knew and when about the Ingenix study (hearing exhibits 46 and 61).

(f) Provide for the hearing record a copy of all documents and communications related to the Ingenix study, including but not limited to the regulatory filings, regulatory liaison records as well as internal Merck email and email communication between FDA and Merck.

Response:

(a & b) Merck believes it is important from a public health perspective that people understand the limitations of epidemiological studies (such as the Graham study or the Ingenix study) as described in part above and in prior letters to the Committee, particularly when the press reports the study results out of context without making those limitations clear. One illustration of the importance of understanding these limitations is the situation with hormone replacement therapy (HRT), where numerous epidemiological studies pointed to a cardioprotective effect for HRT treatment before an NIH sponsored randomized clinical trial

showed the exact opposite -- that the treatment in fact increased cardiovascular risk. Moreover, the Graham study had significant scientific weaknesses of its own.

(c) No, the Ingenix study did not play a role in Merck's decision to voluntarily withdraw Vioxx from the market. Although Merck believed it would have been possible to continue to market Vioxx with labeling that would incorporate the APPROVe data, given the availability of alternative therapies without, at that time, evidence of a similar cardiovascular risk, and the questions raised by the new data from the APPROVe study, Merck concluded that a voluntary withdrawal was the responsible course to take.

(d) Mr. Gilmartin was first made aware of the Ingenix study shortly before he testified before the Committee.

(e) Merck first became aware of preliminary data from the Ingenix study in late 2003. The preliminary data required substantial work by Ingenix before it could be completely finalized, and the complete finalization did not occur until late Summer 2004, after which the data were disclosed to the FDA. The finalization of the data was delayed somewhat in early 2004 because the primary scientists at both Ingenix and Merck who were working on the study were on maternity leave.

(f) Merck is enclosing documents concerning the Ingenix study from the files of the Merck employees most directly involved with the Ingenix study, as well as Merck's correspondence with the FDA about the study. Please advise whether there are any additional documents you would like for us to produce in response to this request.

Request No. 19: Mr. Gilmartin testified at the hearing that Merck's Vioxx marketing "was appropriate."

(a) Throughout the time that Vioxx was sold in the U.S. it was plagued with serious safety concerns, especially regarding cardiovascular problems, yet Merck engaged in a very aggressive direct-to-consumer marketing campaign, spending more than $160M in 2000 alone. In the interest of putting patients first, did Merck ever consider suspending the marketing of Vioxx while Merck conducted further studies to confirm the cardiovascular safety of the drug?

(b) Merck's representatives were trained with marketing materials entitled, "Dodge Ball," Obstacle Jeopardy," and "Top 10 Obstacle Handlers" (hearing exhibits 50, 51, and 52). Are these training materials representative of Merck's principle of "Putting Patient

Safety First?" Is it Merck's position that doctors would not find it disturbing to know that their questions are viewed as "obstacles" by Merck representatives?

(c) Hearing exhibit 21 is a document entitled "Key Marketing Messages HHPAC May 17, 2000." A section entitled "CV Outcomes Study," states "At present there is no compelling marketing need for such a study." Later in that same document there is a section entitled, "Decisions Requested," which states "Approve decision not to initiate CV outcome study at present." Is it common practice for Merck marketing to participate in matters of drug safety and study design? In order to provide context for the record, provide a copy of all additional documents related to HHPAC meetings, including but not limited to issues related to strategies or discussions on CV risk and/or Vioxx study design.

(d) Are decisions to do safety clinical trials routinely screened by marketing and public relations at Merck?

(e) Mr. Gilmartin testified at the hearing that Merck took the FDA's warning letter very seriously and took corrective actions with regard to the speaker and to the sales representative, but that there was no action requested or required on the press release by the FDA. Please describe in detail Merck's communications with FDA related to the warning letter. Provide for the hearing record a copy of Merck's regulatory liaison records associated with the warning letter that will provide context for the hearing record.

Response:

(a) Merck disagrees with the characterization and accuracy of the statements made regarding the safety of Vioxx and Merck's marketing of the medicine. Merck believed firmly in the safety profile, including the cardiovascular safety profile, of Vioxx the entire time that Vioxx was on the market. Among others, data from large placebo-controlled randomized clinical trials showed no increased cardiovascular risk with Vioxx. Merck therefore believed it was appropriate to market Vioxx in a manner consistent with the FDA-approved prescribing information and the applicable statutes and regulations governing such marketing, and Merck did so. Merck also submitted all of its original direct-to-consumer advertising involving new concepts to the FDA for pre-review before it was used. Merck believes that direct-to-consumer advertising does serve the interest of patients by informing them about medicines that could be beneficial for them and encouraging them to discuss treatment options with their physicians so that the physicians can consider whether these options are appropriate for that patient.

(b) Merck is committed to promoting its medicines in accordance with FDA approved prescribing information and the laws and regulations that govern those activities. Consistent with FDA regulations, Merck representatives are trained to answer questions from doctors in a manner consistent with the FDA-approved prescribing information. Any suggestion otherwise – including suggestions based on misreading of excerpts of training documents -- is inaccurate. The Request appears to misunderstand the terminology used in the training of representatives. The training materials are designed to provide factual information responsive to questions physicians might raise regarding the effects of a medicine in particular circumstances. The documents referenced in the Request are training tools, including games used as breaks during training sessions, which further that purpose. If a Merck representative cannot answer a question posed by a doctor, the representative or the physician can submit the question to Merck, and a Merck physician responds to the question in writing.

(c & d) While members of Merck's marketing department sometimes participate in discussions concerning studies, all decisions by Merck concerning drug safety are made by Merck doctors and scientists and are based on the science. In the case of the discussion at the HHPAC meeting cited in the request, Merck concluded that there was no scientifically compelling need to pursue a separate cardiovascular safety study at that time in large part because the data from placebo-controlled trials were sufficiently reassuring and the pooled data set being assembled from completed and ongoing trials was sufficiently robust. Only after that conclusion had been reached did it become a question whether from a marketing point of view there was sufficient benefit to be derived from such a study to design and conduct it in the absence of scientific need. Enclosed please find Vioxx-specific portions of minutes of HHPAC meetings, Bates Nos. MRK-S013468 – MRK-S013478. Portions of the minutes that do not relate to Vioxx have been redacted.

(e) Merck refers the Committee to the correspondence between Merck and the FDA concerning the FDA's letter. Bates Nos. MRK-AAF0013536—MRK-AAF0013537.

Request No. 20: Mr. Gilmartin testified at the hearing that it's been Merck's policy that all trials associated with the development of a drug and with all the post-marketing studies, have always been published and Merck provided a list of study protocols to the Committee. Describe each Vioxx protocol that has not been published, explain why it was not published, and state whether the study had any results or finding related to CV risk, including any CV adverse events.

Response: Merck believes this characterization slightly misstates Mr. Gilmartin's testimony. As Merck has stated publicly previously, including as part of its publication guidelines issued in 2003, Merck is committed to publishing the primary and key secondary results of its hypothesis-testing clinical trials according to the pre-specified plans for data

analysis. Merck conducts pilot or exploratory studies in all stages of clinical development. In general, these studies (and certain post-hoc analyses) are performed to aid decision making for possible future product development, and are often highly proprietary to the Company. However, if Merck together with the investigators deem such studies or analyses scientifically and medically important, they may be submitted for publication with appropriate caveats for interpreting results.

As previously requested by this Committee, Merck has provided information, including publication information, to the Committee regarding certain clinical studies that have been performed. The spreadsheet providing information concerning these studies, as well as synopses of many of these studies, were provided to the Committee on November 16, 2004 and can be found at Bates Nos. MRK-S006821—MRK-S007207. Moreover, as indicated in its prior letter to the Committee, Merck has continued to collect additional information that may be responsive to this request. Additional study synopses are provided with this letter. Bates Nos. MRK-S013140—MRK-S013359.

Request No. 21: In 2001, Konstam et al. reviewed the cardiovascular thrombotic events in 23 rofecoxib studies (See Konstam MA, Weir MR, Reicin A, Shapiro D, Sperling RS, Barr E, Gertz BJ. Cardiovascular thrombotic events in controlled clinical trials of rofecoxib. Circulation 2001; 104:2280-2288). In 2003, Weir et al. updated the review (Weir MR, Perling RS, Reicin A. Gertz BJ. Selective Cox-2 inhibition and cardiovascular effects: a review of the rofecoxib development program. Am Heart J 2003; 146:591-604.) Provide a copy of all versions of the tables that were developed in the process of producing these two papers, as well as any other tables that examined the cardiovascular outcomes in the clinical trials of Vioxx. In particular, include all versions that may have information about the individual type of events (myocardial infarction, stroke, cardiovascular death, venous thrombosis, and pulmonary embolism) as well as any combined outcomes. Include a description of the methods used to create these tables, the definitions of any combined outcomes, the dose-response analyses, and all documents related to correspondence about the tables and the methods.

Response: As discussed above in response to other Requests, Merck conducted a cardiovascular pooled analysis and submitted that analysis and several updates to the FDA. The tables reflecting the data used in the pooled analysis, including versions that show the data by individual events, and updates to those table, are contained in those submissions made by Merck to the FDA concerning the pooled analysis. Merck refers the Committee to documents Bates numbered MRK-I8940064858—MRK-I8940064921; MRK-01420145847—MRK-01420145961; MRK-S0420000030—MRK-S0420000072; MRK-S013024—MRK-S013095.

After reviewing those materials, please advise whether there are any additional documents you would like for us to produce in response to this request.

Request No. 22: Dr. Kweder testified that the FDA "pursued vigorously" the Vioxx label change to reflect cardiovascular risk and that the label change did take a "very long time, much longer than usual," explain in detail from Merck's vantage point the time line of events between when the advisory committee recommended a Vioxx label change to when the label change was effected. Provide for the hearing record all documents Merck provided to the FDA related to the Vioxx label change.

Request No. 23: Between October 2001 and April 2002, Merck rejected FDA proposed labeling for Vioxx and negotiated removal of the CV risk from the warnings section of the label to the precautions section. Describe in detail the label discussions and negotiations with the FDA and identify the Merck employees who were involved. Provide for the hearing record a copy of all email communications between Merck and FDA as well as all internal Merck email related to the Vioxx label change.

Response: In order to provide a more complete and concise response, Merck responds to both Requests Nos. 22 and 23 below.

Within two weeks of the unblinding of the VIGOR data, Merck informed the FDA about those results. Less than four months after the unblinding, on June 29, 2000, Merck submitted the VIGOR sNDA to the FDA. The sNDA included a thorough analysis of the VIGOR results and cardiovascular safety data from other Vioxx clinical trials as well as proposed labeling incorporating the gastrointestinal and cardiovascular results from VIGOR. Merck requested priority review of the sNDA, but the FDA could not accommodate that request. The FDA requested additional information from VIGOR and from other studies and additional analyses before it would address labeling to incorporate the VIGOR results, and as Dr. Kweder testified, Merck cooperated promptly and fully with the FDA's requests.

The FDA also convened a public Advisory Committee hearing to examine the VIGOR results in February 2001. For a detailed timeline of the events between the Advisory Committee's recommendation in 2001 and the FDA's approval of the label change in April 2002, Merck refers the Committee to the documents reflecting Merck's communications with the FDA concerning the Vioxx label during that time period, Bates Nos. MRK- H003008 – MRK-H004741. Generally, Merck had submitted a proposed label to the FDA as part of its submission of the sNDA in June 2000. Following the Advisory Committee meeting, Merck submitted an updated proposed label incorporating the recommendations of the Advisory Committee. The FDA informed Merck after the Advisory Committee meeting that it needed to wait for additional

data, specifically including data from the completion of the ongoing ADVANTAGE trial, which Merck subsequently submitted upon the completion of that trial, before new labeling could be drafted. In October 2001, the FDA provided Merck with draft labeling, and Merck promptly responded to the FDA's draft.

Merck disagrees with the statement that it "rejected" the FDA's proposed labeling for Vioxx. Merck believed that the initial draft label sent to Merck by the FDA in October 2001, and specifically the inclusion of cardiovascular information in the warning section of the label instead of in the precautions section, was inconsistent with the recommendation of the Advisory Committee, and was not appropriate in light of the existing body of data on Vioxx's cardiovascular safety and the FDA's regulations defining the type of information that is to be included in the warning section of a drug's label. Merck informed the FDA of this belief in a letter from Dr. Robert Silverman dated November 6, 2001 (Bates Nos. MRK-H003826—MRK-H003870). The next draft label that the FDA sent to Merck included cardiovascular safety information in the precautions section rather than the warnings section, and this is where the language was included in the label that was approved by the FDA in April 2002. Merck refers the Committee to the communications between Merck and the FDA for a more detailed description of discussions between Merck and the FDA during this period. (Bates Nos. MRK-H003871—MRK-H004741). Generally, the discussions involved revisions to the prescribing information to ensure that the language clearly and accurately conveyed to physicians the important information about Vioxx's risks and benefits. The discussions also involved additional analyses of the data from both VIGOR and the Alzheimer's placebo-controlled studies that the FDA requested and Merck conducted.

Merck has already provided to the Committee documents from its official regulatory file and documents reflecting its communications with the FDA for this time period regarding this issue, which can be found at Bates No. MRK-H003008—MRK-H004741. Enclosed also please find responsive documents from several key employees involved in the process of communication with the FDA regarding this issue during this time period—Bonnie Goldman, Robert Silverman, and Ned Braunstein, Bates Nos. MRK-YAB0000001 -- 0005794. Please advise whether there are any additional documents you would like for us to produce in response to this request.

As you know, at your request, we have designated Kirke Weaver as Merck's point of contact. Please contact Kirke if you have questions about any of the above.

Sincerely,

Dennis M. Erb

Dennis M. Erb, Ph.D.

PREPARED STATEMENT OF DAVID J. GRAHAM, M.D., MPH

Introduction

Mr. Chairman and members of the committee, good morning. My name is David Graham, and I am pleased to come before you today to speak about Vioxx, heart attacks and the FDA. By way of introduction, I graduated from the Johns Hopkins University School of Medicine, and trained in Internal Medicine at Yale and in adult Neurology at the University of Pennsylvania. After this, I completed a 3-year fellowship in pharmacoepidemiology and a Masters in Public Health at Johns Hopkins, with a concentration in epidemiology and biostatistics. Over my 20-year career in the field, all of it at FDA, I have served in a variety of capacities. I am currently the Associate Director for Science and Medicine in FDA's Office of Drug Safety.

During my career, I believe I have made a real difference for the cause of patient safety. My research and efforts within FDA led to the withdrawal from the U.S. market of Omniflox, an antibiotic that caused hemolytic anemia; Rezulin, a diabetes drug that caused acute liver failure; Fen-Phen and Redux, weight loss drugs that caused heart valve injury; and PPA (phenylpropanolamine), an over-the-counter decongestant and weight loss product that caused hemorrhagic stroke in young women. My research also led to the withdrawal from outpatient use of Trovan, an antibiotic that caused acute liver failure and death. I also contributed to the team effort that led to the withdrawal of Lotronex, a drug for irritable bowel syndrome that causes ischemic colitis; Baycol, a cholesterol-lowering drug that caused severe muscle injury, kidney failure and death; Seldane, an antihistamine that caused heart arrhythmias and death; and Propulsid, a drug for night-time heartburn that caused heart arrythmias and death. I have done extensive work concerning the issue of pregnancy exposure to Accutane, a drug that is used to treat acne but can cause birth defects in some children who are exposed in-utero if their mothers take the drug during the first trimester. During my career, I have recommended the market withdrawal of 12 drugs. Only 2 of these remain on the market today—Accutane and Arava, a drug for the treatment of rheumatoid arthritis that I and a co-worker believe causes an unacceptably high risk of acute liver failure and death.

Vioxx and heart attacks

Let me begin by describing what we found in our study, what others have found, and what this means for the American people. Prior to approval of Vioxx, a study was performed by Merck named 090. This study found nearly a 7-fold increase in heart attack risk with low-dose Vioxx. The labeling at approval said nothing about heart attack risks. In November, 2000, another Merck clinical trial named VIGOR found a 5-fold increase in heart attack risk with high-dose Vioxx. The company said the drug was safe and that the comparison drug naproxen, was protective. In 2002, a large epidemiologic study reported a 2-fold increase in heart attack risk with high-dose Vioxx and another study reported that naproxen did not affect heart attack risk. About 18 months after the VIGOR results were published, FDA made a labeling change about heart attack risk with high-dose Vioxx, but did not place this in the "Warnings" section. Also, it did not ban the high-dose formulation and its use.

I believe such a ban should have been implemented. Of note, FDA's label change had absolutely no effect on how often high-dose Vioxx was prescribed, so what good did it achieve?

In March of 2004, another epidemiologic study reported that both high-dose and low-dose Vioxx increased the risk of heart attacks compared to Vioxx's leading competitor, Celebrex. Our study, first reported in late August of this year, found that Vioxx increased the risk of heart attack and sudden death by 3.7-fold for high-dose and 1.5-fold for low-dose, compared to Celebrex. A study report describing this work was put on the FDA website on election day. Among many things, this report estimated that nearly 28,000 excess cases of heart attack or sudden cardiac death were caused by Vioxx. I emphasize to the committee that this is an extremely conservative estimate. FDA always claims that randomized clinical trials provide the best data. If you apply the risk levels seen in the 2 Merck trials, VIGOR and APPROVe, you obtain a more realistic and likely range of estimates for the number of excess cases in the U.S. This estimate ranges from 88,000 to 139,000 Americans. Of these, 30–40% probably died. For the survivors, their lives were changed forever. It's important to note that this range does not depend at all on the data from our Kaiser-FDA study. Indeed, Dr. Eric Topol at the Cleveland Clinic recently estimated up to 160,000 cases of heart attacks and strokes due to Vioxx, in an article published in the *New England Journal of Medicine.* This article lays out clearly the public health significance of what we're talking about today.

So, how many people is 100,000? The attached Tables 1 and 2 show the estimated percentage of the population in your home State and in selected cities from your State that would have been affected had all 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx occurred only in your State or city. This is to help you understand how many lives we're talking about. We're not just talking numbers. For example, if we were talking about Florida or Pennsylvania, 1% of the entire State population would have been affected. For Iowa, it would be 5%, for Maine, 10% and for Wyoming, 27%. If we look at selected cities, I'm sorry to say, Senator Grassley, but 67% of the citizens of Des Moines would be affected, and what's worse, the entire population of every other city in the State of Iowa.

But there is another way to put this range of excess cases into perspective. Imagine that instead of a serious side-effect of a widely used prescription drug, we were talking about jetliners. Please ignore the obvious difference in fatality rates between a heart attack and a plane crash, and focus on the larger analogy I'm trying to draw. If there were an average of 150 to 200 people on an aircraft, this range of 88,000 to 138,000 would be the rough equivalent of 500 to 900 aircraft dropping from the sky. This translates to 2–4 aircraft every week, week in and week out, for the past 5 years. If you were confronted by this situation, what would be your reaction, what would you want to know and what would you do about it?

Brief history of drug disasters in the U.S.

Another way to fully comprehend the enormity of the Vioxx debacle is to look briefly at recent U.S. and FDA history. The attached figure shows a graph depicting 3 historical time-points of importance to the development of drug safety in the U.S. In 1938, Congress enacted the Food, Drug and Cosmetic Act, basically creating the FDA, in response to an unfortunate incident in which about 100 children were killed by elixir of sulfanilamide, a medication that was formulated using anti-freeze. This Act required that animal toxicity testing be performed and safety information be submitted to FDA prior to approval of a drug. In 1962, Congress enacted the Kefauver-Harris Amendments to the FD&C Act, in response to the thalidomide disaster in Europe. Oversees, between 1957 and 1961, an estimated 5,000 to 10,000 children were born with thalidomide-related birth defects. These Amendments increased the requirements for toxicity testing and safety information pre-approval, and added the requirement that "substantial evidence" of efficacy be submitted. Today, in 2004, you, we, are faced with what may be the single greatest drug safety catastrophe in the history of this country or the history of the world. We are talking about a catastrophe that I strongly believe could have, should have been largely or completely avoided. But it wasn't, and over 100,000 Americans have paid dearly for this failure. In my opinion, the FDA has let the American people down, and sadly, betrayed a public trust. I believe there are at least 3 broad categories of systemic problems that contributed to the Vioxx catastrophe and to a long line of other drug safety failures in the past 10 years. Briefly, these categories are (1) organizational/structural, (2) cultural, and (3) scientific. I will describe these in greater detail in a few moments.

My Vioxx experience at FDA

To begin, after publication of the VIGOR study in November, 2000, I became concerned about the potential public health risk that might exist with Vioxx. VIGOR suggested that the risk of heart attack was increased 5-fold in patients who used the high-dose strength of this drug. Why was the Vioxx safety question important? (1) Vioxx would undoubtedly be used by millions of patients. That's a very large number to expose to a serious drug risk. (2) Heart attack is a fairly common event. And (3) Given the above, even a relatively small increase in heart attack risk due to Vioxx could mean that tens of thousands of Americans might be seriously harmed or killed by use of this drug. If these three factors were present, I knew that we would have all the ingredients necessary to guarantee a national disaster. The first two factors were established realities. It came down to the third factor, that is, what was the level of risk with Vioxx at low- and high-dose.

To get answers to this urgent issue, I worked with Kaiser Permanente in California to perform a large epidemiologic study. This study was carefully done and took nearly 3 years to complete. In early August of this year, we completed our main analyses and assembled a poster presentation describing some of our more important findings. We had planned to present these data at the International Conference on Pharmacoepidemiology, in Bordeaux, France. We concluded that high-dose Vioxx significantly increased the risk of heart attacks and sudden death and that the high doses of the drug should not be prescribed or used by patients. This conclusion triggered an explosive response from the Office of New Drugs, which approved Vioxx in the first place and was responsible for regulating it post-marketing. The response from senior management in my Office, the Office of Drug Safety, was equally stressful. I was pressured to change my conclusions and recommendations, and basically threatened that if I did not change them, I would not be permitted to present the paper at the conference. One Drug Safety manager recommended that I should be barred from presenting the poster at the meeting, and also noted that Merck needed to know our study results.

An e-mail from the Director for the entire Office of New Drugs, was revealing. He suggested that since FDA was "not contemplating" a warning against the use of high-dose Vioxx, my conclusions should be changed. CDER and the Office of New Drugs have repeatedly expressed the view that ODS should not reach any conclusions or make any recommendations that would contradict what the Office of New Drugs wants to do or is doing. Even more revealing, a mere 6 weeks before Merck pulled Vioxx from the market, CDER, OND and ODS management did not believe there was an outstanding safety concern with Vioxx. At the same time, 2–4 jumbo jetliners were dropping from the sky every week and no one else at FDA was concerned.

There were 2 other revelatory milestones. In mid-August, despite our study results showing an increased risk of heart attack with Vioxx, and despite the results of other studies published in the literature, FDA announced it had approved Vioxx for use in children with rheumatoid arthritis. Also, on September 22, at a meeting attended by the director of the reviewing office that approved Vioxx, the director and deputy director of the reviewing division within that office and senior managers from the Office of Drug Safety, no one thought there was a Vioxx safety issue to be dealt with. At this meeting, the reviewing office director asked why had I even thought to study Vioxx and heart attacks because FDA had made its labeling change and nothing more needed to be done. At this meeting a senior manager from ODS labeled our Vioxx study "a scientific rumor." Eight days later, Merck pulled Vioxx from the market, and jetliners stopped dropping from the sky.

Finally, we wrote a manuscript for publication in a peer-reviewed medical journal. Senior managers in the Office of Drug Safety have not granted clearance for its publication, even though it was accepted for publication in a very prestigious journal after rigorous peer review by that journal. Until it is cleared, our data and conclusions will not see the light of day in the scientific forum they deserve and have earned, and serious students of drug safety and drug regulation will be denied the opportunity to consider and openly debate the issues we raise in that paper.

Past experiences

My experience with Vioxx is typical of how CDER responds to serious drug safety issues in general. This is similar to what Dr. Mosholder went through earlier this year when he reached his conclusion that most SSRIs should not be used by children. I could bore you with a long list of prominent and not-so-prominent safety issues where CDER and its Office of New Drugs proved to be extremely resistant to full and open disclosure of safety information, especially when it called into question an existing regulatory position. In these situations, the new drug reviewing division that approved the drug in the first place and that regards it as its own child,

typically proves to be the single greatest obstacle to effectively dealing with serious drug safety issues. The second greatest obstacle is often the senior management within the Office of Drug Safety, who either actively or tacitly go along with what the Office of New Drugs wants. Examples are numerous, so I'll mention just a few.

With Lotronex, even though there was strong evidence in the pre-approval clinical trials of a problem with ischemic colitis, OND approved it. When cases of severe constipation and ischemic colitis began pouring into FDA's MedWatch program, the reaction was one of denial. When CDER decided to bring Lotronex back on the market, ODS safety reviewers were instructed to help make this happen. Later, when CDER held an advisory committee meeting to get support for bringing Lotronex back on the market, the presentation on ways to manage its reintroduction was carefully shaped and controlled by OND. When it came to presenting the range of possible options for how Lotronex could be made available, the list of options was censored by OND. The day before the advisory meeting, I was told by the ODS reviewer who gave this presentation that the director of the reviewing office within OND that approved Lotronex in the first place came to her office and removed material from her talk. An OND manager was "managing" an ODS employee. When informed of this, ODS senior management ignored it. I guess they knew who was calling the shots.

Rezulin was a drug used to treat diabetes. It also caused acute liver failure, which was usually fatal unless a liver transplant was performed. The pre-approval clinical trials showed strong evidence of liver toxicity. The drug was withdrawn from the market in the United Kingdom in December, 1997. With CDER and the Office of New Drugs, withdrawal didn't occur until March, 2000. Between these dates, CDER relied on risk management strategies that were utterly ineffective, and it persisted in relying on these strategies long after the evidence was clear that they didn't work. The continued marketing of Rezulin probably led to thousands of Americans being severely injured or killed by the drug. And note, there were many other safer diabetes drugs available. During this time, I understand that Rezulin's manufacturer continued to make about $2 million per day in sales.

The big picture

The problem you are confronting today is immense in scope. Vioxx is a terrible tragedy and a profound regulatory failure. I would argue that the FDA, as currently configured, is incapable of protecting America against another Vioxx. We are virtually defenseless.

It is important that this committee and the American people understand that what has happened with Vioxx is really a symptom of something far more dangerous to the safety of the American people. Simply put, FDA and its Center for Drug Evaluation and Research are broken. Now, I'm sure you have read the recent proposal to have the Institute of Medicine perform a review of CDER and its drug safety program and make recommendations for fixing things up. Don't expect anything meaningful or effective from this exercise. Over the history of CDER's drug safety program, a number of similar reviews have been done. In the late 1970s, I believe that a blue-ribbon panel recommended that there be an entirely separate drug safety operation in FDA with full regulatory authority. It wasn't implemented. During the 1980s and early 1990s, CDER organized its own "program reviews" of drug safety. The basic premise underlying each of these reviews was that the "problem" was with the drug safety group; it didn't fit into the Center. So, the charge given to the review panel members was always framed as "figure out what's wrong with drug safety, and tell us what to do to get it to fit in." There was and is an implicit expectation that the status quo will remain unaltered.

The organizational structure within CDER is entirely geared towards the review and approval of new drugs. When a CDER new drug reviewing division approves a new drug, it is also saying the drug is "safe and effective." When a serious safety issue arises post-marketing, their immediate reaction is almost always one of denial, rejection and heat. They approved the drug, so there can't possibly be anything wrong with it. The same group that approved the drug is also responsible for taking regulatory action against it post-marketing. This is an inherent conflict of interest. At the same time, the Office of Drug Safety has no regulatory power and must first convince the new drug reviewing division that a problem exists before anything beneficial to the public can be done. Often, the new drug reviewing division is the single greatest obstacle to effectively protecting the public against drug safety risks. A close second in my opinion, is an ODS management that sees its mission as pleasing the Office of New Drugs.

The corporate culture within CDER is also a barrier to effectively protecting the American people from unnecessary harm due to prescription and OTC drugs. The culture is dominated by a world-view that believes only randomized clinical trials

provide useful and actionable information and that post-marketing safety is an afterthought. This culture also views the pharmaceutical industry it is supposed to regulate as its client, over-values the benefits of the drugs it approves and seriously under-values, disregards and disrespects drug safety.

Finally, the scientific standards CDER applies to drug safety guarantee that unsafe and deadly drugs will remain on the U.S. market. When an OND reviewing division reviews a drug to decide whether to approve it, great reliance is placed on statistical tests. Usually, a drug is only approved if there is a 95% or greater probability that the drug actually works. From a safety perspective, this is also a very protective standard because it protects patients against drugs that don't work. The real problem is how CDER applies statistics to post-marketing safety. We see from the structural and cultural problems in CDER, that everything revolves around OND and the drug approval process.

When it comes to safety, the OND paradigm of 95% certainty prevails. Under this paradigm, a drug is safe until you can show with 95% or greater certainty that it is not safe. This is an incredibly high, almost insurmountable barrier to overcome. It's the equivalent of "beyond a shadow of a doubt." And here's an added kicker. In order to demonstrate a safety problem with 95% certainty, extremely large studies are often needed. And guess what. Those large studies can't be done.

There are 2 analogies I want to leave you with to illustrate the unreasonableness of CDER's standard of evidence as applied to safety, both pre- and post-approval. If the weather-man says there is an 80% chance of rain, most people would bring an umbrella. Using CDER's standard, you wouldn't bring an umbrella until there was a 95% or greater chance of rain. The second analogy is more graphic, but I think it brings home the point more clearly. Imagine for a moment that you have a pistol with a barrel having 100 chambers. Now, randomly place 95 bullets into those chambers. The gun represents a drug and the bullets represent a serious safety problem. Using CDER's standard, only when you have 95 bullets or more in the gun will you agree that the gun is loaded and a safety problem exists. Let's remove 5 bullets at random. We now have 90 bullets distributed across 100 chambers. Because there is only a 90% chance that a bullet will fire when I pull the trigger, CDER would conclude that the gun is not loaded and that the drug is safe.

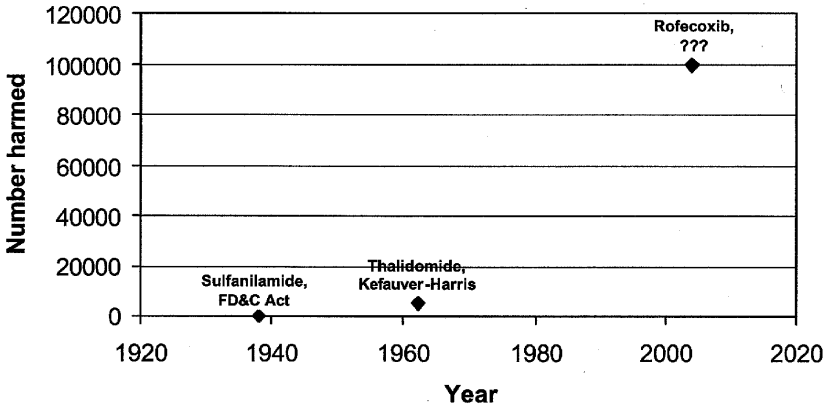
Table 1. The percentage of each State's population age 18 years or older that would be affected if an estimated 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx had all occurred in that State. The States are presented alphabetically. These are the States represented by members of the Senate Finance Committee.

State	Estimated % of population age 18 years or older
Arizona	2
Arkansas	5
Florida	1
Iowa	5
Kentucky	3
Louisiana	3
Maine	10
Massachusetts	2
Mississippi	5
Montana	14
New Mexico	7
North Dakota	21
Oklahoma	4
Oregon	4
Pennsylvania	1
South Dakota	18
Tennessee	2
Utah	6
Vermont	22
West Virginia	7
Wyoming	27

Table 2. The percentage of the population age 18 years or older from selected cities in the U.S. that would be affected if an estimated 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx had all occurred in that city. The cities chosen were from the more highly populated States shown in Table 1. These cities are in States represented by members of the Senate Finance Committee.

State and city	Estimated % of population age 18 years or older
Arkansas	
Little Rock	73
Arizona	
Scottsdale	66
Tuscon	27
Florida	
Orlando	72
Tallahassee	89
Tampa	44
Iowa	
Des Moines	67
All other cities	100
Kentucky	
Louisville	52
Louisiana	
New Orleans	27
Oklahoma	
Oklahoma City	26
Oregon	
Portland	25
Pennsylvania	
Pittsburgh	40
Lancaster	100
Tennessee	
Nashville	23
Utah	
Salt Lake City	73

Figure 1. A brief history of drug safety disasters in the U.S.



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Response to additional questions from Senator Hatch.

1. Provide a complete list of prominent and not-so-prominent safety issues you mention in your testimony.

Over the course of my time at FDA, the following drug safety issues arose in which, in my opinion, FDA was resistant to full and open disclosure of safety information.

SSRI antidepressants. The issue of selective serotonin reuptake inhibitor (SSRI) antidepressants and suicidal thoughts and behavior in children, is a relatively recent example. After Dr. Andrew Mosholder, an FDA epidemiologist in the Office of Drug Safety, concluded that SSRI antidepressants increased the risk of suicidality in December 2003, he was quickly removed from the list of speakers at a planned February 2004 FDA advisory committee meeting, by managers in the Office of New Drugs. His written report was suppressed by FDA management and I believe it wasn't officially made public until September 2004, in preparation for another advisory meeting on the same topic. In addition, Dr. Mosholder was admonished by FDA management not to speak about his analysis or recommendations at the February meeting. He was given a set of prepared responses by management to read if he was asked questions by members of that February advisory committee. FDA management subsequently ordered a criminal investigation to identify whistleblowers within the Office of Drug Safety who may have leaked the fact that FDA had suppressed Dr. Mosholder's report and blocked him from speaking about it at the February advisory meeting. I've been told that this investigation was illegal. Nonetheless, this investigation had a chilling and intimidating effect on scientists within the Office of Drug Safety.

During the interval between December 2003 and September 2004, I am certain that some children in the US undoubtedly completed suicide (killed themselves) as a direct causal effect of their SSRI medication use. Further, most of these SSRI drugs were known by FDA to be no better than placebo (sugar pills) in their ability to effectively treat depression. Indeed, only one drug within the SSRI class, fluoxetine (Prozac), has been shown to be effective in treating depression in children. What does this mean? To me, it signifies a FDA that is focused on serving industry rather than taking safety seriously and protecting the public from harm. In the case of SSRI antidepressants, FDA essentially promoted the off-label use of antidepressant drugs that were scientifically indistinguishable from placebo, yet carried an increased risk of a serious side-effect. FDA's defense was that "just because the clinical trials didn't show that these drugs worked didn't mean that they don't work." Such thinking contradicts the basic premise of all clinical trials which is that the drug is no different than placebo. Only if you show that a difference is real can you conclude that the drug works. But in this instance, FDA presumed that these dangerous drugs worked despite the evidence showing they did not work.

Recently, FDA announced new labeling with the so-called "black box" warning for all SSRI antidepressants. In my opinion, this labeling is false and misleading, and the Office of New Drugs knows this. The new labeling says that SSRI antidepressants carry a 1-2% excess risk of suicidal thoughts and behavior in children. This level of risk was obtained from a meta-analysis of all randomized clinical trials of SSRI use performed in children. However, at the September 2004 advisory committee meeting where this meta-analysis was discussed, Dr. Laughren, a senior official in the Division of Neuropharmacologic Drug Products stated, in response to a question from the committee, that these clinical trials did not systematically identify all instances of suicidal thought and behavior. Dr. Laughren actually said that the cases of suicidality from these clinical trials were voluntarily reported, similar to the way adverse reactions are voluntarily reported through MedWatch for drugs postmarketing. There is a large degree of underreporting.

What Dr. Laughren was saying is that the SSRI clinical trials greatly underestimated the occurrence of suicidal thoughts and behavior. In other word, the 1-2% estimate is far lower than what the actual risk level is. At this same September 2004 advisory meeting, the risk of suicidality in children treated with Prozac during a NIH-sponsored clinical trial was reported to be 7-8%. This study made a more concerted effort to identify suicidal behavior. A risk of suicidal behavior in children of 1 in 15 treated for 6-weeks is much more alarming than the 1 in 50 or 1 in 100 risk implied by FDA's labeling. Additionally, the new labeling does not specifically state that the SSRI drugs other than Prozac don't work any better than placebo in children. Perhaps most significantly, FDA refused to require signed informed consent at the time a physician writes a prescription for an SSRI for a child. This is the only means by which one can assure that

children and their parents know the risks and the absence of benefit, for the majority of SSRI antidepressants.

Accutane. Accutane is the most egregious example of FDA's lax approach to safety. When the drug was approved for the treatment of severe recalcitrant cystic acne in 1982, it was a known teratogen, yet women were not advised to use contraception. In addition, FDA hid the fact that 5 women had experienced pregnancy exposure to the drug during pre-approval clinical trials involving about 100 women while they were using contraception. I was told that the company stopped enrolling women in its clinical trials after this, but that didn't affect marketing. In 1988, a FDA advisory committee meeting was held at which it was shown that over 90% of Accutane's use in women was off-label, that is, for milder forms of acne. It was also shown that 1-3% of women treated with Accutane became pregnant while taking the drug with most pregnancies ending with abortion. In other words, the off-label use of Accutane was responsible for the vast majority of pregnancy exposures to the drug.

In 1989, FDA implemented the Pregnancy Prevention Program with the company, with the stated purpose of eliminating pregnancy exposure. There were numerous criticisms of this program by FDA scientists in both Drug Safety and the New Drugs because it was clear that the program would not be effective and that the off-label use of Accutane would not be reduced. Also in 1989, the Centers for Disease Control and Prevention recommended a restricted distribution system to make Accutane available to patients who had severe cystic acne while substantially reducing off-label use. In 1991, the Accutane Monitoring Group, comprised of scientists from both the Office of Drug Safety and the Office of New Drugs, recommended to Center management a restricted distribution program that improved upon the CDC model. Nothing was done. Between 1989 and 2000, with the Pregnancy Prevention Program in place, Accutane use in women increased by 270%, that is, off-label use increased dramatically, as did the number of pregnancy exposures to the drug.

In 2000, a FDA advisory committee concluded that the Pregnancy Prevention Program had failed and recommended a restricted distribution system. A letter was sent to Roche informing them that the recommendations of the committee would be followed, and then several months later, the Agency changed its position without explanation. Instead, FDA adopted a modified Pregnancy Prevention Program named SMART (System to Manage Accutane –Related Teratogenicity). SMART was never officially reviewed by the Office of Drug Safety, but was unlikely to work given its close resemblance to the Pregnancy Prevention Program. In 2002, I testified before the House Energy and Commerce Committee's subcommittee on Oversight and Investigation about Accutane pregnancy exposures in the US. I performed a series of analyses that showed that over the market history of Accutane, there have been about 2000 each year from 1982-1990, most ending with elective termination (induced abortion). With the increased off-label use during the period 1989-2000, this average rose to 3,500-4,000 per year. After my testimony, I experienced retaliation by FDA management including removal from further work on Accutane and a downgraded performance evaluation in which Accutane was specifically mentioned. In February 2004, another FDA advisory committee concluded that the SMART program had failed and recommended a restricted distribution system. So 13 years after I recommended a restricted distribution system for Accutane, and after the patent on Accutane has expired, FDA has finally said it's serious and will require restricted distribution, but the system it is planning to implement will not substantially reduce the off-label use of the drug.

Although on the issue of abortion, I am pro-life as opposed to pro-choice, my work on Accutane was guided by the science and the analyses I performed to estimate the number of pregnancy exposures to Accutane were based on the most widely accepted data available. I didn't twist the data or misrepresent it; I merely connected the dots and brought it all together. FDA's publicly stated goal was the elimination of pregnancy exposure, not the elimination of children born with birth defects. In my opinion however, FDA relied on abortion as its real risk management program for Accutane. In a private conversation with a very senior FDA manager last year, I was told that "as long as abortion is legal in the US, abortion is a perfectly acceptable way to manage the risk of Accutane." Of course, there were no other witnesses to this conversation and this manager would probably deny having said this. Nonetheless, at the December 2002 subcommittee hearing mentioned above, all House members present, regardless of their position on abortion, found FDA's use of abortion as a risk management strategy to be reprehensible.

Cisapride

Cisparide (Propulsid), a drug for the treatment of "nocturnal heartburn." An announcement was made in March 2000 that Propulsid would be removed from the market the following July. The problem was sudden death due to cardiac ventricular arrhythmia. The drug was not approved for use in infants and children, and several studies by the company in children had shown that the drug did not work in children. Nonetheless, the drug was being widely used in infants to treat reflux, a condition that typically self-resolved by one year of age. FDA learned of the sudden death of an infant who had been treated with Propulsid as part of a very small clinical trial (n=~50 exposed to Propulsid) in Pittsburgh. I reviewed the issue and found that there were about 6 published studies of Propulsid use in children and infants, all very small in size. In 5 of these 6 studies, at least one child experienced a cardiac side effect including arrhythmias and abnormal electrocardiograms. I also calculated that the probability of a sudden infant death occurring in the small clinical trial from Pittsburgh was extremely low. In other words, it wasn't a chance event. The county coroner ruled that Propulsid contributed to the child's death. Between March and July 2000, FDA allowed Propulsid to be marketed to infants and children, knowing that the drug didn't work for them and having been presented with the evidence of severe cardiac toxicity in children. I proposed that if FDA was going to allow Propulsid to remain on the market until July, that it make a Public Health Announcement to warn parents about the risk of death from this drug when used in infants and children. Instead, nothing was done. When Propulsid came off the market, FDA allowed it to be made available through a treatment IND program, and included a program for infants and children. I do not know what the informed consent form said about the risk of sudden death or the fact that the drug didn't work in children. Apparently, after a few years, the company that made Propulsid stopped allowing children to be treated under the IND. I heard a rumor that a child had experienced a serious event under the IND, but I have no details.

Acetaminophen (Tyelenol)

In 2002, CDER convened an advisory committee meeting to discuss liver injury and liver failure caused by acetaminophen. The Office of New Drugs wanted to restrict the discussion to the setting of accidental or inadvertent overdose. Office of Drug Safety staff wanted to include discussion of intentional overdose as well because intentional overdose with acetaminophen is the leading cause of drug-induced liver failure in the US and is responsible for more deaths and liver transplants than accidental overdose. This was vetoed and prohibited by New Drugs. Additionally, Office of Drug Safety staff drafted a series of questions for consideration by the committee related to ways to prevent or substantially reduce the number of intentional and accidental overdoses. The Office of New Drugs did not allow any of these questions to be presented to or discussed by the advisory committee. Of note, a series of regulatory actions were implemented in the United Kingdom to successfully reduce the number of acetaminophen-related suicides and liver transplants. In the US, the Office of New Drugs blocked discussion of this topic and of regulatory actions that could have saved hundreds of American lives each year.

Arava

Arava is a drug approved for the treatment of rheumatoid arthritis. In 2002, Dr. Renan Bonnel and I completed a report describing a markedly increased risk of acute liver failure with Arava, and recommended that it be withdrawn from the market. In the months leading up to the completion of our report, we experienced a barrage of hostile behavior and intimidation, by managers from the Office of New Drugs. At one meeting, we were screamed at by a division director from New Drugs while his supervisor and one of my supervisors looked on without intervening. This action created an extremely hostile work environment and was clearly an attempt to threaten and intimidate us so that we would change our recommendations. My own supervisor later tried to pressure us to change our conclusions and told us that "industry is our client." I was shocked by what I heard and responded that the public was our client. He repeated himself saying, "industry is our client." I answered that "industry may be your client but it will never be my client." At another meeting, managers from the reviewing division in New Drugs responsible for Arava presented their arguments in favor of the drug. Their presentation was peppered with sarcastic and derogatory remarks directed at Dr. Bonnel and me, and no one in attendance (including the Center Director and Deputy Center Director) stopped them.

An advisory committee meeting was convened in 2003 to discuss the issue of liver failure with Arava. No one from the Office of New Drugs was placed on the program to present to the committee. The two main presentations, one by the company and the other by the Office of New Drugs, were virtually identical

in content, organization and conclusions, and sang the praises of the drug. The PBS documentary "Frontline" featured a 45-minute program on this issue and several other examples of FDA's suppression of safety information.

Lotronex

Lotronex was approved for the treatment of diarrhea predominant irritable bowel syndrome in women. It was withdrawn from the market in 2000 because it caused ischemic colitis, a potentially fatal disorder. The withdrawal was based on analyses performed by staff in the Office of Drug Safety, but was fiercely resisted and opposed for a long time by the Office of New Drugs. At some point, a decision was made to bring Lotronex back on the market. This decision was not based on an assessment of the post-marketing safety data. Indeed, staff in Drug Safety were working on analyses to keep Lotronex off the market. When the decision was made by Center management to bring Lotronex back on the market, the Drug Safety staff were ordered to stop working on their efforts to keep the drug off the market, and help bring it back on the market. I was not directly involved, but was told these details by several of the staff who were involved.

An advisory committee meeting was held to discuss the safety issues and options to re-market the drug. Of note, a statistician was selected to present the drug safety data. None of the epidemiology staff familiar with the issue presented. This is highly unusual. Also, a presentation of regulatory options to re-introduce Lotronex on the market was given by someone from Drug Safety. However, a senior manager from the Office of New Drugs heavily censored this presentation the day before the advisory committee meeting was held. She forced the removal from the talk of certain regulatory options and opinions that she did not want the committee to hear. Please note that a manager from New Drugs forced someone from Drug Safety to alter their presentation and keep certain information from an advisory committee. I spoke with the Drug Safety person involved and her comment on this was "it wasn't pleasant".

2. Is one of my co-authors a paid consultant of trial lawyers who are suing Merck? Is this person still working with the trial attorneys who are suing Merck? Don't you thin that creates serious questions about the neutrality of your findings?

Dr. Wayne Ray, from Vanderbilt University School of Medicine has served as a consultant to trial attorneys working with rofecoxib (Vioxx) lawsuits. I don't know if he is still serving as a consultant. Regarding the neutrality of our findings, I don't believe Dr. Ray's activities in this regard have any bearing. First, I was the principal investigator and study leader, and as a FDA employee, have no financial relationship with regulated industry or plaintiffs' attorneys. I was primarily responsible for the design of our study and for specifying the study objectives. These were refined by the study team, which included Dr. Ray and 6 researchers from Kaiser Permanente in California, none of whom had such potential conflicts of interest. Of note, Dr. Ray was invited by me to join our study team because a) he was a recipient of one of FDA's cooperative agreement grants in pharmacoepidemiology, b) he is widely acknowledged to be one of the very best epidemiology methodologists in the world, and c) he has extensive experience studying nonsteroidal pain relievers.

In designing our study, my single greatest concern was that it be designed well enough that regardless of the results, we could have confidence in them. If our study found that rofecoxib did not increase the risk of myocardial infarction, I wanted the study to be designed well enough that I could trust that result and that FDA could trust that result. In our study, the same degree of data was collected from all patients (cases and controls), regardless of which drug they were treated with. The analyses were pre-specified and the findings are the findings. No one had control or influence over the data or the results that we found. Dr. Ray's previous consultation to plaintiffs' attorneys did not influence, could not influence, the study's findings because the study design made that impossible.

Now, could Dr. Ray's previous consultation to plaintiffs' attorneys have influenced his interpretation of our findings? I suppose that is a possibility, but having known Dr. Ray for more than 10 years, it's extremely unlikely because he is above all else, evidence-based. It's also important for you to know that there were no disagreements among the co-authors regarding the interpretation of the study results or its policy implications for public health. In this regard, please note that in addition to Dr. Ray, I had 6 other co-authors working with me from Kaiser Permanente in California, none of whom had a financial interest in Merck, Pfizer or with plaintiffs' attorneys. Their interpretation of the study results were the same as my own. So to summarize, we set out to design a study with a level playing field to test the specific question regarding myocardial infarction risk with rofecoxib. We found convincing evidence that rofecoxib

increased the risk of myocardial infarction and sudden cardiac death, and Dr. Ray's previous work for plaintiffs' attorneys did not influence the neutrality of our study findings or our interpretation of those findings. There is one other point to mention in this regard. At the recent FDA advisory committee meeting on cardiovascular risk with the COX-2 pain relievers, Dr. Richard Platt from Harvard was asked by FDA to give a presentation to the committee on epidemiology and how to distinguish a good study from a bad one. He pointed to our study, recently published in the Lancet, as one of the best studies on this subject.

3. What is an acceptable level of risk and what is an unacceptable level of risk by scientific standards?

All drugs carry some level of risk. The question ultimately is one of how great are the risks and are these risks offset and out-weighed by corresponding health benefits. Now I don't think that a single answer can be given to your question because each drug probably must be considered individually. That is, for each drug, the question of what level of risk is acceptable, must be individually determined. Since this hearing was stimulated by Merck's voluntary withdrawal of Vioxx, let's focus on it for a moment.

At the time FDA approved Vioxx in 1999, there was a theoretical concern that COX-2 pain relievers might increase the risk of heart attacks and other cardiovascular events. As I learned at the November 18 hearing, Merck scientists were apparently aware of this theoretical risk by 1996 and the VIGOR study was apparently designed in a manner that intentionally sought to minimize the possibility of uncovering this cardiovascular risk. Given the theoretical concern that COX-2 inhibitor drugs might increase cardiovascular risk, and given the fact that everyone at Merck and at FDA knew that Vioxx would be used by millions of Americans, why didn't FDA insist on clear proof of cardiovascular safety before approving the drug? As it is, FDA was satisfied with the converse, that is, the absence of proof of harm. I will return to this in a moment because it relates to the concept of "scientific standards" mentioned in your question. In addition, FDA had to be fully aware of how the VIGOR study was designed, and FDA apparently didn't object. Why was this? FDA had to know that the typical Vioxx user would be in his/her 60's and that 80% of 65 year olds in the US have at least one other risk factor for cardiovascular disease in addition to their age. In other words, the typical Vioxx user would have a high probability of underlying cardiovascular disease, either diagnosed or waiting to become symptomatic. So if the typical Vioxx user would be at risk of heart disease, why not insist that they be included in VIGOR? I don't have an answer but I don't think excluding such patients from the clinical trial served the public health By such exclusions, the potential to underestimate the population impact of Vioxx was increased.

Regarding FDA's standards of scientific evidence, I mentioned this in my written and oral testimony. Basically, FDA applies different standards for efficacy and safety. For efficacy, FDA wants to be at least 95% certain that a drug has an effect (e.g., lowers cholesterol level). The clinical trials that are performed before approval are primarily designed to demonstrate this effect, not to prove safety. The starting assumption for a clinical trial (referred to as the "null hypothesis" by scientists) is that the drug does not have an effect. The scientific standard of evidence required by FDA is to show, with at least 95% certainty, that the null hypothesis is false. This standard ends up being fairly protective of patient safety because it protects the public against drugs that don't work.

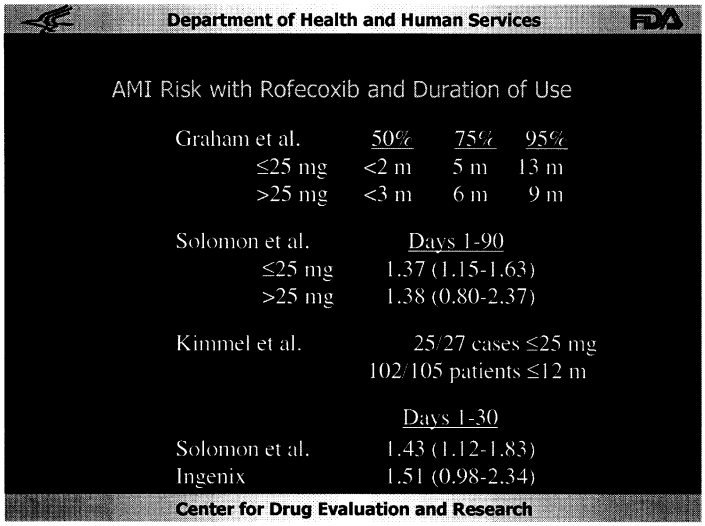
However, when it comes to safety, the FDA standard is lax and protects the drug rather than the public. FDA's starting assumption is that the drug is safe. As a result, there is no incentive for a company to disprove that assumption, and typically, the clinical trials that are performed are too small in size and too short in duration to detect, let alone "prove," the presence of a serious safety problem. This presumption of safety and reliance on studies that are too under-powered to detect important differences in risk, leads to drugs with serious safety problems being approved or marketed in the US. FDA is biased in favor of approval, not safety.

In the case of Vioxx, I believe that the 5-fold increase in heart attack risk associated with use of the high-dose strength was unacceptable from a public health perspective. Cardiovascular disease is the leading killer of adult Americans and a drug that increases that risk by a factor of 5 is quite alarming. A 5-fold increase in risk might be "acceptable" if the event we were talking about was rare rather than common (liver failure-rare; heart attack-common). It might also be "acceptable" if the drug in question treated an immediately life-threatening disease, or would be used by only a very small number of patients with no other alternative for a serious disease. These conditions did not apply to Vioxx.

Additionally, we normally talk about the balance of a drug's benefits with its risks when discussing whether a drug should be marketed or continue to be marketed. For Vioxx, we estimated the population cost in terms of heart attacks and sudden deaths caused by its use. There was no similar estimation of how many lives were saved by Vioxx use, which would be a comparable level of population benefit. As an illustration, take a look at high-dose Vioxx. Its approved indication was "short term treatment of acute pain." When the VIGOR results came to FDA in early 2000, apparently no one at FDA questioned whether the benefits still exceeded the risks. FDA just continued to presume that they did without subjecting that presumption to its proof. This determination was implicit in FDA's settling for a label change, rather than seeking to ban the high-dose use of the drug. But what was FDA's basis for this determination? To my knowledge, there is no document that describes FDA's assessment of the benefits and risks of high-dose Vioxx so that one can see that the benefits clearly exceed the risks. The truth is, the benefits don't exceed the risks. There are many other therapies available for the "short term treatment of acute pain" that do not increase the risk of heart attack and many of which also have no adverse effect on the gastrointestinal tract. Nearly 4 million women per year give birth, and many of these receive "short term treatment for acute pain" with medications that are more effective pain relievers than Vioxx and carry no risk of heart attack. Had FDA banned the high-dose use of Vioxx in early 2000, tens of thousands of heart attack deaths would have been prevented, but these lives were lost because FDA is too beholden to its approval decisions and habitually presumes benefit without demanding hard evidence. In my 20 years of experience at FDA, I have never, not once, seen a safety issue where FDA actually estimated the benefit of a drug product in order to support its claim that the "benefits exceeded the risks." I did this for one drug product (Arava) about three years ago and was roundly criticized for having done so because I showed that for the drug in question, the risks clearly exceeded the benefits.

4. Explanation of how I arrived at the estimate of 88,000 to 140,000 excess cases of heart attacks and sudden deaths, of which 30-40% probably died.

From the VIGOR study, we obtained the relative risk estimate of 5 for the increased risk of heart attack with high-dose Vioxx. From the APPROVe study, we obtained the relative risk estimate of 2 for the increased risk of heart attack with lower dose Vioxx. The APPROVe study did not find a difference in heart attack risk compared with placebo until 18 months of continuous Vioxx use, but this was probably due to the very low statistical power of the study to show a clear difference prior to that time. If you examine the confidence intervals around the estimates for Vioxx and placebo during these first 18 months, you see how very wide they are, and also that it is quite possible that the heart attack risk is present. However, the amount of data we have is too small to show an effect if it's present. Secondly, it's difficult to imagine an underlying mechanism to explain an 18 month lag time in development of increased risk, especially considering that risk is apparent quickly with higher dose Vioxx. But most importantly, I examined the epidemiologic literature to see when heart attack risks with Vioxx became apparent. I recently presented this at an FDA advisory committee meeting on COX-2 inhibitors.



Four epidemiologic studies each found an increased risk of heart attack with the lower dose of Vioxx. In each study, the duration of Vioxx use was far less than 18 months. The difference between the APPROVe study and these epidemiologic studies is that the epidemiologic studies had far greater numbers of cases of heart attack exposed to Vioxx. This higher number of exposed cases translates into greater statistical power to show that the heart attack effect is present virtually as soon as Vioxx use begins. Please understand that if the power of your study is low, you could easily fail to observe an increased risk that is truly present. The power in the APPROVe study was very low, especially during the first 18 months because there were only a handful of heart attack events. In the epidemiologic studies cited above, there were 58, 202, 25 and 83 cases exposed to lower dose Vioxx. In a fifth study from California Medicaid, we had 960 heart attack cases exposed to lower dose Vioxx, and in this study also, the effect was present very early. In any event, there are many reasons to believe that heart attack risk with Vioxx begins as soon as use of the drug begins and this was incorporated into our estimate.

Regarding the case fatality rate for heart attack, I used data from the American Heart Association that shows that about 44% of all serous coronary events (heart attacks and sudden cardiac deaths) are fatal. By using the 30-40% figure, I was being conservative.

To estimate the number of excess heart attack events among Vioxx users, I took the total number of Vioxx prescriptions in the US for the years 1999-2004 (obtained from IMS Health, a commercial data vendor) and multiplied this by the average prescription length. This gave me the total person-time of Vioxx use in the US. IMS data was used to split this usage into that associated with higher dose and lower dose Vioxx. A standard epidemiologic formula was used to calculate the number needed to harm, based on the relative risk values from the VIGOR and APPROVe studies. The resulting number needed to harm was divided into the total person-time of Vioxx use, to obtain estimates of the number of US cases of heart attack and sudden death.

PREPARED STATEMENT OF HON. CHARLES E. GRASSLEY

Good morning. We're here today because Congress has a Constitutional duty to conduct oversight of the executive branch of government. Congressional oversight can expose wrongdoing in the Federal bureaucracy and in the private sector. Congressional oversight can shed disinfecting sunlight. It can result in accountability and necessary reforms for the public good. Today's hearing will consider allegations of mismanagement by the Food and Drug Administration and the Merck pharmaceutical company regarding the safety of the painkiller Vioxx.

On September 30th of this year, Merck withdrew Vioxx from the worldwide market. A blockbuster drug became a blockbuster disaster. Before September 30th, Vioxx was the subject of controversy in the scientific community behind closed doors. Today we will look out in the open at the decisions made about Vioxx. Depending on the perspective you take, Vioxx either changed lives for the better or ended lives prematurely.

Historically the Food and Drug Administration has met its charge to protect the health and safety of the American people. Those who work at the agency are by and large committed to doing no harm. Even so, the FDA has also stood watch over failures when it comes to drug safety.

Likewise, the pharmaceutical industry in the United States has achieved extraordinary advancements in medicine. Drugmakers have helped to save lives and improve the quality of life of people around the world. They've profited by doing so. At the same time, the industry has contributed to the skyrocketing costs of health care and settled billions of dollars in false claims against the government, including both civil and criminal actions.

Merck & Co. has a reputation for excellence in research and development. Yet today Merck is faced with one of the worst drug disasters in history. Merck acknowledged that Vioxx carried with it serious cardiovascular risks when it withdrew the drug from the market. During today's hearing we'll hear about the red flags that were raised about those risks in the years before and the years after Vioxx was approved by the FDA.

The Finance Committee has jurisdiction over the Medicare and Medicaid programs.

Accordingly, the committee has a responsibility to the more than 80 million Americans who receive health care coverage—including prescription drugs—under these programs. Of the 20 million Americans who reportedly took Vioxx, an untold number are Medicare and Medicaid beneficiaries. I asked the Office of the Inspector General for the Department of Health and Human Services how much the Federal Government reimbursed Merck for Vioxx. I was told that the Medicaid program paid in excess of $1 billion for Vioxx while Vioxx was on the market. I've also seen a June 4, 1999 Merck document titled "IN IT TO WIN IT" that said: "As of yesterday, Vioxx became reimbursable on Medicaid in 42 States with the other 8 States close behind." The Medicaid market was clearly going to be a money maker for Merck, and Medicaid has paid Merck well for Vioxx.

Last year Vioxx sales totalled $2.5 billion. Merck's marketing effort included $160 million for direct-to-consumer advertising. It's been said that in the history of pharmaceutical advertising, Vioxx was one of the most directly marketed to consumers prescription drugs ever. In addition to targeting consumers directly, Merck reportedly spent more than that marketing Vioxx directly to physicians. There's nothing wrong with either of these efforts. Such marketing is part of the system, but today's hearing will consider whether Merck followed the letter and spirit of the law with its marketing of Vioxx.

The witnesses here today will help tell the Vioxx story. That story will continue to unfold in the months ahead. It will affect public confidence. When the FDA approves a drug, it's considered a "Good Housekeeping Seal of Approval." However, what's come to light about Vioxx since September 30th makes people wonder if the FDA has lost its way when it comes to making sure drugs are safe. Today's witnesses will describe how danger signals were ignored. They'll offer perspective on how appropriate action wasn't taken. We'll see that the FDA failed to heed the words of its own scientists.

It also looks like the FDA allowed itself to be manipulated by Merck on labeling changes that became necessary after a review by Merck that's known as the VIGOR trial. The VIGOR trial found that heart attacks were 5 times higher for Vioxx patients than for patients on another drug. Even so, nearly 2 years passed before any label change was made by the FDA. Merck completed the VIGOR trial in March, 2000. It gave the findings to the FDA in June, 2000. The trial was the subject of an advisory board meeting in February, 2001. But it was April 11, 2002 before the Vioxx label was actually changed. During these 22 months, Merck aggressively mar-

keted Vioxx, knowing that consumers and doctors were largely unaware of the cardiovascular risks found in the VIGOR trial.

One of my concerns is that the FDA has a relationship with drug companies that is too cozy. That's exactly the opposite of what it should be. The health and safety of the public must be the FDA's first and only concern. I'm interested in changes inside the FDA that result in greater transparency and openness at the Food and Drug Administration. One reform that may be needed is an independent office of drug safety. It doesn't make sense from an accountability standpoint to have the office that reviews the safety of drugs that are already on the market to be under the thumb of the office that put the drugs on the market in the first place.

The bottom line is, consumers should not have to second-guess the safety of what's in their medicine cabinets. The public should feel confident that when the FDA approves a drug, you can bank on it being safe, and if a drug isn't safe, the FDA will take it off the market.

We have three panels of witnesses today. The first witness is Dr. David Graham. He is an epidemiologist for the FDA. Dr. Graham recently completed a study involving Vioxx, and he'll discuss his findings. Dr. Graham will also describe the environment where he works in the FDA's Office of Drug Safety. It's this office that's responsible for monitoring the effect of a drug once it's on the market.

Our next witness is Dr. Gurkipal Singh. Dr. Singh will testify by video conference from California where he is recovering from a heart attack. Dr. Singh is an Adjunct Professor of Medicine at Stanford University. He is a former consultant to Merck on Vioxx. Dr. Singh will describe how he was threatened by Merck in that capacity because of his concerns about Vioxx. Dr. Singh will also explain how drugs like Vioxx work, the information that was available about the cardiac safety of Vioxx, and the labeling changes made to Vioxx. The committee will also hear testimony from Dr. Bruce Psaty. Dr. Psaty is an epidemiologist, a practicing physician and a drug safety expert. He will discuss the studies about Vioxx, the risks and benefits of such drugs, and how similar drug disasters can be prevented. After these three witnesses, we will hear from Dr. Sandra Kweder of the Food and Drug Administration, and Mr. Raymond Gilmartin, the Chief Executive Officer of Merck & Co.

The record for this hearing will remain open for 10 days. Committee members should submit remarks and questions for the record no later than November 29. In addition, a number of documents will be discussed today. They have been made available to the committee members, their staffs and the hearing witnesses. Many of these documents have been provided to the committee by Merck and other parties to litigation involving Vioxx. As a result, they may be considered confidential in the context of those court proceedings. I ask that committee members, their staffs and the hearing witnesses not leave the room with their bound copies of these documents during this hearing today. Committee staff will collect the exhibits from each witness, committee member and from all committee staff at the close of the hearing.

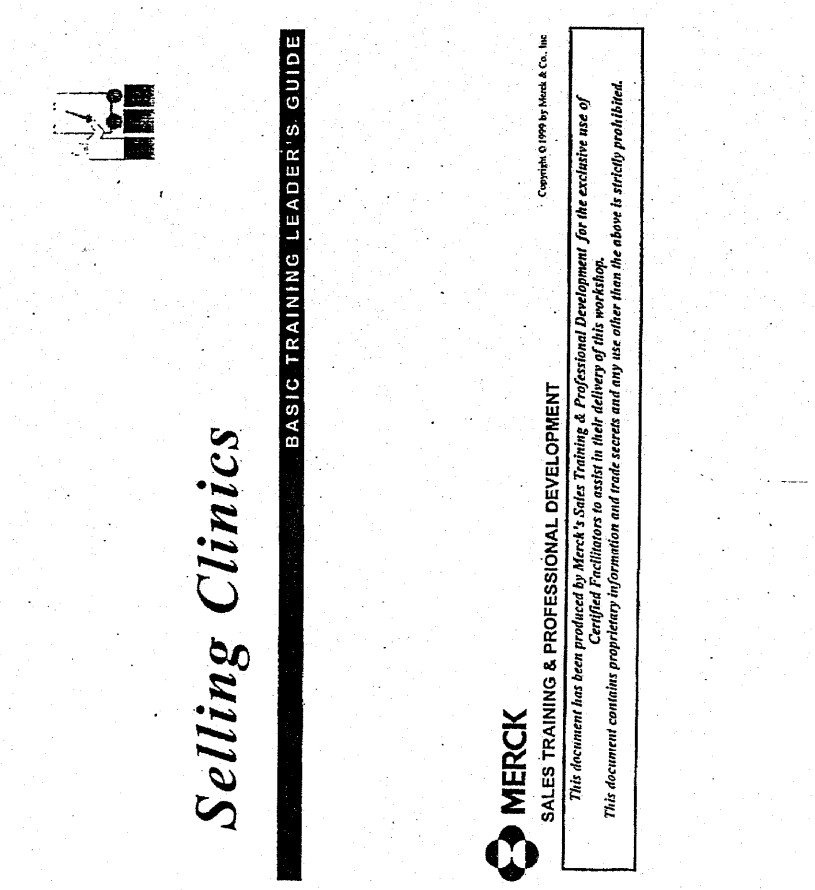
I look forward to the opening remarks of the Ranking Member of the Finance Committee, my colleague, Senator Baucus.

Before the testimony begins, I wish to respond to comments issued last night by the FDA's acting administrator, Dr. Crawford, about Dr. Graham, our first witness. News reports today say the FDA is calling Dr. Graham "a maverick who did not follow Agency protocols."

Today's hearing includes a lot of testimony about scientific findings. It's not about protocols or administrative "he said, she saids." Dr. Graham completed an FDA-sponsored 3-year study under FDA guidance and with Drs. Campen, Levy, Shoor, Ray, Cheetham, Spence and Hui. Dr. Graham's immediate supervisor said the paper that formed the basis of the study was ". . . an excellent study and analysis of a complex topic." So the clarifications provided last night by Dr. Crawford appear intended to intimidate a witness on the eve of a hearing. I want to hear about Dr. Graham's study today. In fact, just 7 days ago—on November 9th—Dr. Crawford met with Dr. Graham and acknowledged that there was a culture problem at the FDA and a problem with drug safety. Dr. Crawford even asked Dr. Graham to consider helping with an "internal FDA drug safety program and developing recommendations for improvements. . . ." So Dr. Crawford knows there's a problem and would better serve the FDA by spending time on the problem rather than going after congressional witnesses who helped identify the problem in the first place.

[SUBMITTED BY HON. ORRIN G. HATCH]

EXHIBIT 1.—MERCK TRAINING MANUAL



Note to Facilitator:

The following is a list of materials and supplies you and your participant will utilize during this workshop.

EQUIPMENT	☒ Overhead Projector ☐ Projection System ☐ TV / VCR ☐ Other
SUPPLIES	☒ Flipchart Markers ☒ Masking Tape ☒ Push Pins ☒ Blank Flip Pads ( ) ☒ Flipchart Stand ( )
OVERHEADS	**Please refer to Appendix to view Overhead Images*
PARTICIPANT MATERIALS/ HANDOUTS	• WP Selling Clinic Participant Workbook • Feedback Forms
OTHER	• Dodge Ball game cards (Obstacles for Products 1-3) • Approved Reprints for Products 1-3 • Product-specific outlines

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TIPS TO FACILITATOR

This workshop is delivered with each product during the West Point weeks of Basic Training. As trainees progress through the products, less time may needed to be spent on setting up the activities. Likewise, the workshop for the first product may take additional time for set up and explanation.

The following is an explanation of the icons used throughout this guide.

Activity or Exercise requires use of blank flipchart

Activity or Exercise requires videotaping

Activity or Exercise requires use of a video

Activity or Exercise requires use of participant workbook

Activity or Exercise requires use of slides

Activity or Exercise requires use of a CD-ROM

When Pre-prepared Flipcharts or Overheads are to be used, actual images will be shown within the guide.

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OVERVIEW

The purpose of this workshop is build on selling skills learned in earlier weeks of training. This workshop will also give representatives an opportunity to formulate messages, develop selling discussions, handle obstacles and competitive usage and target the use of their sales aids to realistic physician types and patient profiles.

OBJECTIVE

At the completion of this workshop, participants will be able to:

- Describe/Discuss marketing strategy and physician segmentation as they relate to each brand.
- Describe/Discuss the rationale for product-specific marketing messages.
- Identify key selling messages that competitors use when comparing their products to Merck products.
- Recognize appropriate sales messages and materials to deliver to specific physician types.
- Explain rationale for message/material selection based on physician type and patient need.
- Formulate messages appropriate for specific physician types and needs.
- Handle obstacles in order to appropriately position Merck products.
- Explain how reprints can be used to deliver appropriate messages to a specific physician type and needs.

MODULE FLOW

Topic	Time	Learning Method	Comments & Tips
Welcome, Debrief of Marketing/Medical Presentation	20 minutes	▪ Trainer-led Discussion ▪ Group Activity	
Point-Counter-Point	40 minutes	▪ Group Activity ▪ Trainer-led Discussion	
Obstacle Handling (dodge ball)	45 minutes	▪ Group Activity	
Resource Review	30 minutes	▪ Small Group Activity ▪ Trainer-led Discussion	
NBS Review	15 minutes	▪ Trainer-led Discussion	
Customizing the Message	2 hours	▪ Trainer-led Discussion ▪ Small Group Activity	
Rapid Role Play & Wrap-Up	30 minutes	▪ Role-Play Activity	
TOTAL TIME	5 hours		

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Welcome & Introduction and Debrief Marketing/Medical Presentations

Time: 20 minutes

At A Glance - Material/Media	Instruction
	■ **Welcome** the participants to the Selling Clinics. ■ **Introduce** any guests that are joining the session (Class Counselors, Business Managers, etc.). ■ **Explain** that the Selling Clinics are a continuation of what they have already learned during their RBG training and that they will participate in Selling Clinics for each of their primary products. ■ **Refer** to **OH: Selling Clinics Agenda** and **review:** Competitive Review Obstacle Handling Resource Review NBS Customizing the Message ■ **Ask** participants if they have any questions about the agenda. **Answer** questions appropriately or **'table'** questions that will be addressed at a later point in training. ■ **Ask:** What outstanding questions do you have from the Marketing or Medical presentations? ■ **Instruct** group to fill out speaker evaluation forms. ■ **Explain** that throughout this workshop they will have an opportunity to incorporate the information that was presented into sales discussions. ■ **Explain** that before getting started, you'd like to take a few minutes to recap some of the information that was just presented in the Marketing/Medical Presentation(s).
Product –Specific Outline	■ **Refer** to the product-specific outline provided and briefly **review** physician segmentation strategy as covered in presentations. ■ **Refer** to the product-specific outline provided and briefly **review** marketing messages as covered in presentations.

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Now that we've recapped the Marketing and Medical information, we're ready to get started. As we progress through training, keep those marketing messages and physician segmentation strategies in mind. Let's start with what we'll call *Point-Counter-Point.*

Point-Counter-Point

Time: 40 minutes

At A Glance - Material/Media	Instruction
	■ Divide class into teams of 3 or 4 (based on class size) and assign each team one of the key competitors for the given Merck product.
	■ Instruct each group to identify and flipchart all of the major selling points of their assigned competitive product on FC: Point.
	■ Allow 8 minutes.
	■ Instruct one of the other groups to be prepared to counter the selling points of competitive product #1 with appropriate selling messages for the Merck product.
	■ Refer participants to WB: Point-Counter-Point for notetaking.
	■ Ask for a volunteer from Competitive Product #1 to present the group's findings.
	■ Ensure that findings are consistent with the product's Package Insert.
	■ Allow the group that is countering Competitive Product #1 2 minutes to record their counter points on FC: Counter-Point.
	■ Instruct a volunteer to review the counter points
	■ **Refer to OH:** Reminder and review: In accordance with Policy Letter 110, you cannot make direct comparisons between Merck products and competitive products during a sales discussion unless explicitly instructed to do so by West Point. Any reference that you make to competitive products must be the result of a physician's question, or to clarify a misconception. All information must be taken directly from the competitive product's package insert.
	■ Instruct one of the other groups to be prepared to counter the selling points of competitive product #2 with appropriate selling messages for the Merck product.

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- Ask for a volunteer from Competitive Product #2 to present the group's findings.
- Ensure that findings are consistent with the product's Package Insert.
- Allow the group that is countering Competitive Product #2 2 minutes to record their counter points on FC: Counter-Point.
- Instruct a volunteer to review the counter points
- Instruct one of the other groups to be prepared to counter the selling points of competitive product #3 with appropriate selling messages for the Merck product.
- Ask for a volunteer from Competitive Product #3 to present the group's findings.
- Ensure that findings are consistent with the product's Package Insert.
- Allow the group that is countering Competitive Product #3 2 minutes to record their counter points on FC: Counter-Point.
- Instruct a volunteer to review the counter points
- Wrap up the session by asking the following debriefing questions:
  - ⇒ What is the value in knowing the selling messages for your competitive products?
  - ⇒ What was challenging about providing the counter points to each competitor?
  - ⇒ When might you be faced with handling competitive information on territory?
  - ⇒ Within the guidelines of Policy Letter 110, how can you utilize this information on territory?

We're off to a great start. In addition to recapping the Marketing and Medical information, we've completed a thorough competitive review. After lunch (or break), we're going to dig in a little deeper by starting off with some obstacle handling in order to apply the counterpoint messages.

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Dodge Ball (Obstacle Handling)

Time: 45 minutes

At A Glance - Material/Media	Instruction
	■ Welcome participants back from lunch (break).
	■ **Divide** the group into 2 teams and **assign** a name to each team.
	■ **Instruct** the groups to sit in a circle around the table/podium.
	■ **Ask:** How many of you have ever played Dodge Ball? **Acknowledge** responses.
	■ **Say:** Think of this next session as recess after lunch. We are going to play a variation of Dodge Ball, so let's take a look at the rules.
	■ **Refer** to **OH: Dodge Ball Rules** and **explain:** 1. I will ask one person from each team a question. The first person to put his/her hand on the table/podium and give the correct answer wins (similar to Family Feud). 2. The winner will then select a game card. If s/he selects a card with an Obstacle, then s/he must read the card information and handle the obstacle using the CRCT method. 3. If the obstacle is handled appropriately then that team receives a point. If the obstacle was not handled appropriately, then the other person has the opportunity to handle the obstacle and receive a point. 4. If the winner selects a Dodge card, then s/he doesn't have to handle an obstacle and instead receives two points. 5. Each player will then select another person on his/her team to step up to the podium and we'll repeat the process. 6. Once all of the game cards have been selected, the game is over and the team with the most points wins!
	■ **Instruct** each team to select the team's first player.
	■ **Refer** participants to **WB: Obstacle Handling** for notetaking during the game.
	■ **Call** the first two players to the front of the room and **remind** them of how the game is played: The first person to put his/her hand on the table and give the correct answer wins.

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- Ask a general trivia question (ex. "What does the letter 'W' stand for in George W. Bush?). The first person to put his/her hand on the table/podium *and* give the correct answer wins and his/her team receives the opportunity to pick a card. If that person answers incorrectly, then the other person has the chance to answer the question and pick a card.
- **Instruct** the winner to select a game card.

  If s/he selects a Dodge Ball: that team receives two points.

  If s/he selects an Obstacle: the person must handle the obstacle using the CRCT method. If s/he handles the obstacle appropriately, then that team receives one point. If s/he does not handle the obstacle appropriately then the other player has the opportunity to answer for one point.

- **Record** any points under the appropriate team name on **FC: Score.**
- **Instruct** each player to select another player from his/her team to step up to the table/podium.
- **Call** the next two players to the front of the room.
- **Repeat** process of asking a question, then card selection until all game cards are selected or there are **5 minutes** remaining in the workshop.
- **Add** up the points for each team and determine who the winners are.
- **Congratulate** the winners and distribute their prizes.

- **Remind** participants of **WB: Obstacle Handling** and **wrap up** the workshop by **asking** the following debriefing questions:
  - ⇒ What did you learn from this game?
  - ⇒ What was your biggest challenge when it was your turn to handle an obstacle?
  - ⇒ What would you do differently next time?
  - ⇒ How will you apply this information on territory?

You've done a great job so far on identifying and responding to the selling points of your competitors, as well as handling additional obstacles. You certainly know your stuff, including the sales aids that you've been using during your RBG training. Now we're going to take a look at some additional resources that you can use during sales discussions, approved reprints.

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SELLING CLINICS

Resource Review

Time: 30 minutes

At A Glance - Material/Media	Instruction
	■ **PRIOR** to the workshop, **ensure** that your class counselor has reviewed and broken down (or S.O.A.P.ed) the approved reprints designated by the point trainer. S/He will be responsible for reviewing this information for the class. ■ **Say:** We've had the opportunity to practice handling specific obstacles that may get thrown our way when out on territory. Now we're going to take our sales discussions one step further by incorporating the use of approved reprints. ■ **Say:** During training at your RBG, you had the opportunity to review at least one approved reprint for each of your primary products. Now you are going to review some other approved reprints. ■ **Instruct** trainees to take out their copy of Approved Reprint #1 and to follow along as the class counselor reviews, incorporating the S.O.A.P. format. ■ **Refer** participants to **WB: Resource Review** and **instruct** them to take notes as needed. ■ **Using** the notes that s/he made prior to class, the class counselor **reviews** the contents of Approved Reprint #1 for the trainees. **Ensure** that s/he highlights the key messages that can be found in this reprint. ■ **Ensure** that trainees understand where/how they can use this reprint by **asking** the following questions: ⇒ Which obstacles can be handled with this reprint? ⇒ Which physician type would most likely be interested in this reprint? ⇒ How would you use this resource on territory? ■ **Ensure** that all answers are in compliance with Policy Letters 110 and 118. ■ **Demonstrate** how to incorporate the approved reprint into a sales discussion by role-playing a discussion with a physician. ■ **Ask:** What questions do you have about this reprint or about using approved reprints in sales discussions? Answer questions appropriately. ■ **Say:** Now let's take a look at another approved reprint.

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SELLING CLINICS

- **Instruct** trainees to take out their copy of Approved Reprint #2 and to follow along as the class counselor reviews.
- Using the notes that s/he made prior to class, the class counselor **reviews** the contents of Approved Reprint #2 for the trainees. Ensure that s/he highlights the key messages that can be found in this reprint.
- **Ensure** that trainees understand where/how they can use this reprint by **asking** the following questions:
  - ⇒ Which obstacles can be handled with this reprint?
  - ⇒ Which physician type would most likely be interested in this reprint?
  - ⇒ How would you use this resource on territory?
- **Ensure** that all answers are in compliance with Policy Letters 110 and 118.
- **Demonstrate** how to incorporate the approved reprint into a sales discussion by role-playing a discussion with a physician.
- **Ask:** What questions do you have about this reprint? **Answer** questions appropriately.
- **Say:** As you have just seen, approved reprints can play an important role in your sales discussions. Not only do you need to know the information in the reprint, you also need to know how that information can be best utilized.

Before we move on, we're going to circle back and take a brief look at the Needs-Based Selling model, just to ensure that we're all still on the same page.

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NBS Review

Time: 15 minutes

At A Glance - Material/Media	Instruction
	■ **Say:** We all know the Needs-Based Selling model inside and out, right? Not only did you have a few days of training on the steps of the model, but you've been applying that model in your sales discussions over the past few weeks.
	■ **Say:** Despite your obvious expertise in this area, we are going to conduct a brief review, just to ensure that we're all on the same page.
	■ **Refer** participants to **WB: NBS Review** and **Instruct** them to take notes as needed.
	■ **Say:** First, let's look at the Patient Profile. As we know, a physician only reviews a chart for a few seconds before entering the exam room, so what could they be looking for? **Record** responses on **FC: Patient Profile.** *Possible Response:* *Age, gender, symptoms*
	■ **Say:** That's right. The physician is looking for the patient's age, gender and the symptoms s/he presented with. That's exactly what we need to focus on for our patient profile. This creates the need for our product.
	■ **Ask:** What are a few examples of specific patient profiles? *Possible Responses:* *Responses are product-specific, refer to product-specific outlines for examples.*
	■ **Say:** Once you've painted your patient profile, it's time to move to the next step - Assessment.
	■ **Ask:** What are two key question types we always need to ask? **Record** responses on **FC: Assess.** *Possible Responses:* *WHAT Questions* *WHY Questions*

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- **Say:** These two question types help us gather the information that we need in order to move forward in our sales discussion.
- **Say:** Sometimes the physician does not respond to your questions with enough detail.
- **Ask:** What can you do to bring forth additional information that will strengthen your support/limit statement?

  Possible Response:

  Ask a leading question
- **Ask:** What are a few examples of a leading question?

  Possible Response:

  Would you agree that the safety of a product is also important to you, Doctor?
- **Say:** Now you have enough information to move into Support/Limit.
- **Ask:** Why do you want to "support" the physician?

  Possible Response:

  We support the physician's intent to diagnose, treat, or prescribe. Support "WHY" s/he is using a competitive product.
- **Ask:** Where do you find the information to include in your support statement?

  Possible Response:

  After assessing "WHY," you can support the attributes of competitive product: efficacy, safety, outcomes, indications, etc.
- **Ask:** Why do you want to "limit" the physician?

  Possible Response:

  Plant a seed of doubt that the competitive product provides the optimal solution.
- **Ask:** Where do you find the information to include in your limit statement?

  Possible Response:

  The physician's response to the "WHAT" question.
- **Ask:** What are some examples of assessment questions used to develop information needed for Support/Limit statements?

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Possible Response:

What agent do you typically prescribe for this type of patient?

Why is it that you typically start with x?

What are your goals when using this therapy?

- **Ask:** What is a corresponding support/limit statement that you would use in this situation?

  Possible Responses:

  Responses are product-specific. Refer to product-specific outline for examples.

- **Ensure** that support/limit statements are within the guidelines of Policy Letters 110 and 118.
- **Remind** trainees that they cannot make direct comparisons between the Merck product and a competitor's product unless explicitly instructed to do so by West Point. Any information presented about a competitor's product must be taken directly from that product's Package Insert and be provided as the result of a direct question by a physician, or to clear up a misconception on the part of the physician.
- **Ask:** What does Support/Limit set you up for? That's right – your Compelling Message.
- **Ask:** What is the purpose of the compelling message?

  Possible Response:

  To frame our discussions in a way that matches our product's unique attributes to the customer's previously identified needs.

- **Ask:** What are some examples of a compelling message?

  Possible Responses:

  Responses are product-specific. Refer to product-specific outline for examples.

- **Say:** Okay. We've delivered our compelling message. Are we finished? Absolutely not - we need to Close.
- **Ask:** What are some common closing statements? **Record responses on FC: Close.**

  Possible Response:

  Will you prescribe (product) for patients who....

- **Say:** Asking the physician if there is any reason s/he will not prescribe the product is a Trial Close.

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SELLING CLINICS

- You must follow this up with a true close.
- **Say:** Other good, actionable closes include:
  - Will you now prescribe (product)?
  - Will you continue to prescribe (product)?
- **Say:** That was the much abbreviated, Reader's Digest version of Needs-Based Selling. What questions do you have? Answer questions appropriately.

You've had the opportunity to counter your competitor's selling message and handle a laundry list of obstacles. You've also looked at utilizing approved reprints in selling discussions. Our brief review of the NBS model has set the stage for us to pull everything together. Now it's time to practice customizing your sales discussion based on a particular scenario.

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Customizing the Message

Time: 2 hours

At A Glance - Material/Media	Instruction
	■ **Introduce** this segment to trainees by **explaining** that along with leveraging our product, we must be sure that our messages are targeted/focused on a specific patient profile, the physician needs/concerns and the needs/concerns of the patients they treat. ■ **Refer** to **OH: Customizing the Message** and **review** the format of this segment: Review Scenario 1 Trainer Demo 5 min. Role Play, 3 min. Feedback, Switch Role Play, Feedback Repeat for next Scenario
	■ **Refer** participants to **WB: Customizing the Message** for note taking.
Role-Play Scenarios	■ **Referring** to the product-specific outline, **explain** the first scenario including physician type, competitive agent, obstacle and patient profile. ■ **Ask** participants the following questions. ⇒ Based on this scenario, what would a good support/limit statement sound like? ⇒ Which resource would you use for this scenario? ⇒ Which key messages would you deliver for this scenario? ⇒ How would you handle this obstacle? ■ **Ensure** participants answer appropriately in conjunction with all applicable Policy Letters. ■ **Role-play** Scenario #1 with the help of a class counselor.

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At A Glance - Material/Media	Instruction
	■ **Ask:** What are some common closing statements? **Record** responses on **FC: Close.** *Possible Response:* *Will you prescribe (product) for patients who....* ■ **Say:** Asking the physician if there is any reason s/he will not prescribe the product is a Trial Close. You must follow this up with a true close. ■ **Say:** Other good, actionable closes include: Will you now prescribe (product)? Will you continue to prescribe (product)? ■ **Say:** That was the much abbreviated, Reader's Digest version of Needs-Based Selling. What questions do you have? **Answer** questions appropriately.
	**You've had the opportunity to counter your competitor's selling message and handle a laundry list of obstacles. You've also looked at utilizing approved reprints in selling discussions. Our brief review of the NBS model has set the stage for us to pull everything together. Now it's time to practice customizing your sales discussion based on a particular scenario.**

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Customizing the Message

Time: 2 hours

At A Glance - Material/Media	Instruction
	■ **Introduce** this segment to trainees by **explaining** that along with **leveraging** our product, we must be sure that our messages are targeted/focused on a specific patient profile, the physician needs/concerns and the needs/concerns of the patients they treat.
	■ **Refer** to **OH: Customizing the Message** and **review** the format of this segment: Review Scenario 1 Trainer Demo 5 min. Role Play, 3 min. Feedback, Switch Role Play, Feedback Repeat for next Scenario
	■ **Refer** participants to **WB: Customizing the Message** for note taking.
Role-Play Scenarios	■ **Referring** to the product-specific outline, **explain** the first scenario including physician type, competitive agent, obstacle and patient profile. ■ **Ask** participants the following questions. ⇒ Based on this scenario, what would a good support/limit statement sound like? ⇒ Which resource would you use for this scenario? ⇒ Which key messages would you deliver for this scenario? ⇒ How would you handle this obstacle? ■ **Ensure** participants answer appropriately in conjunction with all applicable Policy Letters. ■ **Role-play** Scenario #1 with the help of a class counselor.
	■ **Refer** to **OH: Feedback** and **WB: Customizing the Message Feedback Form** and **review** guidelines for providing feedback: Be specific and descriptive Focus on behaviors (what was done or said)

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At A Glance - Material/Media	Instruction
	■ **Break** participants into pairs, with one trainee playing the representative, the other the physician. ■ **Instruct** participants to role-play Scenario #1. ■ **Allow** 5 minutes. **NOTE to Trainer:** Time is negotiable, depending on the skill level of the group and their familiarity with the workshop. ■ **Instruct** role-play physician to provide feedback. ■ **Allow 3 minutes.** ■ **Call** time and **instruct** pairs to switch roles. ■ **Allow** 5 minutes. ■ **Instruct** role-play physician to provide feedback. ■ **Allow 3 minutes.** ■ **Call** time. ■ **Repeat** this process (introduce scenario, demo, role-play activity) for scenario #2, #3, #4, etc as time allows, such that you are finished with 10 minutes left in the workshop. On average, each participant should have the opportunity to practice 4 – 5 sales discussions. ■ **Ask** the following debriefing questions: ⇒ What did you learn from this activity? ⇒ What would you do differently next time? ⇒ What are some skills/behaviors that seemed to work well? ⇒ How will you apply this on territory? ■ **Close** and **transition** to next section.
ZDM	**Now that we've targeted our sales messages, identified how to use our resources effectively and handled key obstacles, let's streamline our sales discussions a bit further.**

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Rapid Role Play

Time: 30 minutes

At A Glance - Material/Media	Instruction
	■ **Explain** that participants have been decreasing the time needed for conducting sales discussions as the workshop has progressed. ■ **Ask** Which areas of your selling discussion can you streamline? How can you get to the point faster? *Possible Responses:* *patient profile, compelling message, close* ■ **Say:** Keep in mind that we are NOT downplaying the importance of a full sales discussion, including assessment and support/limit. The short sales discussion can happen only after you understand the prescription habits of your physicians. ■ **Role-play** a brief (2 minute) sales discussion. ■ **Ask** the following questions about your role-play discussion: ⇒ What was particularly effective about that discussion? ⇒ What could I have done differently? ⇒ How will you utilize the short sales discussion on territory? ■ **Break** participants into pairs, with one trainee as the representative, the other as the physician. ■ **Explain** that the representative will role-play a 2-minute sales discussion, and the physician will provide feedback, then they will switch roles. ■ **Refer to OH: Feedback** and review the guidelines for providing feedback: Be specific and descriptive Focus on behaviors (what was done or said) ■ **Instruct** pairs to start role-play. ■ **Allow** 2 minutes. ■ **Instruct** physician to provide feedback.

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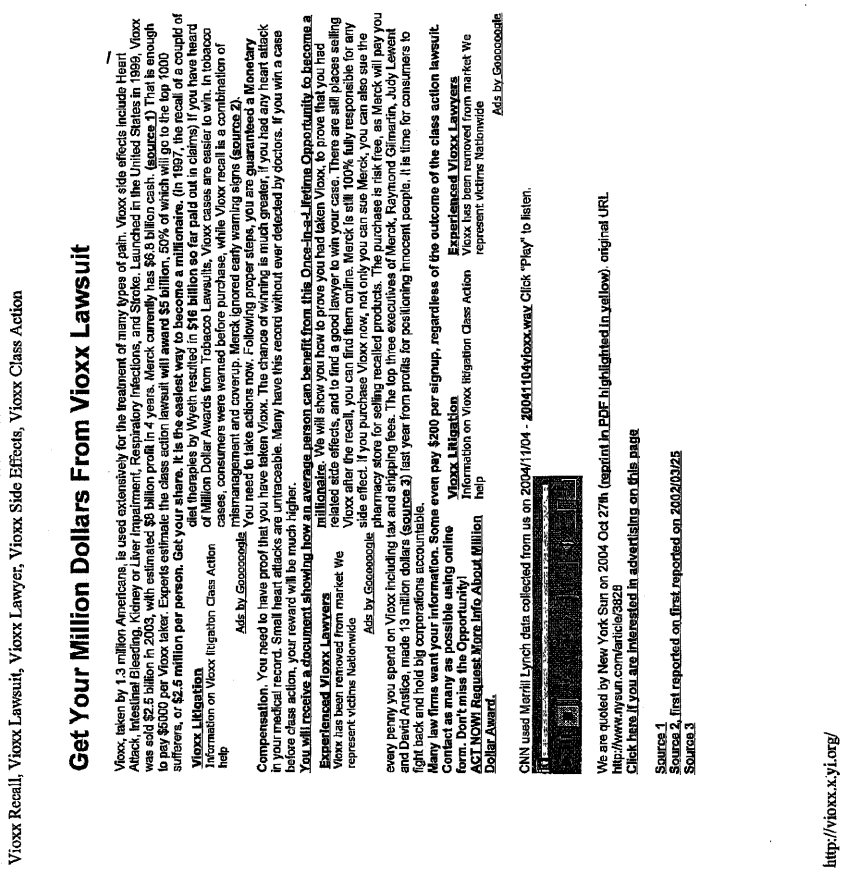
EXHIBIT 2.—GET YOUR MILLION DOLLARS FROM VIOXX LAWSUIT


Vioxx Recall, Vioxx Lawsuit, Vioxx Lawyer, Vioxx Side Effects, Vioxx Class Action

Get Your Million Dollars From Vioxx Lawsuit

Vioxx, taken by 1.3 million Americans, is used extensively for the treatment of many types of pain. Vioxx side effects include Heart Attack, Intestinal Bleeding, Kidney or Liver Impairment, Respiratory Infections, and Stroke. Launched in the United States in 1999, Vioxx was sold $2.5 billion in 2003, with estimated $6 billion profit in 4 years. Merck currently has $6.8 billion cash. (source 1) That is enough to pay $5000 per Vioxx taker. Experts estimate the class action lawsuit will award $5 billion, 50% of which will go to the top 1000 sufferers, or $2.5 million per person. Get your share. It is the easiest way to become a millionaire. (In 1997, the recall of a cocktail of diet therapies by Wyeth resulted in $16 billion so far paid out in claims) If you have heard of Million Dollar Awards from Tobacco Lawsuits, Vioxx cases are easier to win. In tobacco cases, consumers were warned before purchase, while Vioxx recall is a combination of mismanagement and coverup. Merck ignored early warning signs (source 2).

Vioxx Litigation
Information on Vioxx litigation Class Action help

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Compensation. You need to have proof that you have taken Vioxx. The chance of winning is much greater if you had any heart attack in your medical record. Small heart attacks are untraceable. Many have this record without ever detected by doctors. If you win a case before class action, your reward will be much higher.

You will receive a document showing how an average person can benefit from this Once-in-a-lifetime Opportunity to become a millionaire. We will show you how to prove you had taken Vioxx, to prove that you had related side effects, and to find a good lawyer to win your case. There are still places selling Vioxx after the recall, you can find them online. Merck is still 100% fully responsible for any side effect. If you purchase Vioxx now, not only you can sue Merck, you can also sue the pharmacy store for selling recalled products. The purchase is risk free, as Merck will pay you every penny you spend on Vioxx including tax and shipping fees. The top three executives of Merck, Raymond Gilmartin, Judy Lewent and David Anstice, made 13 million dollars (source 3) last year from profits for positioning innocent people. It is time for consumers to fight back and hold big corporations accountable.

Many law firms want your information. Some even pay $200 per signup, regardless of the outcome of the class action lawsuit. Contact as many as possible using online form. Don't miss the Opportunity!
ACT NOW! Request More Info About Million Dollar Award.

Experienced Vioxx Lawyers
Vioxx has been removed from market We represent victims Nationwide

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PREPARED STATEMENT OF SANDRA L. KWEDER, M.D.

INTRODUCTION

Mr. Chairman and Members of the committee, I am Dr. Sandra Kweder, Deputy Director of the Office of New Drugs at the Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA or the Agency). We appreciate the opportunity to participate in this hearing regarding drug safety and the worldwide withdrawal by Merck & Co., Inc. of Vioxx.

I. BACKGROUND ON DRUG SAFETY

Modern drugs provide unmistakable and significant health benefits. It is well recognized that FDA's drug review is a gold standard. Indeed, we believe that FDA maintains the highest worldwide standards for drug approval. FDA grants approval to drugs after a sponsor demonstrates that they are safe and effective. Experience has shown that the full magnitude of some potential risks does not always emerge during the mandatory clinical trials conducted before approval to evaluate these products for safety and effectiveness. Occasionally, serious adverse effects are identified after approval either in post-marketing clinical trials or through spontaneous reporting of adverse events. That is why Congress has supported and FDA has created a strong post-market drug safety program designed to assess adverse events identified after approval for all of the medical products it regulates as a complement

to the pre-market safety reviews required for approval of prescription drugs in the United States. Monitoring the drug safety of marketed products requires close collaboration between our clinical reviewers and drug safety staff to evaluate and respond to adverse events identified in ongoing clinical trials or reported to us by physicians and their patients. The most recent actions concerning the drug Vioxx (rofecoxib) illustrates the vital importance of the ongoing assessment of the safety of a product once it is in widespread use.

It is important to understand that all approved drugs pose some level of risk, such as the risks that are identified in clinical trials and listed on the labeling of the product. Unless a new drug's demonstrated benefit outweighs its known risk for an intended population, FDA will not approve the drug. However, we cannot anticipate all possible effects of a drug during the clinical trials that precede approval. An adverse drug reaction can range from a minor, unpleasant response to a drug product, to a response that is sometimes life-threatening or deadly. Such adverse drug reactions may be expected (because clinical trial results indicate such possibilities) or unexpected (because the reaction was not evident in clinical trials). It may also result from errors in drug prescribing, dispensing or use. The issue of how to detect and limit adverse reactions can be challenging; how to weigh the impact of these adverse drug reactions against the benefits of these products on individual patients and the public health is multifaceted and complex, involving scientific as well as public policy issues.

II. VIOXX

The Vioxx approval

FDA approved Vioxx in May, 1999 for the reduction of signs and symptoms of osteoarthritis, as well as for acute pain in adults and for the treatment of primary dysmenorrhea. Vioxx received a 6-month priority review because the drug potentially provided a significant therapeutic advantage over existing approved drugs due to fewer gastrointestinal side effects, including bleeding. A product undergoing a priority review is held to the same rigorous standards for safety, efficacy, and quality that FDA expects from all drugs submitted for approval.

As with many other new molecular entities, this product was taken before the Arthritis Advisory Committee, April 20, 1999, prior to its approval. It was the second of a new class (COX-2 selective) of non-steroidal anti-inflammatory drugs (NSAIDs) approved by FDA. The original safety database for this product included approximately 5,000 patients on Vioxx and did not show an increased risk of heart attack or stroke.

In the clinical trials conducted before approval, the risk of gastrointestinal (GI) side effects was determined through the use of endoscopy. At the time that FDA approved Vioxx, the available evidence from these endoscopy studies showed a significantly lower risk of gastrointestinal ulcers, a significant source of serious side effects such as bleeding and death, in comparison to ibuprofen.

The VIGOR study

After Vioxx was approved in 1999, Merck continued studies of Vioxx designed to look at clinically meaningful GI effects, such as stomach ulcers and bleeding (Vioxx Gastrointestinal Outcomes Research, or VIGOR study). This study was designed to provide longer-term clinical outcome data to confirm the shorter-term endoscopy findings and to evaluate overall safety. The VIGOR study was a large (8,000-patient) study designed to evaluate the GI safety of Vioxx as compared to naproxen. This study was done in a rheumatoid arthritis population who typically require a higher dose (50 mg was used) of anti-inflammatory medication.

VIGOR did not have a placebo group because to do so would have meant patients with rheumatoid arthritis would have been randomized to receive no pain relief. Use of a placebo would have been intolerable, because untreated patients would have suffered and left the study. The study also excluded subjects taking low-dose aspirin for cardiovascular (CV) prevention because use of aspirin might have contributed to increased rates of GI bleeding in the study and confounded the results. However, the exclusion of patients on low-dose aspirin may have influenced CV events in the study, since low-dose aspirin has been shown to reduce CV risk.

In April, 2002, FDA approved extensive labeling changes to reflect the findings from the VIGOR study. FDA also approved a rheumatoid arthritis indication at the 25 mg dose based on separate efficacy trials. The new label provided additional information to the Clinical Studies, Precautions, Drug Interactions and Dosage and Administration sections to reflect all that was known at the time about the potential risk of cardiovascular effects with Vioxx. These labeling changes included detailed information about the increase in risk of cardiovascular events relative to naproxen,

including heart attack. It also included data from the ongoing placebo-controlled Alzheimer's study at the 14-month time-point which did not show an increase in CV risk. The new labeling change also noted that Vioxx 50 mg was not recommended for chronic use.

Other Vioxx studies

In the years following the 1999 FDA approval of Vioxx, Merck began conducting a series of clinical trials exploring other potential indications of this product. All trials for chronic use were designed to monitor carefully for CV safety, and included data safety monitoring committees as well as blinded experts to assess all CV events in the trials. Some of these studies included placebo-controlled studies of Vioxx in Alzheimer's disease, prostate cancer, and colon polyps. Following the 2001 Advisory Committee meeting and the 2002 labeling changes, FDA focused on ensuring that all clinical trials conducted with Vioxx were designed to include careful monitoring of CV risk, and required that Merck submit all available CV data in ongoing trials.

In the period following the 2002 Vioxx labeling changes, FDA also continued to monitor the scientific literature, reviewing several retrospective epidemiologic studies. Some of these studies suggested an increased risk for CV events with Vioxx, primarily with the 50 mg dose, while others did not. Epidemiologic studies in real world populations of conditions such as heart attack or stroke are difficult to conduct and interpret because of the need to carefully and adequately account for the many known powerful risk factors for these diseases. Merck, or Pfizer, the manufacturer of Celebrex (another COX-2 inhibitor), sponsored, directly or indirectly, many of these epidemiology studies.

Given the need for data to distinguish the impact of the use of these drugs on cardiovascular risk from factors such as smoking, hypertension, diabetes, low-dose aspirin use, high cholesterol and others, the long-term, placebo-controlled trials that were being conducted offered the best opportunity to carefully assess both the existence of and the magnitude of these cardiovascular effects.

III. MERCK'S WORLDWIDE WITHDRAWAL OF VIOXX

Merck contacted FDA on September 27, 2004, to request a meeting to discuss with the Agency the Data Safety Monitoring Board's decision to halt Merck's long-term study of Vioxx in patients at increased risk of colon polyps. Merck and FDA officials met the next day, September 28, and during that meeting the company informed FDA of its decision to remove Vioxx from the market voluntarily. The data presented demonstrated an increase in cardiovascular risk and stroke starting at the 18-month time-point compared to placebo. This was the first demonstration of a difference in comparison to a placebo group, and supported the previous signal seen in the VIGOR trial and some of the epidemiologic studies.

IV. THE KAISER STUDY ON VIOXX

In follow-up to the VIGOR findings, FDA worked with Kaiser Permanente California HMO as part of a collaborative agreement to provide an alternative means of evaluating the CV safety signal using a managed-care database. In 2001, the forerunner of the Office of Drug Safety (ODS) and Dr. David Graham began informal discussions with Kaiser Permanente about projects of mutual interest. At the same time, FDA's Arthritis Advisory Committee was reviewing the cardiovascular risk observed in clinical trials for Vioxx and recommended the need to collect additional information regarding this risk. Dr. Graham indicated that Kaiser was interested in the CV safety of the COX-2 agents in general and in pursuing a scientific collaboration with ODS on this topic even if Agency funding were not available for the full study. FDA provided funding to partially support this pilot scientific collaboration in August, 2001 and again in August, 2002. A protocol for the study was developed to study the risk of myocardial infarction among users of selective (COX-2) and nonselective non-steroidal anti-inflammatory agents (NSAIDs). Dr. Graham was designated the ODS project officer for this study to work with his counterparts at Kaiser Permanente. Dr. Wayne Ray, an epidemiologist at Vanderbilt University and a cooperative agreement grantee of FDA, was added to the study team during the course of the study. Dr. Graham periodically discussed his work with his supervisors to provide updates on the progress of the study.

In February, 2004, Dr. Graham and his coauthors submitted an abstract to the International Society for Pharmacoepidemiology (ISPE) for possible presentation at the August, 2004 meeting in Bordeaux, France. No study results were included in this abstract, which was accepted for a poster presentation in August, 2004. In May, 2004, Dr. Graham and his coauthors submitted an abstract of their study findings to the American College of Rheumatology (ACR) for possible presentation at their

October, 2004 meeting in San Antonio. The deadline for submitting abstracts for the San Antonio meeting was May 13, 2004. Dr. Graham informed his supervisor about his authorship role in the ACR abstract in early September, 2004.

On August 11, 2004, David Graham first shared a draft of his ISPE poster presentation with his supervisors to obtain their review and clearance, as is required of any FDA author or presenter. At that time, Dr. Graham's supervisors in ODS informed him of the importance of this work and the need to promptly complete a study report for circulation within the Agency and for broader dissemination in a scientific journal. In reviewing the poster presentation, scientists within ODS and within the Office of New Drugs with specific expertise in COX-2s provided comments and raised questions regarding the study design and statistical modeling, which were not detailed in the poster. The conclusion that high-dose Vioxx should never be used was questioned, as the label for the drug already recommended limiting high-dose use to no more than 5 days based on the cardiovascular risks identified in clinical trials. A concern was expressed that the data presented in the poster and in the medical literature did not support the recommendation of never using high-dose Vioxx. These comments and concerns were shared with Dr. Graham, who chose to revise his conclusions voluntarily. A disclaimer was placed on the poster to reflect that some of the conclusions and statements in the poster were those of the authors and did not necessarily reflect Agency policy.

Dr. Graham presented his poster in Bordeaux, France, on August 23–24, 2004, and participated in press coverage that discussed the findings. (Graham et al. at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management, August, 2004 reporting an elevated cardiovascular risk for the 50 mg dose of Vioxx).

Upon Dr. Graham's return from Bordeaux in late August, given the data's potential application to regulatory actions, Dr. Graham was asked to submit a draft report for Agency review within 2 weeks. He asked for a September 30, 2004, deadline and on that date, Dr. Graham provided a first draft of his report to his supervisors. Discussions concerning the report are ongoing between Dr. Graham and his supervisors. Dr. Graham has meanwhile submitted a manuscript version of the report to *Lancet* for publication.

V. FDA INITIATIVES TO STRENGTHEN DRUG SAFETY

At FDA, we are constantly searching for ways to improve our processes and methods, and thereby better serve the public health. On November 5, 2004, FDA announced a five-step plan to strengthen its drug safety program. First, CDER will sponsor an Institute of Medicine (IOM) study on FDA's drug safety system. An IOM committee will study the effectiveness of the United States' drug safety system, with an emphasis on the post-market phase, and assess what additional steps could be taken to learn more about the side effects of drugs as they are actually used. We will ask IOM to examine FDA's role within the health care delivery system and recommend measures to enhance the confidence of Americans in the safety and effectiveness of their drugs.

Second, CDER will implement a program for addressing differences of professional opinion. Currently, in most cases, free and open discussion of scientific issues among review teams and with supervisors, managers and external advisors, leads to an agreed course of action. Sometimes, however, a consensus decision cannot be reached, and an employee may feel that his or her opinion was not adequately considered. Such disagreements can have a potentially significant public health impact.

In an effort to improve the current process, CDER will formalize a program to help ensure that the opinions of dissenting scientific reviewers are formally addressed in a transparent decision-making process. An ad hoc panel, including FDA staff and outside experts not directly involved in disputed decisions, will have 30 days to review all relevant materials and recommend to the Center Director an appropriate course of action.

Third, CDER will conduct a national search to fill the currently vacant position of Director of the Office of Drug Safety, which is responsible for overseeing the postmarketing safety program for all drugs. The Center is seeking a candidate who is a nationally recognized drug safety expert with knowledge of the basic science of drug development and surveillance, and has a strong commitment to the protection of public health.

Fourth, in the coming year, CDER will conduct workshops and Advisory Committee meetings to discuss complex drug safety and risk management issues. These consultations may include emerging concerns for products that are investigational or already marketed. Examples of areas where FDA may seek input include:

- Whether a particular safety concern alters the risk-to-benefit balance of a drug;

- Whether FDA should request a sponsor to conduct a particular type of study to further address an issue;
- What types of studies would best answer safety questions;
- Whether a finding is unique to one product or seems to be a drug class effect;
- Whether a labeling change is warranted and, if so, what type; and
- How to otherwise facilitate careful and informed use of a drug.

These consultations will include experts from FDA, other Federal agencies, academia, the pharmaceutical industry, and the healthcare community.

Finally, by the end of this year, FDA intends to publish final versions of three guidances that the agency developed to help pharmaceutical firms manage risks involving drugs and biological products. These guidances should assist pharmaceutical firms in identifying and assessing potential safety risks not only before a drug reaches the market but also after a drug is already on the market. These guidances will rely on the use of good pharmacovigilance practices and pharmacoepidemiologic assessment. These documents are:

- "Premarketing Guidance," which covers risk assessment of pharmaceuticals prior to their marketing;
- "RiskMAP Guidance," which deals with the development and use of risk-minimization action plans; and
- "Pharmacovigilance Guidance," which discusses post marketing risk assessment, good pharmacovigilance practices and pharmacoepidemiologic assessment.

VI. CONCLUSION

In summary, FDA worked actively and vigorously with Merck to inform public health professionals of what was known regarding CV risk with Vioxx, and to pursue further definitive investigations to better define and quantify this risk. FDA also reviewed and remained current on new epidemiologic studies that appeared in the literature. Indeed, the recent study findings disclosed by Merck, leading to its decision to voluntarily withdraw Vioxx from the marketplace, resulted from FDA's vigilance in requiring these long-term outcome trials to address our concerns.

Detecting, assessing, managing and communicating the risks and benefits of prescription and over-the-counter drugs is a highly complex and demanding task. FDA is determined to meet this challenge by employing cutting-edge science, transparent policy, and sound decisions based on the advice of the best experts in and out of the agency. We are confident that the additional activities discussed above will strengthen the agency's program to greater ensure the safety of medical products that make a major contribution to the health and quality of life of millions of Americans. Medicines that receive FDA approval are among the safest in the world, and the measures we are taking are designed to strengthen this quality, as well as consumer confidence that FDA's processes ensure the highest protection of the public health.

RESPONSES TO QUESTIONS FROM SENATORS GRASSLEY AND BAUCUS

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

JAN 14 2005

The Honorable Charles E. Grassley
Chairman
Committee on Finance
United States Senate
Washington, DC 20510-6200

Dear Mr. Chairman:

Thank you for the letter of December 22, 2004, containing follow-up questions from the hearing entitled, "FDA, Merck and Vioxx: Putting Patient Safety First?" We have restated your questions below with our response for the record.

1. **The Committee has asked the FDA on at least 6 separate occasions to advise FDA employees that they may speak to Congress without fear of reprisal. State whether or not it is FDA policy that FDA employees are free to speak to Members of Congress without advising any FDA official, including the Office of Legislation?**

The response to this question is forthcoming.

2. **Dr. Kweder was asked by Chairman Grassley a question she was unable to answer, specifically involving hearing exhibit 60, an email dated October 7, 2004, which lists an action item that says, "Merck will critique the Graham paper in a teleconference with the agency." Is it common practice for the FDA to permit a drug company to critique an unpublished FDA study of that company's drug? Provide a detailed description and timeline of events related to the FDA sharing documents associated with Dr. Graham's study with Merck, including but not limited to the study abstract, poster, and manuscript. Provide for the hearing record a copy of all documents and communications between FDA and Merck related to Dr. Graham's Vioxx study abstract, poster, and/or manuscript, including but not limited to the file record related to FDA administrative action, as well as internal FDA email and email between FDA and Merck.**

Sometimes FDA does provide sponsors the opportunity to review draft articles before they are submitted or before they are accepted for publication. Some of the reasons for allowing such review include having the sponsor verify facts related to their studies or products, or providing a sponsor with advance notice of a matter that may generate press inquiries.

Timeline of Events:

- August 16, 2004 – Dr. Paul Seligman E-mailed Merck (Peter Honig, Martin Himmel, and Linda Hostelley), providing a copy of Dr. Graham's poster. The E-mail states that FDA had not had the opportunity to evaluate the methods at the date of email.
- August 17, 2004 – Martin Himmel responded to August 16th E-mail, asking if the document had been cleared by Office of New Drugs.
- August 17, 2004 – Anne Trontell responded to Dr. Himmel's E-mail, stating that Dr. Graham's presentation included a disclaimer: views are those of author, not FDA.
- August 17, 2004 – Linda Hostelley responded to August 16th E-mail, thanking us for the information.
- August 17, 2004 – Peter Honig responded to August 16th E-mail, stating that at some point FDA and Merck should discuss.
- August 25, 2004 – Merck left a telephone message with Brian Harvey, Deputy Director, Office of Drug Evaluation V. Merck's call was referred to Office of Drug Safety.
- August 26, 2004 – E-mail from Dr. Ned Braunstein, Senior Director, Regulatory Affairs, Merck, to Dr. Seligman thanking FDA for offering to share FDA questions and answers developed to handle press inquiries about Vioxx.
- August 26, 2004 – An E-mail was received by Dr. Seligman from Dr. Braunstein, discussing the preparation of questions and answers to handle press inquiries.
- August 26, 2004 – E-mail from Dr. Seligman to Dr. Braunstein apprising him that questions and answers for press inquiries were not yet finalized.
- August 27, 2004 – E-mail from Dr. Braunstein to Dr. Seligman and Dr. John Jenkins, Office of New Drugs, CDER. Dr. Braunstein requested that due to all of the media and patients being alarmed, FDA issue a press release or publish questions and answers to respond to media.
- August 27, 2004 – E-mail from Dr. Jenkins to Dr. Braunstein and Dr. Seligman, deferring decision on release of questions and answers for handling press inquiries.
- August 27, 2004 – E-mail from Dr. Braunstein to Drs. Seligman and Jenkins, providing a pasted copy of original press release from Kaiser and PRNewswire release from Bordeaux, France.
- August 27, 2004 – E-mail from Dr. Braunstein to Drs. Seligman and Jenkins providing web address of the MSNBC article.
- August 30, 2004 – Jonca Bull, Director, Office of Drug Evaluation V, received two telephone calls: 1) Paul Roufeill, Health Canada and 2) Dennis Erbe, Merck, regarding Kaiser Study.
- October 4, 2004 – The Wall Street Journal (WSJ) requested an interview with Dr. Steven Galson, Acting Director, Center for Drug Evaluation and Research regarding David Graham manuscript. WSJ had a copy although it had not been released by FDA.

- October 4, 2004 – Senator Grassley requested a copy of Dr. Graham's report through FDA's Office of Legislation (OL).
- October 4, 2004 – E-mail from Karen Meister, OL, requested CDER (Lee Lemley) provide a copy of the report to their office to comply with congressional request.
- October 4, 2004 – Dr. Graham E-mailed a copy of the report to Lee Lemley.
- October 4, 2004 – Lee Lemley provided a copy of the report to Karen Meister, OL.
- October 5, 2004 – Pat Ronan, OL E-mailed a copy of the report to Dr. Galson.
- October 5, 2004 – Dr. Galson spoke with Dr. Braunstein, notifying Merck that the WSJ had obtained a copy of Dr Graham's manuscript. Dr. Galson requested Chris Bechtel, Director, CDER Executive Operations Staff to forward a copy of the manuscript to Dr. Ned Braunstein.
- October 5, 2004 - Ms. Bechtel spoke with Dr. Braunstein and forwarded a copy of the manuscript by email to Merck.
- October 7, 2004 – Lee Lemley, CDER Executive Operations Staff, requested by E-mail that Merck not release the manuscript any further, as it contained IMS data and FDA had not been given authority to release.

The E-mails noted here are currently being reviewed for redaction for use in public domain.

3. Dr. Psaty commented at the hearing that drug companies make commitments for post-marketing studies and that reportedly only about 40 percent of these ever get started, much less completed or published.

A) What authority does FDA have to require post-marketing studies?

- FDA can require an applicant to conduct studies to verify and describe clinical benefit for a drug or biological product approved in accordance with the accelerated approval provisions (21 U.S.C. 356, 21 CFR 314.500-314.560 and 601.40-601.46).
- For a drug or biological product approved on the basis of animal efficacy data because human efficacy studies are not ethical or feasible, an applicant must conduct studies when feasible, to verify and describe clinical benefit and to assess the product's safety (21 CFR 314.600-314.650, 601.90-601.95).
- Section 2 of the Pediatric Research Equity Act of 2003 (PREA) authorized FDA to require pediatric studies of marketed drugs that are not adequately labeled for children. These studies may be deferred if the drug is ready for approval in adults before pediatric studies are completed or due to concerns about the safety or effectiveness of the drugs in pediatric populations (21 U.S.C. 355B(a), P.L. 108-155).
- Although not specifically authorized in the statute, at or shortly before approval of an application, applicants may also make commitments to conduct post-marketing studies to further explore concerns raised during the application review (e.g., studies in a certain subpopulation of patients expected to use the drug).

B) In practice, how does FDA ensure that drug companies comply with post marketing study commitments?

For drugs approved under accelerated approval or the animal efficacy provisions, FDA may withdraw approval (described further under 21 CFR 314.530 and 314.620) if:

- A postmarketing clinical study fails to verify clinical benefit;
- The applicant fails to perform the required postmarketing study with due diligence; or
- Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

If a manufacturer fails to submit a supplemental application containing the information or request for approval of a pediatric formulation within the time specified by FDA (i.e., deferred pediatric studies under PREA), the drug product may be considered misbranded or an unapproved new drug or unlicensed biologic.

In accordance with the Food and Drug Administration Modernization Act of 1997, a provision was added related to postmarketing studies requiring sponsors of approved drugs and biologic products report to FDA annually on the progress of their postmarketing study commitments, both those that are required and those that are agreed upon in writing. In concert with industry's reporting requirements, FDA is obligated to track the progress of postmarketing study commitments, make certain information about commitments available to the public, and to report annually in the Federal Register on the performance of postmarketing study commitments. This tracking and reporting allows for the FDA to monitor compliance of postmarketing study commitments.

C) Is it not the case that FDA is able to require a sponsor, as part of the drug approval process, to conduct mandatory post-marketing studies?

See 3A above for examples of when FDA can require postmarketing studies.

D) Has any drug company with a drug withdrawn from the U.S. market during the past 10 years failed to initiate, complete or publish a post-marketing commitment study for the withdrawn drug?

For the drugs withdrawn from the U.S. market in the past 10 years, none have had open required commitments (e.g., confirmatory studies under accelerated approval or animal efficacy provisions or deferred pediatric studies) at the time of withdrawal. For applications that have open agreed-upon study commitments at the time of withdrawal, FDA assesses the objective of these commitments respective of any potential plans for future development of the drug (i.e., investigational studies) or other outstanding scientific issues to determine whether

the postmarketing study is still needed. Generally, the study commitment is released if the information is no longer needed.

4. **Dr. Psaty commented that drugs are re-reviewed every 5 years in Europe: what is FDA's position on periodic mandatory post-marketing drug reviews?**

Many have suggested that the U.S. should develop a system like the European system that would conduct mandatory periodic drug reviews. The benefits and costs associated with such a system would need to be fully explored before a decision could be made about whether to adopt such a system here. The Institute of Medicine may provide its views on such a system as part of a study FDA has recently requested.

5. **Dr. Psaty testified at the hearing that if he knew about Vioxx in 1998, he would have recommended a "complete, symmetrical, and fair evaluation of the hypothesized GI benefits and risks." Dr. Kweder also testified that before approving Vioxx the FDA knew there was potential for increased cardiovascular risk with Vioxx, as well as a relatively clear suggestion of a GI benefit. Did FDA conduct such an evaluation or analysis before approving Vioxx? Please explain in detail. Why FDA did or did not conduct an evaluation or analysis as Dr. Psaty described related to the GI benefit versus the risk of Vioxx?**

At the time of the approval of Vioxx in May 1999, FDA was aware that the literature had raised the theoretical concern of a potential prothrombotic effect of COX-2 selective agents (McAdam et al. Systemic biosynthesis of prostacyclin by COX-2: The human pharmacology of a selective inhibitor of COX-2, *PNAS*, January 1999). However, neither the clinical studies from the Vioxx application (with over 3,000 patients exposed in multiple-dose studies) nor those from the previously approved Celebrex application (approved in December 1998, with approximately 8,000 patients) showed any increased cardiovascular/thrombotic risk that would have justified a further analysis at that time. Both Celebrex and Vioxx showed evidence of fluid retention, edema, and hypertension; all well-known adverse events associated with the NSAID class, but no evidence of increased cardiovascular thrombotic risk.

Of note, International Conference in Harmonization guidelines recommend that before approval, a new drug should have a minimum database of 1,500 patients exposed to the new drug, of whom 300 should be exposed for at least 6 months and 100 should be exposed for at least one year at clinically relevant doses. In the case of Vioxx, the new drug application (NDA) involved approximately 5,400 patients of whom 371 received Vioxx 12.5 mg and 381 received 25 mg daily (the approved doses for chronic use) for at least one year. This was a database larger than most NDAs and above minimum international guideline recommendations.

6. **Dr. Kweder testified that when Vioxx was approved there was tremendous hope for reducing the substantial morbidity and mortality associated with GI bleeding and ulcers from NSAIDs. Dr. Psaty testified at the hearing that "the best available evidence suggests that Vioxx was primarily responsible for the 500 percent increase in CV risk, and if naproxen had the full anti-platelet effect of aspirin, Vioxx would be expected to increase the risk by about 380 percent." Dr. Kweder also testified that one cannot just look at the cardiovascular risk of this drug· one has to look at the full spectrum of risks and potential benefits. Please explain in detail why FDA did or did not conduct an evaluation or analysis as Dr. Psaty described on the GI benefit versus the risk of Vioxx after the VIGOR study results were available.**

The issue of gastrointestinal (GI) benefit and cardiovascular (CV) risk was addressed in detail at the February 7, 2001, Advisory Committee meeting. The GI findings were clear: Vioxx 50 mg, a dose twice the labeled dose for chronic use, was safer than naproxen. It could be assumed that the 12.5 and 25 mg doses would also be safer. On the other hand, the cardiovascular findings were difficult to interpret because of 1) a population limited to patients with rheumatoid arthritis (known to be at higher cardiovascular risk than other rheumatologic conditions, such as osteoarthritis); 2) the potential but unmeasured anti-platelet effect of naproxen; 3) the exclusion of the use of low dose aspirin; and 4) the fact that the difference was driven by a five-fold risk in myocardial infarction (MI) but was no difference in the number of strokes or cardiovascular deaths. As described in the response to question 19, appropriate studies would have been difficult to design and conduct. In addition, as described in the response to question 13, some placebo controlled trials were already being conducted that were expected to address the CV risk of Vioxx.

7. **Dr. Kweder testified that the FDA "pursued vigorously" the Vioxx label change to reflect cardiovascular risk and that the label change did take a "very long time, much longer than usual." Between October 2001 and April 2002, Merck rejected FDA proposed labeling for Vioxx and negotiated removal of the CV risk from the warnings section of the label to the precautions section. Describe in detail the label discussions and negotiations with Merck, including a timeline of events and identifying the FDA employees who were involved. Provide for the hearing record a copy of all documents and communications between FDA and Merck related to the Vioxx label change, including but not limited to the file record related to FDA administrative action, as well as internal FDA e-mail and e-mail between FDA and Merck.**

On October 10, 2001, FDA transmitted changes to the sponsor's proposed labeling submitted as part of NDA 21-042, S007 (June 29, 2000). FDA received the sponsor's response on November 6, 2001. Merck's response showed little change from their original proposed labeling. During a November 21, 2001, teleconference arranged

between FDA and the sponsor, the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (DAAODP or the Division) explained its position on the need for the labeling changes. DAAODP requested that the sponsor reconsider its proposal in light of the Division's comments and resubmit a new proposed label.

Merck submitted a revised response on December 5, 2001. Because there were still substantial differences between the sponsor's and the Division's positions, the Division presented an update of the labeling discussions regarding CV safety at a pre-decisional meeting at the Center level on January 6, 2002. This venue allowed for open discussion of difficult issues with experienced leaders in the Center. There was a consensus that the data from the various large databases were of concern and that labeling should include information related to CV findings associated with Vioxx. This consensus was similar to comments made by multiple Advisory Committee members at the February 2001 meeting.

FDA sent Merck a response on January 7, 2002, and discussed the response by phone with Merck on January 30, 2001. There were still substantial differences between Merck and the Division. FDA continued labeling discussions with Merck in teleconferences on February 8 and 20, and March 7 and 20, 2002, until a final label was issued on April 11, 2002.

In April 2002, FDA approved the rheumatoid arthritis indication along with labeling changes that included the results of the VIGOR study and changes to the Precautions, Drug Interactions and Dosage and Administration sections of the label to reflect all that was known at that time about the potential risk for CV thrombotic events with Vioxx.

CDER Staff Involved in VIGOR labeling:

Jonca C. Bull, MD	Acting Director, Deputy Director, Office of Drug Evaluation V
**Larry Goldkind, MD	Deputy Division Director
James Witter, MD, Ph.D.	Acting Medical Team Leader
Maria L. Villalba, MD	Medical Reviewer
Joel Schiffenbauer, MD	Medical Reviewer
Stan Lin, Ph.D.	Biostatistics Team Leader
Carmen DeBellas, R.Ph.	Chief, Project Management Staff
Barbara Gould	Project Manager
Robert Temple, MD	Director, Office of Medical Policy
Laura Governale	Project Manager, Office of Medical Policy, DDMAC
Lisa Hubbard, RPh	Labeling Reviewer
Robert O'Neill, Ph.D.	Director, Office of Biostatistics
Mohammed Huque, Ph.D.	Director, OB III

** No longer with Agency

8. **Dr. Kweder testified that the FDA worked extremely closely with Merck to make label changes where new signals were coming up in the adverse event database. Describe in detail all FDA action(s) related to signals in the adverse events including a brief description and timeline of all adverse events related to Vioxx and CV risk.**

The attached chart illustrates the multiple assessments of Vioxx's safety profile conducted by the Office of Drug Safety over the drug's marketing history. Please see #7 above and attached chart.

9. **Merck filed its letter to the FDA about the Ingenix study on October 12, 2004. Describe in detail what the FDA knew about the Ingenix study and when the FDA teamed about it, including a description of all FDA action(s) with respect to the study to date. Provide for the hearing record a copy of all documents and communications between FDA and Merck related to the Ingenix study, including but not limited to the file record related to FDA administrative action, as well as internal FDA email and email between FDA and Merck.**

The Ingenix study was an epidemiological observational study sponsored by Merck. The study report was submitted to FDA on October 12, 2004. Until that time, FDA was not aware that such study was being conducted. An overview of the submission was conducted by Dr. Villalba, the primary FDA reviewer for Vioxx, on November 1, 2004. However, as this was an epidemiologic study, a request for a consultation with the Office of Drug Safety with more expertise on the subject has been initiated. Documents responsive the this question are forthcoming.

10. **Dr. Graham referred in his testimony to a clinical testimony trial on Serevent that was cancelled and a letter to the FDA from the Data Safety Monitoring Board explaining why the trial was cancelled. Describe in detail what action FDA took in response to the cancellation of this study. In addition, provide a copy of that letter and any additional correspondence related to that letter.**

FDA Activity Related to the Salmeterol Multi-center Asthma Research Trial (SMART)

Serevent Inhalation Aerosol (Serevent), manufactured byGlaxoSmithKline, is a metered dose inhaler formulation of salmeterol xinafoate, a long-acting beta-agonist bronchodilator. Serevent was approved in 1994 for use in patients with asthma (IND#30,905; NDA# 20-236). Salmeterol is also the active drug substance in Serevent Diskus (IND# 43,097; NDA# 20-692), a dry powder inhaler product, and is one of the two active drug substances in Advair Diskus (IND# 50,703; NDA# 21-077), a dry powder

formulation that also contains the corticosteroid, fluticasone. At the time of the approval of Serevent, there were a number of short-acting beta-agonists approved for use in asthma. These were, and remain, a cornerstone of the treatment of asthma. However, at the time of approval of Serevent there was some controversy in the medical community about possible adverse effects of long-term, regular use of this class of medications (beta-agonist bronchodilators). Although clearly beneficial in terms of their ability to reverse the airway narrowing characteristic of asthma, there was some scientific and epidemiologic data to suggest that chronic use might be associated with decrements in overall asthma control. These issues were carefully considered by the Agency and by the Pulmonary-Allergy Drugs Advisory Committee, which held a meeting on February 26, 1993, prior to approval.

In order to explore this issue further, in 1996, following discussions with the Agency, the manufacturer initiated a large safety trial intended to explore the possibility that chronic use of salmeterol might result in an increased frequency of serious asthma events. This was the Serevent Multicenter Asthma Research Trial (SMART).

In the SMART trial, asthma patients who were 12 years of age and older were randomly assigned to receive either Serevent Inhalation Aerosol at the approved dose, or placebo, for a period of 28 weeks. The study was conducted at over 6,000 sites in the U.S. Patients were followed for the occurrence of important safety outcomes such as death, ventilatory failure, and other serious adverse events. An independent Data Safety Monitoring Board (DSMB) was empanelled to monitor the trial. Initially, a total enrollment of 30,000 patients was planned. In 1999, after approximately 15,000 patients had been enrolled, it was observed that the number of outcome events was lower than expected, prompting an increase in the planned enrollment to 60,000 patients.

On October 10, 2002, GSK notified FDA that the DSMB had completed a planned interim analysis and, at a meeting on September 11, 2002, had made recommendations regarding the study (Attachment 1). In its interim analysis, the DSMB had observed an increase in serious asthma events among patients treated with Serevent. Although the finding was not statistically significant, the DSMB was concerned that, in a post-hoc subset analysis, it appeared that the risk may be particularly notable among African Americans. This was problematic because the study was not designed to test this hypothesis, and it was not clear that the question of whether African Americans were at particular risk with this drug could be answered even if the study were completed. Finally, the DSMB also observed that the rate of recruitment was slow. This may have been due to the fact that enrollment required patients who had not previously been treated with a long-acting beta-agonist. In the time since approval, Serevent had become very commonly used, and it was difficult to identify patients who had not received either Serevent of another long-acting beta-agonist. The DSMB had recommended to GSK that, if the study could not be completed within a reasonable period of time (e.g. two years), the study should be terminated and the findings disseminated.

The following timeline summarizes the events and actions taken by the Agency following GSK's October 10, 2002, notification to the Agency of the DSMB's recommendations. Broadly, there were three phases to the FDA actions. The first phase related to the initial notification by GSK of its decision to halt the study, and how to communicate this to investigators, the medical community, and the public. The second phase related to FDA's decision that the product label for all drug products containing salmeterol should be updated to include the findings of the study, even though the currently available data were preliminary. The third phase related to a second round of labeling changes to reflect the final study results, when they became available.

Phase 1:

- 10/10/02: GSK notifies FDA of the DSMB recommendations. Additionally, GSK asks FDA concurrence with its plan to review unblinded study data in order to determine how to proceed.
- 10/16/02: FDA requests that GSK submit aggregate blinded data (telephone call)
- 10/25/04: GSK submits information in response to FDA's 10/16/02 request [Attachment 2)
- 11/1/02: FDA fax to GSK in response. FDA states that the decision to perform an internal review of unblinded study data should be the decision of GSK, the study steering committee, and the DSMB, but that FDA would have no specific objection to the proposal. FDA invites GSK to request a meeting to discuss the data should GSK choose to unblind the study [Attachment 3].
- 12/02: GSK unblinds and analyzes the SMART data.
- 1/6/03: GSK submits by a summary of the interim analysis, and requests a meeting with the Agency [Attachment 4]. Meeting subsequently scheduled for 2/26/03.
- 1/10/03: FDA/GSK telecon to discuss. FDA strongly encourages GSK to issue a public announcement about the termination of the study, rather than simply notifying the investigators, as GSK proposed. FDA advises GSK that FDA has already drafted a talk paper on the issue, which it plans to release once GSK makes its announcement. [Attachment 5]
- 1/15/03: GSK submits by fax drafts of their proposed "Dear Healthcare Professional" (DHCP) and "Dear Investigator" letters, along with draft GSK press statement. [These draft documents are included as attachments to the 1/15/03 telecon minutes below]
- 1/15/03: FDA/GSK telecon to discuss the documents faxed today. FDA provides input regarding the proposed language in an effort to be sure the message is clear [Attachment 6: telecon minutes]
- 1/17/03: GSK submits revised drafts of DHCP and Investigator letters [These draft documents are included as attachments to the 1/17/03 telecon minutes below].
- 1/17/03: FDA/GSK telecon to discuss the latest draft DHCP and Investigator letters. Specific language and timing of the announcements are agreed upon. [Attachment 7: telecon minutes]

- 1/19-21/03: GSK submits by fax further iterations of the DHCP letter, Investigator letter, and the GSK public statement. [Attachment 8- as formally submitted on 1/22/03]
- 1/23/03: GSK terminates the study
- 1/23/03: FDA releases Talk Paper [Attachment 9]

Phase 2:

- 2/4/03: GSK submits briefing package for 2/26/03 meeting. This package includes GSK's proposed labeling changes. [Attachment 10]
- 2/26/03: FDA meets with GSK at FDA headquarters. Among others, this meeting includes the directors of FDA's Office of New Drugs, Office of Medical Policy, and Office of Biostatistics. FDA outlines its interpretation of the preliminary data, and outlines appropriate changes to the product label to reflect the data. FDA states that the findings merit a boxed warning for all products containing salmeterol. These are Serevent Inhalation Aerosol, Serevent Diskus (a dry powder formulation of salmeterol), and Advair Diskus (a combination drug product containing salmeterol and a corticosteroid, fluticasone propionate). GSK objects to the addition of a boxed warning, particularly for the Advair product. [Attachment 11: meeting minutes]
- 3/5/03: GSK submits revised proposed labeling changes intended to reflect the 2/26/03 discussion.
- 4/8/03: FDA faxes response to 3/5/03 proposed language [Attachment 12]
- 4/16/03: GSK responds to FDA's 4/8/03 communication [Attachment 13]
- 5/31/03: FDA meets with GSK at FDA headquarters to discuss labeling language. Agreement is reached on many points, but GSK cannot agree to add a boxed warning to the Advair label. GSK asks to take the issue to the Director of the Center for Drug Evaluation and Research, Dr. Woodcock. [Attachment 14]
- 6/13/03: FDA meets with GSK, with Dr. Woodcock in attendance. After presentation by GSK and further discussion, Dr. Woodcock states that she will consider the issues and make a determination whether the boxed warning will be required for Advair. [Attachment 15: meeting minutes]
- 6/17/03: Dr. Woodcock notifies GSK that the boxed warning will be required for Advair (telephone conversation).
- 6/19/03: GSK submits revised labeling [Attachment 16]
- 6/25/03: GSK submits proposed plan for adjusting promotional activities in response to new boxed warning [Attachment 17]
- 6/27/03: FDA issues a letter to GSK requesting that GSK submit a prior approval supplement with labeling changes to reflect the findings of the SMART trial. This letter includes the specific labeling changes sought. [Attachment 18]
- 7/2/03: GSK submits proposed alternative labeling language [Attachment 19]
- 7/21/03: FDA issues a second, modified supplement request [Attachment 20]

- 7/28/03: GSK submits proposed labeling along with draft DHCP letter [Attachment 21]
- 7/31/03: GSK submits revised draft labeling [Attachment 22]
- 8/1/03: FDA advises GSK it is in agreement with draft labeling language (telephone conversation)
- 8/6/03: GSK submits formal prior approval labeling supplements for Serevent Inhalation Aerosol, Serevent Diskus, and Advair Diskus. [Attachment 23]
- 8/11/03: FDA approves the labeling supplements for all three products. This action now formally amends the product labels for all drugs containing salmeterol, to reflect the preliminary findings of the SMART trial. Among other changes, a boxed warning is added to all of the product labels. The text of the boxed warning for Serevent Inhalation Aerosol is: "Warning: Data from a large placebo-controlled U.S. study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in placebo patients receiving salmeterol (13 deaths out of 13,174 patients treated for 28 weeks) versus those on placebo (4 our of 13,179). Subgroup analyses suggest the risk may be greater in African-American patients compared to Caucasians (see WARNINGS and CLINICAL PHARMACOLOGY; Clinical Trials: *Asthma: Salmeterol Multi-center Asthma Research Trial*)." [Attachment 24: Project Manager memos and approval letters]
- 8/14/03: FDA releases Talk Paper describing the new labeling changes [Attachment 25].

Phase 3:

- 2/24/04: GSK submits Prior Approval Labeling Supplements to all three NDAs. This submission includes the final study report for the SMART trial. In this submission, GSK proposes to alter the labeling language describing the findings of the study. [Attachment 26]
- 4/19/04: Review of the final study report is underway. FDA faxes a request for information to GSK [Attachment 27]
- 4/26/04: GSK submits a response to the 4/19/04 request for information [Attachment 28]
- 4/27/04: FDA issues letter to GSK formally acknowledging receipt of the 2/24/04 submission [Attachment 29]
- 5/7/04: FDA faxes a request for information to GSK [Attachment 30]
- 5/24/04: GSK submits a response to the 5/7/04 request for information [Attachment 31]
- 6/4/04: FDA faxes a request for information to GSK [Attachment 32]
- 6/8/04: GSK submits a response to the 6/4/04 request for information [Attachment 33]
- 7/23/04: Telecon between GSK and FDA to discuss the application. [Attachment 34: telecon minutes]
- 7/26/04: FDA faxes a request for information to GSK [Attachment 35]

- 7/29/04: GSK submits a response to the 7/26/04 request for information [Attachment 36].
- 8/12/04: GSK submits revised labeling for Advair to reflect the 4/17/04 approval of Advair for children aged 4-11 years [Attachment 37].
- 8/13/04: FDA faxes a request for information to GSK [Attachment 38].
- 8/25/04: GSK submits a partial response to the 8/13/04 request for information [Attachment 39].
- 8/27/04: GSK submits a complete response to the 8/13/04 request for information [Attachment 40].
- 9/8/04: GSK submits proposed labeling in Word format [Attachment 41].
- 9/10/04: FDA faxes revised labeling language. This language is based on FDA's findings after review of the final study report. [Attachment 42].
- 9/13/04: Telecon between GSK and FDA to discuss FDA's 9/10/04 fax.
- 9/14/04: GSK submits revised proposed labeling language [Attachment 43]
- 9/28/04: FDA approves the labeling supplement. This action now formally amends the product labels for all drugs containing salmeterol, to reflect the findings of the SMART trial. The new text for the boxed warning for Serevent Inhalation Aerosol is: "Warning: Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT Inhalation Aerosol) or placebo added to usual asthma therapy showed a small but significant increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks) versus those on placebo (3 out of 13,179) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*)." The labeling language differs from the language originally proposed by GSK, and is based on FDA's review of the data and conclusions regarding the most appropriate datasets and statistical analyses. [Attachment 44: Approval letter] [Attachment 45: Medical Officer Review] [Attachment 46: Biometrics Review].
- 11/24/04: GSK submits a new "Final Study Report." During review of the 2/24/04 submission, FDA had requested certain additional statistical analyses. These were completed during the review of that submission, and the results were considered by FDA before approval on 9/28/04. The 11/24/04 submission represents the incorporation of these analyses into the study report. [Attachment 47: 11/24/04 Submission] [Attachment 48: Medical Officer Review].

Documents responsive this question are forthcoming.

11. **Dr. Galson wrote in an email to Richard Horton, the editor of Lancet, that FDA's publication clearance policy is "ambiguous." Please explain in detail the why Dr. Galson contacted Mr. Horton about Dr. Graham's Vioxx study and why the FDA has yet to fully evaluate and clear it.**

Dr. Galson, Director, Center for Drug Evaluation and Research (CDER) contacted *The Lancet* to ensure the journal's editor, Mr. Horton, was aware that Dr. Graham had submitted his paper to the journal without completing the FDA's internal peer review process for scientific papers, and that some scientists at FDA questioned some of the conclusions in Dr. Graham's paper. Dr. Galson expressed the hope that some of the concerns could be addressed through the peer review process before publication.

CDER cleared Dr. Graham's manuscript CDER for submission to *The Lancet* for publication. Dr. Graham notified the Center that he resubmitted his manuscript to *The Lancet* on January 4, 2005.

12. **By 1999, the FDA was already concerned about potential heart attack risk from Vioxx. At that time, there were at least 30 other NSAIDs on the market. In combination with stomach protecting drugs like prilosec, they provided a treatment that was as safe and effective as Vioxx. What was the urgency in approving Vioxx as a priority review without requiring additional large long-term studies?**

There were no other approved treatments that provided the same amount of GI protection as it appeared would be provided by Vioxx and the other COX-2 inhibitors without the requirement of a second medication.

13. **After the VIGOR trial, FDA reviewers recommended cardiovascular studies. Such studies were required for Arcoxia and Prexige. Why not Vioxx?**

Long-term, placebo controlled studies that could potentially address cardiovascular risks with Vioxx were already being conducted. In fact, the APPROVe (colon polyp prevention) study was one of these studies along with VICTOR (recurrent colon cancer, protocol 145) and PCPS (prostate cancer chemoprevention study, protocol 201) evaluating cardiovascular safety. Although the primary endpoint for these studies was for tumor prevention, cardiovascular outcomes were prospectively defined and collected. A pooled analysis of these three studies was prospectively planned. Additionally, cardiovascular data from long-term placebo-controlled trials in the prevention of Alzheimer's disease had recently been submitted to the Agency and were under review at the time of product withdrawal. We worked with Merck to ensure that all of their ongoing studies collected appropriate CV data.

14. **Why was data unfavorable to Merck not included in label change after VIGOR? For example, mortality rates in Alzheimer studies, results from 085 and 090?**

Individual study results are not included in the label unless they are associated with a specific claim or they have important safety findings. Cardiovascular mortality rates in the Alzheimer studies were actually included in the April 2002 label, along with the number of CVcardiovascular thrombotic events.

Studies 085 and 090 involved the lowest approved dose of Vioxx (12.5 mg daily), for an approved indication (osteoarthritis) and with short duration of exposure (6 weeks). By April 2002, FDA had reviewed multiple studies of larger size, dose, and duration than the ones for studies 085 and 090.

Studies 085 and 090 were identical and compared Vioxx with nabumetone 1000 mg daily and placebo, with a 2:2:1 randomization scheme (approximately 400 patients exposed Vioxx 12.5 mg, 400 exposed to nabumetone and 200 exposed to placebo in each study).

In Study 085, there was one MI in the Vioxx 12.5 mg group, with no CV/T in the nabumetone and placebo groups. There were no CV/T deaths.

Study 090 showed five CV/T events in the Vioxx 12.5 mg group (3 myocardial infarctions and 2 strokes); one myocardial infarction in the nabumetone group and no CV/T events on placebo. There were no CV/T deaths. The total number of CV/T events in study 090 would suggest an increased CV/T risk on Vioxx 12.5 mg as compared to placebo. However, the small size of the study and small number of events precluded any meaningful conclusion or statistical analysis. Additionally, the findings were not replicated in study 085, a study with identical design to 090.

For these reasons, the results of 085 and 090 were not considered to be relevant in the context of all the other available information.

15. Dr. Kweder stated during the hearing that there was no alternative drug for arthritis that reduced GI bleeding. Please clarify for the record whether Dr. Kweder misspoke or was unaware of the combination drug with Prilosec and Motrin?

No alternative drugs, including a Motrin/Prilosec combination, that reduce GI bleeding have been approved for treatment of arthritis or rheumatoid arthritis pain.

16. Why did the FDA not conduct a statistical analysis of study 090 relating to excess deaths, heart attacks, and strokes?

FDA could not conduct a meaningful statistical analysis of study 090 because of the small size of the study and the small number of reported events. Please see response to question 14.

17. State whether the FDA questioned Merck's assertion that the heart attacks and strokes "were not study drug related" in study 090. Please state yes or no and provide a detailed explanation stating why or why not.

No. Upon review of the narratives of cardiovascular events, FDA agreed with the conclusion that the CV events were likely not related to study drug.

18. Why did the FDA not stop the direct to consumer advertising for Vioxx, particularly when Merck continued to issue multiple press releases "reconfirming the safety of Vioxx" long after the FDA had informed them of concerns about cardiovascular toxicity?

Merck's DTC advertising for Vioxx was consistent with its labeling at the time. When the labeling was changed to include new information about possible cardiovascular concerns, Vioxx's DTC advertising was revised accordingly. Therefore, there was not a regulatory basis to object to the DTC advertising because of this issue at the time.

19. According to a New York Times article dated November 14, 2004, "the [FDA] consulted with Merck and discussed the idea of a study designed solely to answer questions about the heart risks. As Merck officials had done in May 2000, the agency concluded that such a trial was difficult to envision. Giving placebos and Vioxx to groups of at-risk patients solely for the purpose of comparing side effects would be unethical, Dr. Kweder said." Why is it unethical or difficult to design a study to answer questions about heart risks? Are there not studies that could have been designed and required (including a study of Vioxx vs. Tylenol in osteoarthritis; or Vioxx vs. placebo for colon cancer prophylaxis (powered to detect a cardiovascular difference); or Vioxx vs. NSAID in patients on aspirin (designed to rule out a differential cardioprotective effect of NSAID)?

Dr. Kweder did not say that conducting a study to answer questions about heart risks in all situations was unethical. It would generally be considered unethical to administer Vioxx (or any drug) for long term studies (CV studies usually require many months to years) to patients at high cardiovascular risk who do not stand to benefit from the drug or comparator. A study in which Vioxx was to be administered for pain had already been done, with VIGOR, raising questions about how to interpret CV safety data when the comparator was another NSAID, not a placebo. The optimal study would be one that compared Vioxx to placebo. Such work was already underway with the Alzheimer study and APPROVe in the U.S., or being planned (i.e., another polyp prevention study in Europe).

20. The FDA issued a warning letter to Merck in September 2001, stating "[Merck's] claim in the press release that Vioxx has a favorable cardiovascular profile, is simply incomprehensible." Mr. Gilmartin testified at the hearing that Merck took the FDA's warning letter very seriously and took corrective actions with regard to the speaker and to the sales representatives, but that there was no action requested or required on the press release by the FDA. Please describe in detail FDA's communications with Merck related to the warning letter. Provide for the hearing record a copy of all documents and communications between FDA and Merck related to the FDA warning letter, including but not limited to the rile record related to FDA administrative action, as well as internal FDA email and email between FDA and Merck.

FDA issued a Warning Letter to Merck on September 17, 2001. The Warning Letter did not make any conclusions about the safety of Vioxx but objected to the selective conclusions made by Merck in its promotion about the results of the VIGOR trial. Merck's promotional campaign asserted that Vioxx did not increase the risk of MI compared to the control group of naproxen and that the VIGOR finding was consistent with naproxen's ability to block platelet aggregation like aspirin. The Warning Letter stated that this was a possible explanation, but objected to the fact that Merck failed to disclose that this explanation was hypothetical and that there may be another reasonable explanation, that Vioxx may have pro-thrombotic properties.

On October 1, 2001, Merck responded to FDA and agreed to do the corrective action plan that FDA requested. The letter listed the 5-point action plan including a plan to disseminate Dear Healthcare Professional letters to correct the information in the promotion that FDA stated was misleading. The letter also noted that Merck disagreed with a number of assertions in the Warning Letter including FDA's assertion that Merck had "engaged in a promotional campaign for Vioxx that minimized the potentially serious cardiovascular findings that were observed in the Vioxx Gastrointestinal Outcome Research (VIGOR) study."

Merck and FDA agreed that a meeting would be productive and in a letter dated October 11, 2001, Merck confirmed that it would attend a meeting on October 24, 2001 and listed its planned attendees. On October 12, 2001, FDA responded to Merck's letter and confirmed the meeting and listed FDA's planned attendees.

Merck submitted proposed draft corrective Dear Healthcare Professional letters on October 20, 2001. On November 8, 2001, Merck submitted another set of proposed corrective Dear Healthcare Professional letters that were revised based on comments from FDA. On November 14, 2001, Merck submitted its proposed corrective Dear Healthcare Professional letters in final format for final review by FDA. Merck confirmed in its letter to FDA dated November 19, 2001, that it had mailed the corrective Dear Healthcare Professional letters and submitted the final version of the letters for FDA's records. Documents responsive the this question are forthcoming.

21. Dr. Kweder testified that the FDA is engaged in discussions with a number of groups about how to improve access to positive and negative clinical trial data. Describe in detail the nature of those discussions and the specific parties involved, including the nature of their affiliation with the FDA. State what the FDA's regulatory policy position is with respect to a mandatory clinical trial data registry?

The collection and dissemination of information about clinical trials and their outcomes is an important consumer and health practitioner issue. Working together and in collaboration with our sister agencies in the DHHS, we implemented section 113 of the Federal Food and Drug Administration Modernization Act of 1997 (FDAMA) with the establishment of ClinicalTrials.gov in February 2000. Today, ClinicalTrials.gov contains information on more than 11,000 publicly and privately funded trials. Most of the trials

are efficacy studies of treatments for serious or life-threatening diseases or conditions. In addition, for some of the completed studies in ClinicalTrials.gov, links are also provided to publications or abstracts describing the study's outcome.

Section 113 of FDAMA does not require that sponsors submit all clinical drug trial information to ClinicalTrials.gov. Congress originally authorized the registry to provide patients with information to expand their access to clinical trials. NIH also includes information not now required by section 113, sometimes including links to results, so long as doing so does not conflict with section 113's provision for sponsor consent.

Recent public attention to the increasing availability of clinical trial information has made pharmaceutical companies more aware of the responsibility to list clinical trials in ClinicalTrials.gov. Moreover, many companies that previously listed "pharmaceutical company" in the drug sponsor field are now identifying themselves by their company name. More changes are still needed. FDA wants to continue to work with industry and encourage them to put more data into the registry. FDA and NIH will continue to work with sponsors to put required information into the registry.

FDA has met with PhRMA (Dr. Janet Woodcock, Acting Deputy Commissioner for Operations; Dr. Robert Temple, CDER's Associate Director for Medical Policy; Daniel Troy, former Chief, Office of General Counsel; Thomas Abrams, Director and Carol Barstow, CDER's Division of Drug Marketing, Advertising and Communications) on August 26, 2004 and with Lilly (Dr. Robert Temple, CDER's Associate Director for Medical Policy; Thomas Abrams, Director and Carol Barstow, CDER's Division of Drug Marketing, Advertising and Communications). Each organization described plans to make more data available for planned and completed trials. These meetings were generally intended to inform us of their plans. In each case, the Agency generally expressed the view, widely shared in the biomedical community, that making this information public appeared to be good for the public health. FDA also expressed concern that the interpretation of the results of the studies made public needed to avoid promotional features.

Additional meetings that have taken place in which FDA participated are as follows:

- December 1, 2004 – FDA/IOM Meeting with Dr. Robert Temple.
- October 28-29, 2004 – WHO International Clinical Trials Registry Platform Meeting, FDA Attendee, Theresa Toigo, Office of the Commissioner.
- January 10, 2005 – Fordham University Summit on Clinical Trials Registries: Responsible Policies & Public Access, FDA Attendee – Theresa Toigo, Office of the Commissioner.

22. Vioxx is a drug of convenience and not a drug of necessity like a cancer treatment. Yet the FDA gave priority review to Vioxx and it went on the market within 6 months. Why did the FDA push this drug out into the market when there was no analysis supporting the GI benefit for Vioxx?

Priority review is granted when the drug appears to represent a therapeutic advantage

with respect to available therapy by providing effective treatment or diagnosis for a disease not adequately treated or diagnosed by any marketed drug, or providing impoved treatment of a disease through greater effectiveness or safety (including decreased abuse potential) or having a modest, but real, advantage over available marketed drugs, e.g., 1) significant greater patient convenience; 2) elimination of an annoying, but not necessarily dangerous adverse event; or 3) usefulness in a specific subpopulation of patients.

Vioxx was given a priority review based on the potential GI protective effect of COX-2 selective agents over other available agents. This potential GI benefit was preliminarily shown in the NDA for the 12.5 and 25 mg doses as compared to ibuprofen in two six-month endoscopic studies, findings that the Agency was aware of before full review of the NDA.

23. **Dr. Kweder testified about the FDA's announcement of a five-step plan to strengthen its drug safety program, including working with and sponsoring an Institute of Medicine study on the FDA's drug safety system. Describe in detail the scope and methodology of this study. Provide for the hearing record a copy of all documents related to the Institute of Medicine study, including but not limited to the file record related to FDA administrative action and the contract for the study between the FDA and the Institute of Medicine.**

IOM met with Dr. Steven Galson, Dr. Paul Seligman, Dr. Theresa Mullin and Ms. Deborah Henderson on November 24, 2004, to discuss the study with documentation attached. The scope of work and tasks to be performed were discussed. The Agency recently received the IOM's formal proposal and cost estimate (Attachment). Expected time from initiation of study, which at this time has not been identified, to a completed final report is 20 months. Documents responsive the this question are forthcoming.

Questions from Senator Hatch to the FDA

1. **Don't all drugs have some level of risk? What is an acceptable level of risk for drugs? What is an unacceptable level of risk for drugs?**

Under current law, all new drugs must be proven safe and effective for their intended use before thay can be approved. No drug is absolutely safe, there is always some risk of an adverse reaction. However, when a proposed drug's benefit outweigh known risks, CDER considers it safe enough to approve. There is no set standard that allows us to measure the balance of risk versus benefit that would allow us to define acceptable or unacceptable levels. The data submitted in clinical studies are evaluated for risks and benefits to determine whether a drug is safe and effective based on sound science and the expert judgment of our reviewers.

2. **While I applaud the FDA on initiating the 5-point proposal on how to strengthen the drug approval process, how do we know that it is going to work? When will the Institute of Medicine's study recommendations be available for congressional review? And when will these recommendations be implemented?**

We are confident that implementing this new 5-point system can only strengthen FDA's current drug safety system. We look forward to any changes deemed necessary. Expected time from initiation of study, which at this time has not been identified, to a completed final report is 20 months.

Without seeing recommendations, it is impossible to project a timeframe for implementation of recommendations, an outcome of the IOM study that has not yet began. However, once the Agency receives the recommendations we will quickly evaluate them recommendations and take appppropriate action.

3. **Dr. Kweder, you were not able to provide a response at the hearing about the Administration's position on health care liability reform in the Patients First Act, S. 11. Please supply the Administration's position on this legislation for the record.**

Attached is a July 7, 2003, Statement of Administrative Policy on S.11, Patients First Act of 2003. We have received assurance from the Office of Management and Budget that this SAP is current Administration policy.

Thank you again for your continued interest in this issue. Please call us if you have further questions.

Sincerely,

Patrick Ronan

Patrick Ronan
Assistant Commissioner
for Legislation

Enclosures

VIOXX POSTMARKET ADVERSE EVENT MONITORING CHRONOLOGY

ROFECOXIB (VIOXX)				
	ODS review and recommendations		**550 actions***	
	Date completed	Recommendations	Action dates	Safety issues
US Deaths related to GI bleeding, obstruction, perforation or stenosis	12-29-00	Recommend to add fatal outcomes from GI bleeding and an information regarding fatalities with concomitant use of aspirin or warfarin to Drug Interactions section of the labeling.	Post-ODS review	Fatal GI events in the elderly mentioned under the Precautions (Geriatric use) section of the labeling. Fatalities with concomitant use with ASA or warfarin are not included in the labeling.
Drug interaction with warfarin, Upper GI bleeding, Renal failure, Hypersensitivity reactions	1-10-00	*No recommendations.* This review was performed 6 months post-approval of rofecoxib.	N/A	No action required.
Aseptic meningitis, seizures, psychiatric events	2-28-00	Recommend to include aseptic meningitis and hallucinations into the labeling. Continue to monitor seizure cases.	Post-ODS review	Aseptic meningitis and hallucinations are included in the Adverse reactions (as post-marketing experience) section.
Hepatobiliary events	7-20-00	Recommend to add hepatitis, cholestasis/cholestatic hepatitis and notable liver enzyme elevations in the post-marketing section of the label.	Post-ODS review	Hepatitis, jaundice, and liver failure are included in the Adverse reactions (as post-marketing experience) section.
Hematological events	8-9-00	Recommend to add thrombocytopenia to the labeling and continue to monitor hemolytic anemia, leucopenia, pancytopenia, agranulocytosis and thrombocythemia.	Post-ODS review	Agranulocytosis, aplastic anemia, pancytopenia and leucopenia are included in the Adverse reactions (as post-marketing experience) section.
Colitis (Epidemiology review with comparison to three nonselective NSAIDs)	1-5-01	The results generate hypothesis that colitis can be evaluated in the CLASS and VIGOR RCTs for events suggestive of colitis, including further study on the thromboembolic potential of rofecoxib.	N/A	Hypothesis communicated but no recommendations of action required. Will continue to monitor.

ROFECOXIB (VIOXX)				
	ODS review and recommendations		*** 550 Actions**	
	Date completed	Recommendations	Action dates	Safety issues
Thrombotic vascular events	2-6-01	CVA, MI, PE, VT, TIA are in the product labeling. *No recommendations.* Phase 4 RCT data is needed to determine drug causality due to high background rate of these events in elderly.	N/A	Taken into account, ongoing study design.
Renal Failure	2-14-01	Recommend to include the following in the labeling: 1.Life-threatening renal failure including fatalities and the need for dialysis in patients with normal or impaired renal function with short-term therapy. 2. An advise that kidney function in high-risk populations be closely monitored 3. Information for patients section of labeling to adequately warn about the signs and symptoms of serious renal toxicities.	Post-ODS review	Acute renal failure, interstitial nephritis, and worsening chronic renal failure are included under the post-marketing experience. Fatal acute renal failure in the elderly is mentioned in the Precautions (Geriatric use) section of the labeling.
Severe Hyponatremia and the Syndrome of Inappropriate Antidiuretic Hormone (SIADH)	4-5-01	Recommend to include hyponatremia the labeling.	4/11/02	Hyponatremia is included edema in the Adverse reactions (as post-marketing experience) section of the labeling.
Congestive heart failure	6-1-01	Recommend to include new-onset or worsening of CHF and severe pulmonary edema.	Post-ODS review	Heart failure and fluid retention are included in the Precautions section, and pulmonary edema in the Adverse reactions (as post-marketing experience) section.

VIOXX POSTMARKET ADVERSE EVENT MONITORING CHRONOLOGY

ROFECOXIB (VIOXX)				
	ODS review and recommendations		*** 550 Actions**	
	Date completed	Recommendations	Action dates	Safety issues
Eye disorders	6-27-01	*No recommendations.* Continue to monitor.	N/A	Monitor
Hearing Loss	7-10-01	*No recommendations.* Continue to monitor.	N/A	Monitor
Quantitative update of thrombotic vascular events	3-14-02	FDA continues to receive post-marketing serious, life-threatening cardiovascular thrombotic events with rofecoxib.	April, 2002	Labeling changes made to incorporate findings. New warnings implemented.
Impaired bone healing/fracture nonunion	6-5-02	Recommend to continue to monitor.	N/A	Monitor
Myopathy and rhabdomyolysis	7-08-02	Recommend to include serum CPK elevation, myopathy and rare cases of rhabdomyolysis to the adverse reactions or postmarketing section of the labeling.	N/A	Recommendations and existing labeling evaluated.
Update aseptic meningitis	12-13-02	It is a labeled event. Reports continue to exist in AERS. No new recommendations.	N/A	Monitor
Ischemic colitis	6-11-03	Recommend to include under the post-marketing information section of the labeling.	N/A	Recommendations discussed and existing labeling evaluated.
DCRCS Review of Patient Labeling	2-25-04			

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HFD- 550/sponsor action dates on ODS recommendations could not be determined in most situations because ODS did not receive supplemental labeling information and action letters from the reviewing division. However, we were able to estimate the timing of 550/sponsor actions from the dates of new information in product labeling for rofecoxib.

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
WASHINGTON, D.C. 20503

July 7, 2003
(Senate)

STATEMENT OF ADMINISTRATION POLICY

(THIS STATEMENT HAS BEEN COORDINATED BY OMB WITH THE CONCERNED AGENCIES.)

S. 11 - Patients First Act of 2003

(Sen. Ensign (R) NV and 10 cosponsors)

The Administration strongly supports Senate passage of S. 11, legislation to reform the Nation's badly broken medical liability system. This bill is an important step toward ensuring that our liability system fairly compensates those who are truly harmed, does not drive good doctors out of medicine, and increases access to quality, affordable health care.

The President strongly believes that patients who are hurt due to the negligence of a doctor should be able to collect full damages for current and future medical care, therapy, rehabilitation, lost wages, and other economic losses. In cases of egregious misconduct, doctors may be responsible for reasonable punitive damages. Victims of malpractice should also be able to collect non-economic damages, such as for pain and suffering, but within a reasonable limit. The Administration is especially pleased that S. 11 encompasses these reforms.

The Administration believes that these reforms must be enacted to improve our health care system and give more Americans access to the best, most innovative care. Urgent Congressional action is needed because the medical liability crisis has forced some doctors to close their practices and has made it more difficult for patients to access affordable, quality health care throughout the country. In many States that have not enacted meaningful reforms like those contained in S. 11, health care providers are facing enormous increases in their medical liability insurance premiums or are unable to obtain any coverage. Physicians forced to quit their practice leave patients with limited access to trauma care, childbirth care, and other basic medical services. This problem is especially troublesome in rural areas. The fear of massive, unreasonable awards deters efforts to identify and correct errors and drives wasteful expenditures on defensive medicine. The liability crisis, particularly the use of defensive medicine, adds to the costs of Medicare and Medicaid, imposing substantial costs on the Federal government and the Federal taxpayer. Higher costs also frustrate initiatives to improve access to quality, affordable care.

The Administration looks forward to working with the Congress to enact legislation that meets the President's goals of reducing medical malpractice premiums and overall health care costs by limiting excessive non-economic and punitive damage awards, and minimizing frivolous lawsuits and time consuming legal proceedings.

PREPARED STATEMENT OF BRUCE M. PSATY, M.D.

Mr Chairman and members of the committee, thank you for the opportunity to testify before the committee on the cardiovascular risks associated with Vioxx. Let me introduce myself briefly, describe several key scientific issues, and summarize some of the studies of Vioxx and their findings. Finally, I will make recommendations about how to prevent similar problems in the future.

Introduction

I am a practicing general internist at Harborview Medical Center, Seattle, WA, and a cardiovascular disease epidemiologist with an interest and expertise in

pharmacoepidemiology, pharmacogenetics, and drug safety. I have experience in the design, conduct, analysis and interpretation of clinical studies, and I am currently the principal investigator on four large epidemiologic studies funded by the National Institutes of Health (NIH) or the American Heart Association (AHA). I have major roles in several multi-center NIH-funded epidemiologic studies and clinical trials, including the Cardiovascular Health Study, the Multi-Ethnic Study of Atherosclerosis, and the Women's Health Initiative. Regularly, I review research in several capacities. As a public-health scientist, I serve as chair of the Group Health Cooperative Research Committee and am currently a member of the NIH Epidemiology of Chronic Disease Study Section. I have chaired or participated in various committees and review groups constituted by the AHA, the NIH, and the World Health Organization. I also teach and mentor students, fellows and junior faculty in medicine and epidemiology. I have no financial interest in this matter. In 1991, the Society of Epidemiological Research selected me for a career development award for a pilot study of the risks of stroke associated with the use of progestins by post-menopausal women. This 3-year award was funded by the Merck Company Foundation.

Epidemiology

Epidemiology is the study of patterns and causes of disease in human populations. One of the primary purposes of studying the causes of disease is to identify approaches or treatments that can prevent disease. Epidemiologic studies, for instance, have identified high blood pressure and cholesterol as risk factors for heart attack and stroke. Subsequently, major prevention efforts based on proven therapies have reduced the burden of cardiovascular disease in the United States. My comments today are directed toward prevention.

For the purposes of our discussion today, the primary question is: what are the health outcomes associated with the use of a medicine such as Vioxx? Implicit in this question is the notion of a comparison group, who may receive a placebo (no medicinal effects) or another active treatment. The two basic types of studies in humans are the clinical trial and the observational study. In a clinical trial, patients are assigned randomly to receive the active or the comparison treatment, and they are followed for the health outcomes of interest. The clinical trial is the optimal method of assessing the health effects of medications, and the design of the clinical trial varies according to the question to be answered. For instance, trials that evaluate the relief from the pain of arthritis can be conducted in a few hundred patients who are followed for 6 weeks. But such a study is too small to evaluate the effects of a medication on health outcomes such as heart attack or stroke. Studies of thousands of patients followed for several years are often needed to provide confidence in the evaluation of these cardiovascular outcomes.

In observational studies, investigators examine the associations between risk factors and health outcomes that occur naturally in the community. The adverse health effects of smoking—lung cancer, heart disease and stroke—are one example. Pharmacoepidemiologic studies assess the association between the use of medications as risk factors and various health outcomes. The key distinction between clinical trials and observational studies involves the allocation of the use of the medication. In large clinical trials, randomization creates groups that are on average balanced in terms of their baseline risk for the health outcome of interest with the result that the treatment-control comparison represents a fair test. In observational studies, patients and their physicians select the medication, and the factors associated with this selection rather than the medication itself may affect the risk. In some observational studies, appropriate design and analysis can eliminate or minimize the potential biases. In the absence of evidence from clinical trials, however, observational studies often provide the best available evidence for the health effects of medications widely used in the population. These two approaches—clinical trials and observational studies—are complementary.

Duty to patients

In order to make recommendations about drug therapies, physicians must have information about both the benefits and the risks so that patients can make informed decisions. This duty to obtain and provide information about risks and benefits of drug therapies or other interventions devolves to all who work in medicine, including the pharmaceutical industry (1).

Blood clots, heart attacks, and strokes

Clotting is important to stop the loss of blood from a cut or an injury (2,3). At the site of an injury, platelets stick together and with other proteins form a gel-like plug. Under normal conditions, a delicate balance between the forces that promote clotting and the forces that prevent clotting maintains the flow of blood and prevents the loss of blood from injuries. In a heart attack or a stroke, a blood clot

forms, often at the site of an injury, in a vessel that brings oxygen and nutrients to the heart or the brain. When the flow of blood is stopped by the clot, a part of the heart or the brain is injured or dies.

Aspirin and COX-2 inhibitors

Aspirin, which prevents platelets from clumping, is well known to prevent heart attacks in patients who are at moderate to high risk of heart disease. COX-2 inhibitors such as Vioxx do not disable platelets as aspirin does. In November, 1996, Merck scientists hypothesized that patients taking Vioxx would have higher rates of heart disease than those taking an aspirin-like comparison treatment (4). By April, 1998, Merck scientists knew of evidence that COX-2 inhibitors such as Vioxx reduce the production of prostacyclin, which prevents platelet aggregation (5–7). In other words, Vioxx not only lacks the anti-platelet effects of aspirin, but it also disables one of the blood vessel's main defenses against the clumping of platelets. On the basis of this biologic evidence, it would be reasonable to hypothesize that the treatment of patients with Vioxx might increase the risk of heart attack and stroke compared with either an aspirin-like treatment or with placebo (no active treatment). For Vioxx to be used safely, the potential cardiovascular risks need to be defined clearly so that physicians and patients can be informed about the risks as well as the benefits of therapy.

Underlying causes of the Vioxx problem

From the point of view of prevention, three interventions would help to avert a Vioxx-like problem in the future. First, large long-term clinical trials to define key risks and benefits should be done early in the approval process. Second, high-risk patients likely to use medication should be included in these clinical trials in adequate numbers. Third, specific pro-active post-marketing trials or studies should be conducted and completed soon after approval. The optimal balance among the three approaches will depend on the specific medication under review. The following narrative highlights some of these issues in relation to Vioxx.

Studies of Vioxx

As part of the FDA drug-approval process, Merck conducted a number of small short-term clinical trials of Vioxx. Patients taking aspirin were excluded from many of these studies. The review by the FDA medical officer describes 58 studies that included 5,771 patients, 3,629 of whom received Vioxx (8). Most of the use was short-term [page 7]. Only 371 and 381 patients had received doses of 12.5 mg or 25 mg for more than 1 year, and 272 had received doses of 50 mg for at least 6 months [page 74]. These studies were adequate to evaluate relief from pain as well as some of the more common adverse effects such as high blood pressure, fluid retention, and abnormal laboratory tests for kidney function.

These same studies were not adequate to evaluate the effects of Vioxx on less common but important health outcomes such as heart attack and stroke. The FDA medical officer, aware of the possibility that Vioxx might promote clotting and thus increase the risk of cardiovascular disease, observed that in the 6-week studies, "thromboembolic events [such as heart attack and stroke] are more frequent in patients receiving Vioxx than placebo . . ." [page 105]. Among 412 patients taking placebo, one had a cardiovascular event (0.24%); and among the 1,631 patients receiving 12.5 mg or more of Vioxx daily, 12 had a cardiovascular event (0.74%). Especially in view of the known effects of COX-2 inhibitors on clotting, this three-fold difference represents a basis for concern. Before Vioxx was ever approved, the FDA medical officer noted: "With the available data, it is impossible to answer with complete certainty whether the risk of cardiovascular and thromboembolic events is increased in patients on rofecoxib. A larger database will be needed to answer this and other safety comparison questions" [page 105]. In May, 1999, Vioxx was approved for several indications.

The VIGOR trial

All non-steroidal anti-inflammatory drugs (NSAIDs) reduce pain to a similar degree. Epidemiologic studies had shown that NSAIDs were also associated with an increased risk of stomach ulcers and gastrointestinal (GI) bleeding. The novelty of the COX-2 inhibitors such as Vioxx was the possibility that they would treat pain effectively and spare patients the risk of stomach ulcers and bleeding. Although small studies that evaluated ulcers by invasive measures such as endoscopy had suggested the possibility of a reduced risk, the effects of Vioxx on major upper-GI clinical events such as bleeding, perforation or obstruction were not known.

The VIGOR trial, which was started in January, 1999, included patients 40 years and older with rheumatoid arthritis. Patients with recent cardiovascular events and patients taking aspirin were excluded. The investigators randomized 4,047 patients

to Vioxx 50 mg daily and 4,029 to naproxen 500 mg twice daily. In this active-comparison trial, the primary health outcome was the occurrence of major upper-GI clinical events, and patients were followed for an average of 8 months. Cardiovascular events were not identified as a safety outcome at the start of the trial.

Complete results for the cardiovascular events in the VIGOR trial were not available for the publication in the *New England Journal of Medicine* (9), but they were described in the report by the FDA medical officer for the hearing in February, 2001 (10). Patients assigned to receive Vioxx had lower rates of GI events than naproxen patients (2.1 versus 4.5 events per 100 person-years of therapy). For the combined outcome of all cardiovascular deaths, heart attacks and strokes, Vioxx patients had higher rates than naproxen patients (1.30 versus 0.67 events per 100 person-years). For the outcome of heart attack alone, the rate was 5 times higher in Vioxx patients than in naproxen patients (0.74 versus 0.15 per 100 person-years). In 1,000 patients followed for 1 year, Vioxx treatment would likely be associated with 24 fewer GI events (about 8 of them complicated or severe) and 6 more heart attacks than naproxen treatment. Because VIGOR excluded high-risk patients taking aspirin, the balance of GI benefit and heart-disease risk in these patients is not known.

The FDA medical officer also noted trends toward higher rate of cardiovascular events in her comments on studies 085 and 090 [page 34]. The FDA medical officer correctly concluded: "There is an increased risk of cardiovascular thrombotic events, particularly myocardial infarction [heart attack], in the Vioxx group compared with the naproxen group" [page 34]. The size of the VIGOR trial was large enough to exclude chance as a credible explanation for the differences in the rates of GI and cardiovascular events.

These findings—GI benefit and cardiovascular harm—present patients, physicians, regulators and industry with an exceedingly difficult choice. On the one hand, GI events are more common than cardiovascular events in the population included in VIGOR; although they are potentially serious, they are not usually fatal, and recovery is generally complete. On the other hand, about 25% of heart attacks are fatal. For persons who survive an initial heart attack or stroke, the quality of life and the duration of survival are usually compromised. The VIGOR trial results were available in December, 1999. If these safety results had been available to the FDA 7 months earlier, it is possible that Vioxx might not have been approved in May, 1999, at least not without additional studies.

On the basis of the VIGOR trial, some physicians and scientists did not think that the benefits of Vioxx outweighed their risks. The Pharmacy and Therapeutics Committee of Group Health Cooperative, a health plan where I conduct many of my studies, reviewed these data and chose not to add Vioxx to their formulary. The cumulative review of Vioxx studies by Juni and colleagues suggests that, shortly after the results of the VIGOR trial were available, "an increased risk of myocardial infarction [heart attack] was evident from 2000 onwards" (11).

Vioxx is not the first instance of mixed findings. Some years ago, clofibrate was evaluated as a treatment for patients with high cholesterol levels. Compared with placebo, clofibrate treatment was associated with lower rates of heart attack but higher rates of death (12). This experience encouraged the FDA to insist on large long-term trials of cholesterol-lowering agents such as the "statins." As a result of this approach, we now have excellent evidence from large long-term clinical trials about the substantial health benefits of lovastatin, pravastatin, simvastatin, and atorvastatin. Although these trials were expensive to conduct, the high quality of the evidence and the expanding indications for these effective medicines has helped to promote the health of the public as well as the pharmaceutical industry. The importance of conducting these large long-term trials early in the evaluation of drugs that will be used by millions of patients for many years cannot be overemphasized.

Because the VIGOR trial included active treatment with naproxen for the control group, there are three potential interpretations of the cardiovascular findings. Vioxx increases risk, naproxen decreases risk, or both. From the point of view of public health and medicine, this question is an open one that deserves careful scrutiny of the design and conduct of additional studies of Vioxx. In the original publication and in other materials, Merck settled on the hypothesis that naproxen had decreased the risk of heart attacks. Oddly, the authors called for confirmation of their naproxen findings "in larger studies" (9). This naproxen explanation is highly unlikely for several reasons. First, the five-fold difference in the risk of heart attacks is too large to be explained by an aspirin-like effect of naproxen. In 1996, Merck scientists had hypothesized an effect size of 25% to 30% for aspirin (4). Second, observational studies suggest that the beneficial effects of naproxen on the risk of heart attack are probably about 15% or 20% rather than 500% (11,13,14). In September, 2001, the FDA Division of Drug Marketing, Advertising, and Communications (DDMAC) concluded that some of Merck's promotional activities and materials were "false, lack-

ing in fair balance, or otherwise misleading." The letter specifically notes that the naproxen explanation is merely "hypothetical" rather than factual, and calls the press release claiming a "favorable cardiovascular safety profile" for Vioxx "simply incomprehensible."

I would like to focus for a moment on the issue of extrapolation of the results of clinical trials. Trial results are directly generalizable to patients who were eligible for the study and who, if asked, would have enrolled. Generalization to other patients must be done with caution. As I have indicated, patients with cardiovascular disease and patients taking aspirin were often excluded from the clinical trials of Vioxx. The major indication for low-dose aspirin is the prevention of cardiovascular disease in patients who are at moderate to high risk (2,3). In most of the early studies, Vioxx was not evaluated adequately for the large number of Americans at especially high risk of cardiovascular disease. In one observational study, 42% of the Vioxx users had a clinical history of major cardiovascular disease (15). Among naproxen users in the community, the heart attack rate was about 8 times higher than the rate for naproxen users in VIGOR (1.16 per 100 person years versus 0.15 per 100 in VIGOR). In a population with a moderate to high rate of heart attacks, in other words, Vioxx might cause more heart attacks than the number of GI events prevented.

It is not at all clear whether or how either the GI benefits or cardiovascular harms of Vioxx might be influenced by the use of low-dose aspirin (16,17). For instance, the results of Merck protocol 136 (18) suggest that the cumulative incidence of gastroduodenal ulcers >=3 millimeters as assessed by GI endoscopy was similar in patients who took ibuprofen (17.1%) and in patients who took both low-dose aspirin and Vioxx (16.1%), but higher than in patients who took low-dose aspirin (7.3%) or in patients who took placebo (5.8%). Vioxx was not adequately studied in the large numbers of high-risk patients who would eventually take it.

The FDA did request that Merck revise the product label to reflect the cardiovascular risks observed in the VIGOR trial. While the FDA public review of the VIGOR trial results occurred in February, 2001, the revisions to the Vioxx product label were not completed until April 11, 2002. These revisions were added to the "Precautions" section, under "Cardiovascular Effects" (19). No black-box warning about adverse cardiovascular effects, the most prominent warning, was added to the Vioxx product label. In contrast, black-box warnings about an increased risk of cardiovascular events were added to estrogens and progestins after the results of the NIH-funded Women's Health Initiative were published (20). The public health rationale for the two different approaches remains unclear.

Post-marketing surveillance studies

After approval, aggressive direct-to-consumer marketing of Vioxx led to increased sales, and soon large numbers of Americans were using Vioxx. This high level of use permitted various investigators to conduct observational studies of the association between Vioxx and the risk of heart attack. For assessing this association, the FDA MedWatch system is not adequate (21).

Some observational studies have found no increase in the heart-attack risk associated with Vioxx (22). Others report an increase risk, especially for patients taking high-dose Vioxx (15,23). One of the best-designed observational studies was conducted by Dr. Graham and colleagues (24). In this study, users of Vioxx were compared with users of CELEBREX (celecoxib, another COX-2 inhibitor). The analysis was adjusted for potential confounding factors. Vioxx at doses of 25 mg or less daily was associated with a 50% increase in the risk of heart attack; and doses of greater than 25 mg daily were associated with a 370% increase in the risk of heart attack. These risk estimates from this observational study are consistent with the findings from the randomized trials, VIGOR and APPROVe.

APPROVe trial

In this clinical trial, patients aged 40 years or older with benign tumors (adenomas) in the large intestine were randomly assigned to receive Vioxx 25 mg daily (n = 1287) or placebo (n = 1299). The purpose of the trial was to evaluate whether Vioxx prevented the recurrence of the adenomas. Patient enrollment began in February of 2000. Initially, patients taking low-dose aspirin were not eligible; but in June, 2000 as a result of the VIGOR findings, the APPROVe protocol was amended to allow up to 20% of patients taking low-dose aspirin into the trial. After 18 months of follow-up, the cardiovascular event rates for the two groups diverged. Vioxx patients had higher rates of heart attack or stroke than placebo patients (1.08 versus 0.48 events per 100 person-years of therapy; rate ratio [RR] = 2.25; 95% confidence interval [CI] = 1.24 to 4.08). This risk of heart attack or stroke was lower in patients taking aspirin (RR = 1.29; 95% CI = 0.28 to 6.50) than in patients not

taking aspirin (RR = 2.57; 95% CI = 1.31 to 5.06) although there was no significant difference between the two strata (interaction p-value = 0.37). On the basis of these data, the Data Safety and Monitoring Board recommended stopping the clinical trial, and Merck withdrew Vioxx from the market in September, 2004.

In 1000 patients who have a baseline risk of 5 heart attacks or strokes over a 1-year period, Vioxx treatment would likely increase the number of heart attacks or strokes to a total of 11. For patients with a higher baseline risk, the number of additional heart attacks or strokes would be larger. As commentators have pointed out (19), tens of thousands of patients may have had heart attacks or strokes that are attributable to the use of Vioxx.

The Merck-sponsored reviews of the early pre-existing small short-term clinical-trial data could provide only limited information (25,26). Importantly, it was the results of a large long-term clinical trial, APPROVe, that convinced Merck to remove Vioxx from the market. The failure to conduct large long-term randomized trials in a more timely fashion permitted millions of Americans to use a drug whose cardiovascular safety profile was in question.

In the development of Vioxx, Merck had invested a enormous amount of time and money. In the evaluation of whether and when to withdraw Vioxx, Merck has an almost insurmountable conflict of interest. To protect the health of the public, this sort of decision should be referred to an independent group of reviewers.

Recommendations

Attention to the following recommendations may help prevent future Vioxx-like problems.

1. Large long-term trials to assure patient safety. Arthritis is a chronic condition, and treatment is often required for many years. Medicines for common chronic conditions have large potential markets with the result that even small increases in risk can affect tens of thousands of people. Medicines that will be used by large numbers of Americans for long periods of time are best evaluated in large long-term clinical trials that are started as early as possible in the approval process. The clinical trial of lumiracoxib is a recent example of a large trial (16,17). This approach, used for the statin drugs, has benefited patients, physicians and the pharmaceutical industry. If the VIGOR trial results had been available in May, 1999 rather than December, 1999, it is possible that Vioxx might not have been approved by the FDA, at least not without additional studies.

2. Evaluation of medicines in patients who are likely to use them and may be especially vulnerable to adverse effects. Initially, Merck excluded patients with recently diagnosed cardiovascular disease and patients taking aspirin. This approach maximized the possibility of finding a GI benefit and, at the same time, minimized the possibility of uncovering convincing evidence about cardiovascular harm. It also provides physicians and patients taking aspirin with no information about the risks and benefits of Vioxx therapy. For a large number of patients, it was not clear whether Vioxx was, at the time of approval, safe and effective for the intended use.

3. Improvements in post-marketing surveillance by the FDA. In the last decade, with the emphasis on rapid drug-approvals, new drugs (new molecular entities) often first appear on the U.S. market. Perhaps because of the attention devoted to the speed of the review, less emphasis has been placed on attention to patient safety. The FDA should reorient priorities and devote more attention and resources to patient safety. The recognition of new adverse effects—those that are not recognized prior to approval—will require the monitoring of patients who take these drugs. The FDA MedWatch data can only provide information about rare and serious side effects that are unrelated to the indication of the drug, so other means of evaluating safety must be employed for newly marketed drugs. Specific pro-active post-marketing trials or studies should be designed, conducted and completed in a timely fashion (27). The optimal balance between clinical trials and observational studies will depend on the specific drug and the safety questions that may remain or arise. Moreover, new post-marketing surveillance systems and approaches should be developed or enhanced. For instance, Coordinated Clinical Studies Network, which was just recently funded as part of the NIH Roadmap Initiative, includes 4% of the U.S. population and is moving toward the use of a coordinated system of electronic medical records. An almost on-line assessment of risk may be possible in the near future.

4. Independent Office of Drug Safety and conditional approval of new medications. To implement improvements in post-marketing surveillance, the FDA needs a new Independent Office of Drug Safety that can pursue potential "signals" or "biologic hypotheses" in a pro-active way. This new office should be separate from the FDA office that originally approved the drug. A system of conditional approvals for new medications (or regular re-review of all medications) would provide the FDA the au-

thority and the opportunity to insist on timely revisions to labels, to assure that post-marketing commitments have been completed, and to compel new post-marketing commitments when they may be indicated. Finally, to balance the interests of patients and industry, decisions about label changes, new studies, suspension of sales or withdrawal of drugs might best be made by the new Independent Office of Drug Safety in consultation with an outside group of disinterested reviewers.

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PREPARED STATEMENT OF GURKIPAL SINGH, M.D.

Chairman Grassley, Senator Baucus, Senators, and ladies and gentlemen, thank you for inviting me to testify before the Senate Finance Committee. I apologize for not appearing in person, and giving this testimony by a video conference. I am unable to travel because exactly 2 weeks ago today, I had a heart attack—and before the plaintiff's attorneys rush out of this room to call me—no, I was not taking Vioxx. I have been asked to review the science of COX-2 inhibitors, the link of rofecoxib to heart attacks, the timeline of different studies, and my own role in teaching physicians about these issues. Hindsight is always 20/20, and I do not intend to be a Monday morning quarterback today. Instead, I will try to highlight the learning and knowledge that we can derive from this episode so that early signals are not missed again with another drug. At the end of my presentation, I will make recommendations that I believe are essential to avoid a repetition of this unfortunate incident where millions of Americans were unknowingly subjected to serious harm.

I am a rheumatologist by clinical training with research interests and expertise in drug safety and epidemiology. My group and I were instrumental in pointing out the risks of painkillers such as motrin and aleve (a class of drugs called NSAIDs), identification of patients who have a risk of serious stomach bleeding from such drugs and potential ways to avoid such risks. I have been working in the research area of drug safety and outcomes research for almost 15 years, and have published extensively in the medical literature. I am currently working with large public datasets such as Medicare and Medicaid to study early safety signals of medications. I lecture medical students, residents and other physicians, both at Stanford, and in conferences worldwide, on many of these issues.

Science of specific COX-2 inhibitors

There are 2 enzymes in the human body—COX-1 and COX-2 (*see* attachments). COX-1 enzyme is needed for the normal functioning of stomach and platelets. COX-2 enzyme, on the other hand, is thought to be responsible for the pain and swelling of arthritis. Traditional painkillers such as ibuprofen (the chemical in motrin) inhibit both COX-1 and COX-2. This means that while these drugs are effective in reducing pain, they increase the risk of stomach bleeding. A few years ago, my colleagues and I estimated that there are over 103,000 hospitalizations and 16,500 deaths every year from the stomach bleeding complications of these drugs (1,2). The specific COX-2 inhibitor drugs such as Vioxx and Celebrex, were developed to inhibit only COX-2, and not COX-1. It was hoped that these drugs would relieve pain but not have any stomach problems. Indeed, this seems to be the case. In May, 2004, I presented data that showed a significant reduction in the number of stomach bleeds in the U.S. after the launch of these drugs (3). However, it is important to remember that drugs such as Vioxx do not cure arthritis—they are used only for control of pain, and are medicines for convenience and quality-of-life improvement rather than for savings lives or preventing disabilities. There are many other ways to effectively control pain as well.

Heart attacks

It is believed that most heart attacks occur when the blood vessels supplying blood to the heart become narrowed because of cholesterol deposits (*see* attachments), and a blood clot forms at this narrowing, stopping the flow of oxygen to the heart muscle. The blood clot is formed by cells called platelets, and it is the COX-1 enzyme in the platelets that is responsible for this function. Aspirin destroys this enzyme in a permanent fashion and prevents blood from clotting in the heart blood vessels, thus helping reduce the risk of heart attacks. Other painkillers such as ibuprofen and naproxen also inhibit the enzyme in the platelets, but only temporarily and incompletely. While it is possible that these non-aspirin painkillers may also reduce the risk of heart attacks, this has never been shown in any randomized clinical trial, despite claims to the contrary (4). These drugs are not used for preventing heart attacks, since, even if they were to be effective, the effect of temporary and incomplete inhibition of platelets would be much less beneficial than the complete and permanent inhibition caused by aspirin.

Vioxx and risk of heart attacks

The Senate Finance Committee provided me with information on events surrounding the approval and withdrawal of Vioxx, and the supporting documents attached to my testimony. I have been asked to comment on this with the specific purpose of identifying key events that should have alerted scientists and the public to the potential problems with Vioxx so that a similar problem can be avoided in the future with another drug.

Before I review the attachments, I wish to reiterate that the fundamental principle of medicine—one that every physician swears by is *primum, non nocere*—"first, do no harm." A second principle is a careful evaluation of the risk-benefit ratio of any treatment. It is easier to accept a more serious side-effect such as heart attack in a drug that cures cancer, for example, than in one that is used to treat skin rash.

We now know that by November of 1996, Merck scientists (5) were seriously discussing a potential risk of Vioxx—association with heart attacks (*see* attachments). At that time, it was not known that Vioxx might itself cause heart attacks. Rather, the discussion focused on the issue that other painkillers, by inhibiting platelets, may protect against heart attacks. Vioxx has no such effect on platelets, and thus may seem to increase the risk of heart attacks in studies comparing it to other painkillers. This was a serious concern, because the entire reason for the development of Vioxx was safety—please note, once again, that it is no more effective than other NSAIDs. If the improved stomach safety of the drug was negated by a risk of heart attacks, patients may not be willing to make this trade-off. Merck scientists, considered by many to be the best and brightest in the pharmaceutical industry, were among the first to recognize this. At this point in time, scientists should have started a public discussion about this potential trade-off, and designed studies that would more carefully evaluate the risk-benefit ratio of the drug.

It appears from the internal Merck e-mails provided to me that, in early 1997, Merck scientists were exploring study designs that would exclude people who may have had a weak heart so that the heart attack problem would not be evident. The discussion also focused on the fact that if aspirin were permitted in these trials, there may not be any significant safety advantage of Vioxx on the stomach. On the other hand, as one scientist pointed out, if aspirin was excluded, patients on Vioxx may have more heart attacks and this would "kill the drug." He also points out that in the real world, "everyone is on it." Clinical trials should be designed to test a drug under "real world" circumstances—on patients who are most likely to use the drug. Clinical trials should not be designed to selectively favor one outcome over another by excluding people similar to those who would take the drug after its approval. Certainly, clinical trials should not be designed to put marketing needs in front of patient safety—we need to know how a drug behaves in people who are going to take it, even if it "kills the drug." It is better to kill a drug than to kill a patient.

According to documents provided to me by the Senate Finance Committee, there were many other internal discussions within Merck on these concerns of heart attack: stomach bleed trade-offs, although the practicing physician did not learn of any of this till many years later. In 1998, Dr. Doug Watson, a Merck scientist, presented an analysis of serious heart problems with Vioxx compared to patients enrolled in studies of other Merck drugs. This analysis (*see* attachments) concluded that men taking Vioxx had a 28% greater risk (not statistically significant), but in women, the risk was more than double (216%, statistically significant) compared to people not taking any drug in other Merck studies. To the best of my knowledge, these data were never made public. This is when a public scientific discussion of the pros and cons of the medication should have started.

By 1999, an even more serious problem was emerging. By the time Merck had filed for the approval of Vioxx, there were several small studies evaluating the efficacy and safety of Vioxx in patients with pain and arthritis. None of these studies were large enough to study the risk-benefit trade-offs of stomach bleeds versus heart attacks. But in a careful FDA review of Merck's new drug application for Vioxx, Dr. Villalba noticed that "thromboembolic events [such as heart attack and stroke] are more frequent in patients receiving Vioxx than placebo . . ." [page 105]. Among 412 patients taking placebo, 1 had a cardiovascular event (0.24%); and among the 1,631 patients receiving 12.5 mg or more of Vioxx daily, 12 had a cardiovascular event (0.74%) (6). This meant that not only did Vioxx not inhibit the platelets, but for some reason, it was likely to promote heart attacks directly. Many scientists would consider this three-fold difference as an early warning sign. But there were no adequate data to make a firm conclusion one way or another. In fact, the FDA reviewer went on to point out that: "With the available data, it is impossible to answer with complete certainty whether the risk of cardiovascular and thromboembolic events is increased in patients on rofecoxib. A larger database will be needed to answer this and other safety comparison questions" [page 105]. It is my opinion that at this point in time, larger and more definitive studies should have been done before the drug was approved. After all, the drug was no more effective than any other available pain-killer—and there were nearly 30 such drugs available in the U.S. Another drug (Celebrex) that had no such signal had also been available in the market for 6 months prior. A combination of two older drugs—a pain-relieving drug such as Motrin with a drug that protects the stomach such as Prilosec—is as effective and almost as safe on the stomach as Vioxx, with no heart attack risk. There was certainly no emergent need to approve Vioxx without further studies if there were lingering safety concerns. The trade-off of heart attacks for the rare instances of stomach bleeds is not a reasonable one. Remember, *primum non nocere*—"first, do no harm." Instead, the drug was approved by the FDA in a priority review within 6 months—with no discussion on the heart attack trade-off. The prescribing physicians remained unaware of any of these data or discussions, till much later—with the new label change in April, 2002.

VIGOR trial and my interaction with Merck

The VIGOR trial, which will be discussed in detail later, was the first public release of heart attack stomach bleed trade-off concerns. At the time VIGOR study results were announced, I was actively involved in research and teaching in this area. Some of my medical education lectures were sponsored by Merck and other drug companies. I was strongly in favor of this new class of drugs and, before the VIGOR trial, was unaware of any significant heart attack issues. The results of the VIGOR trial—a 500% increase in the risk of heart attacks with Vioxx—stunned me. Clearly, the trade-off of 500% increase in heart attacks for a 50% reduction in stomach bleeds did not seem attractive—at least, not without a further discussion of data. Merck's press release on this issue and a brief mention of the heart attack data were not enough for me to continue to educate physicians in my lectures. I asked Merck for more detailed data, including information on high blood pressure and heart failure rates. When I was unable to obtain this data after multiple requests, I added a slide to my presentations that showed a man—representing the missing data—hiding under a blanket (*see* attachments). Up until this point in time, Merck had responded to all my requests promptly and in a scientific fashion. With VIGOR, suddenly it was as if the Company had to think what questions to answer. I persisted in my enquiries—and I was warned that if I continued in this fashion, there would be serious consequences for me. I was told that Dr. Louis Sherwood, a Merck senior vice-president, and a former Chief of Medicine at a medical school, had extensive contacts within academia and could make life "very difficult" for me at Stanford and outside. But as a research scientist, I felt that it was unethical for me not to discuss my concerns in public. An open scientific debate was important—it is only through open debate and discussion that we advance science. Dr. Sherwood called several of my superiors at Stanford to complain. Subsequently, I learned that this was a persistent pattern of intimidation by Dr. Sherwood. Professor Fries too felt that this suppression of scientific discussion was unethical and complained to Mr. Raymond Gilmartin. Mr. Gilmartin and Mr. David Anstice took immediate action, and the threats stopped immediately. From then onwards till today, Merck scientists and officials have treated me and my colleagues with appropriate respect and have always shared scientific data promptly.

We have not always agreed with the interpretation of data, but to the best of my knowledge, nothing has been hidden, suppressed or falsified by any Merck scientist since this episode. All my requests for scientific information are handled promptly

and courteously, and for this I thank Merck in general, and Dr. Alise Reicin in particular.

Publication of VIGOR data

Scientific publications in a medical journal are the most credible way to disseminate data about a medication. VIGOR data were published in the *New England Journal of Medicine* in November, 2000. A few weeks ago, Merck announced that the published VIGOR data were "preliminary" and that the "final" data were presented to the FDA. In my view, and of all my colleagues that I have consulted with, it is inappropriate to publish "preliminary" or incomplete data without clearly stating that the data are preliminary. This is especially true if the favorable data are complete but the unfavorable data are "preliminary" and likely to get worse. To the best of my knowledge, the VIGOR paper did not indicate anywhere that the data were preliminary or incomplete. Nor, did I ever see a correction or erratum indicating this fact subsequently—up until a few weeks ago, almost 4 years later.

The VIGOR publication minimized the significance of heart attacks. While it prominently discussed the reduction of stomach bleeds in patients taking Vioxx, it did not mention that in spite of this, patients on Vioxx had more serious adverse events, and more hospitalizations than patients on naproxen. The true rates for cardiovascular thrombotic adverse events (a prespecified study endpoint in the protocol), hypertension and congestive heart failure—which were all higher in the Vioxx group—were not shown in the paper at all.

The FDA review of VIGOR correctly pointed out that the explanation advanced by the authors—that naproxen reduced the risk of heart attacks—could not explain the 500% difference between Vioxx and naproxen. The reviewers also highlighted data from many other studies showing that this was not an isolated finding in VIGOR. However, Merck continued to claim "favorable cardiovascular safety profile" of Vioxx in multiple press releases and company-sponsored lectures and conferences. In September, 2001, in a Warning Letter to Merck, the FDA Division of Drug Marketing, Advertising, and Communications (DDMAC) called the press releases claiming a "favorable cardiovascular safety profile" for Vioxx "simply incomprehensible," and pointed out that the naproxen explanation was merely "hypothetical" rather than factual. These facts had previously been discussed by FDA reviewers as well (7).

Post-VIGOR label change

The VIGOR data were first made public in May, 2000. However it was not until almost 2 years later that the FDA requested Merck to revise Vioxx's product label to reflect the heart attack risks observed in the VIGOR trial. These revisions were added to the "Precautions" section, under "Cardiovascular Effects," instead of being prominently displayed as a "Warning." While the stomach bleed safety data were added in a prominent fashion, the heart attack information seemed to support Merck's contention that Vioxx did not increase the risk by adding statements such as "Because of its lack of platelet effects Vioxx is not a substitute for aspirin for cardiovascular prophylaxis." Was there a single physician in the world who had prescribed Vioxx for cardiovascular prophylaxis? Why not also say "Because of its lack of anti-tumor effect, Vioxx is not a treatment for brain cancer" or "Do not use Vioxx for erectile dysfunction or depression"? The favorable data for Alzheimer's disease studies was included at Merck's insistence, but no unfavorable data from studies such as 085 or 090 were added. Even the Alzheimer's disease studies data were favorably biased—while the label showed that there was no difference in heart attacks between Vioxx and placebo in these studies, it did not mention that the mortality rate of patients on Vioxx was almost twice that of those on placebo. Negotiations certainly succeeded for Merck.

Many people claim that the heart attack-stomach bleed data trade-off was a favorable one, since there are many more stomach bleeds prevented than heart attacks caused by Vioxx. As the FDA review of VIGOR data pointed out, this was simply not true (7).

No long-term safety studies

More importantly, there were no attempts to design and carry out large safety studies to prove or disprove the link of Vioxx to heart attacks. Apparently, a 30,000-patient study had been announced in November, 2001 but never started. Last week, the *New York Times* reported that Merck had considered a cardiovascular outcome study, but decided that it would send the "wrong" marketing and public relations signal. "At present, there is no compelling marketing need for such a study," said a slide prepared for a meeting of senior executives. "Data would not be available during the critical period. The implied message is not favorable." It is regrettable that scientific decisions on patient safety are influenced by perceived marketing and

public relations concerns. In my opinion, it is better to kill a drug than to kill a patient.

It is important to note that the APPROVe study, which conclusively proved the increased risk of Vioxx, was not a safety study—it was an efficacy study, designed to add another indication for Vioxx treatment. It was not large enough to detect a heart attack risk—that it did find a risk was a lucky break for patients, but this is not what it was designed to do.

The failure to conduct large long-term safety studies subjected millions of patients over 4 years to a drug whose safety had been questioned by the FDA even before its approval. This is not the proudest chapter in drug approval in the U.S.

Recommendations

What can we do to prevent this from happening again? First, we must find out exactly what went wrong.

1. A public enquiry should be conducted by an independent group of scientists with free access to all Merck internal documents, to study all aspects of safety data surrounding Vioxx, with a particular emphasis on (a) if earlier, better studies could have shown the heart attack risk, (b) if such studies had indeed been suppressed by marketing and public relations worries, and (c) if a discussion of this heart attack risk was suppressed in an unethical fashion.

2. A public discussion of the role of FDA in approving drugs and labels. As the delay in the Vioxx label change shows, the current process of labeling is one of negotiations—if the "sponsor" does not agree with what the FDA wants, it can continue to stall or worse. It took 2 years for the label change of Vioxx to take effect, and even then, the label change supported mostly Merck's position, not the one advanced by FDA's own reviewers in public hearings. This process needs to be fixed, if need be, by new legislation. The FDA should be given the authority that is accorded to our judicial system—to make unilateral decisions on issues of public health and safety, without having to negotiate and reach agreement with drug companies. The FDA should regulate the drug companies, not collaborate or negotiate with them if there is any question of public safety.

3. The FDA approval process needs to be more open and subject to public scrutiny. Once a drug is approved, all the data supporting such approval should be put in the public domain. If this had been done with Vioxx, perhaps independent scientists would have been able to spot early signals. Similarly, all clinical study data submitted to the FDA should be available to the public after the drug is approved. Claims of "trade secrets" should not take precedence over public health and safety. Pharmaceutical companies should not be allowed to selectively disseminate only positive data.

4. On drugs that need further safety data, a system of conditional or time-limited approvals should be instituted. For example, since the FDA reviewer had concerns about heart attacks before the approval of Vioxx, but there was not enough data to decide the issue one way or other, the FDA could have provided a conditional approval (if any) that would have required Merck to complete large safety studies within a certain time period.

5. An independent office of drug safety which does not report to the FDA new drug approval section should be established. Safety data on all new drug approvals must be vetted through this office. This office should have an independent authority to conduct safety studies on approved drugs, or require that such studies be conducted if there are safety signals. Only then will be able to adhere to the principle of *primum, non nocere*—"first, do no harm."

Thank you.

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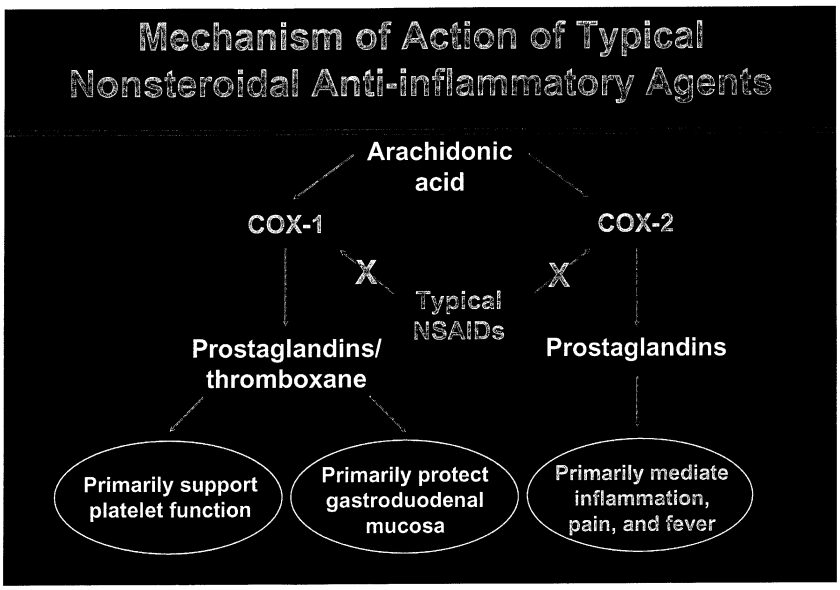
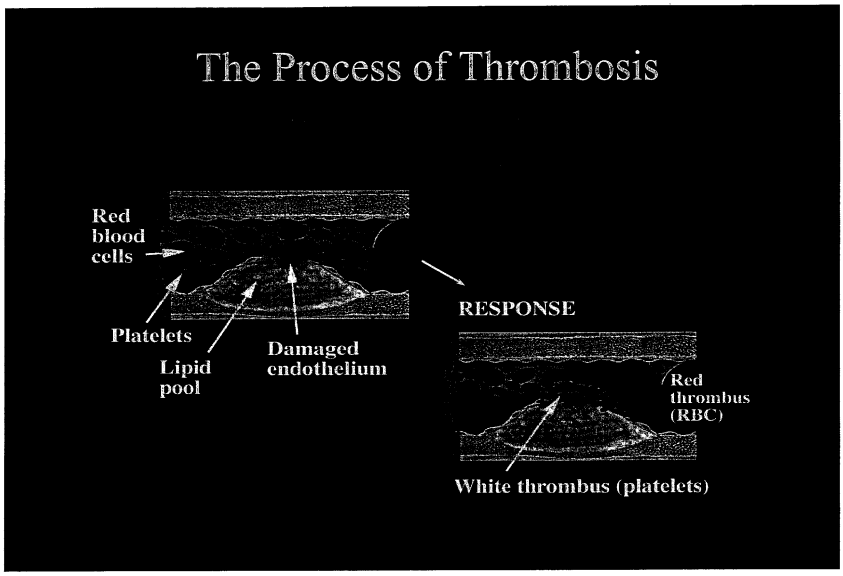
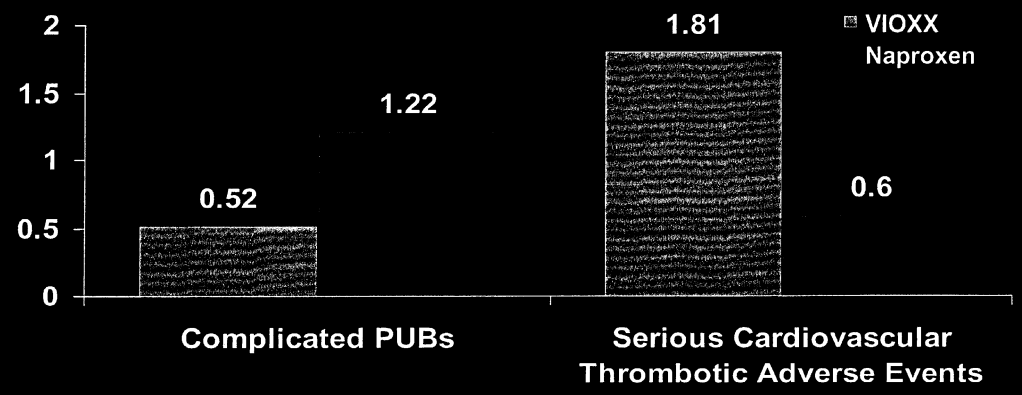

Mechanism of Action of Typical Nonsteroidal Anti-inflammatory Agents
Arachidonic acid
COX-1
COX-2
X
X
Typical NSAIDs
Prostaglandins/ thromboxane
Prostaglandins
Primarily support platelet function
Primarily protect gastroduodenal mucosa
Primarily mediate inflammation, pain, and fever


The Process of Thrombosis
Red blood cells
Platelets
Lipid pool
Damaged endothelium
RESPONSE
Red thrombus (RBC)
White thrombus (platelets)

Risk-Benefit Comparison of Complicated PUBs and CV Events

Kaplan-Meier Cumulative Rate of complicated PUBs and CV Thrombotic Adverse Events



[1]Kaplan-Meier cumulative rate at end of study when at least 500 patients remained (approximately 10 ½ months)
[2]Confirmed by blinded adjudication committee
VIOXX Prescribing Information (http://www.merck.com/product/usa/vioxx/product_info/pi/9183810.pdf) accessed April 19,2002

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VIOXX (MJ)

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ALISE REICIN
MAR 3 2000

MRL Epidemiology Department
Technical Report No. EP07006.005.98

Final Results of an Analysis of the Incidence of Cardiovascular SAEs in the Phase IIb/III VIOXX Osteoarthritis Clinical Trials

February 2, 1998

Doug Watson, Ph.D.
Epidemiology

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EXECUTIVE SUMMARY

This report provides the results of an analysis of the incidence of selected thrombotic cardiovascular (CV) serious adverse events (SAEs) among patients in the VIOXX Phase IIb and III Osteoarthritis (OA) trials and their extensions. The objective of the analysis was to provide information on which to base a recommendation to the VIOXX project team regarding the need for more formal monitoring of the risk of CV SAEs in trials of VIOXX.

The CV SAEs included in the analysis were selected based on the clinical impression that they were likely to represent acute thrombotic CV events. The incidence of CV SAEs from VIOXX patients (all treatment groups) was compared to those of placebo patients from selected PROSCAR and FOSAMAX trials and the overall rate for both men and women was compared to a population-based, epidemiologic study (Cardiovascular Health Study).

Descriptive analyses of the demographics of the patient populations showed them to be similar in age and age distribution, proportion of current smokers, and predominantly Caucasian. Mean weights of the men from VIOXX trials and men from PROSCAR trials were comparable. Women in the VIOXX trials were considerably heavier than those of the FOSAMAX trials. The prevalence of hypertension, diabetes, and hypercholesterolemia at baseline was higher in the VIOXX population than in either of the placebo control populations. The time on therapy in the VIOXX trials was much shorter than that for PROSCAR and FOSAMAX placebo patients. The total number of patients with one or more CV SAEs of interest was 27 (8 in men, 19 in women) in the VIOXX program, 97 in PROSCAR placebo patients , and 163 in FOSAMAX placebo patients. Two female patients from the VIOXX program with CV SAEs were less than 50 years of age; since there were no control patients less than 50 years, data from this age group was not included in the incidence rate calculations.

The pooled incidence rate of CV SAEs in men in the VIOXX program was 19.4/1000, while the rate for women was 15.5/1000 patient-years at risk. These rates are not elevated compared to those of persons aged 65 and older in the Cardiovascular Health Study. The overall, pooled incidence rate for men in the VIOXX program was not statistically significantly different from PROSCAR placebo controls (age- and time-period-at-risk-adjusted rate ratio 1.28, 95% CI 0.53 - 2.82). The overall incidence rate for women was elevated compared to FOSAMAX placebo controls (adjusted rate ratio 2.16, 95% CI 1.14 - 3.94). The increased rate in women is driven by very low rates in two of the FOSAMAX placebo strata ($\leq$ 6 weeks, and >6 but $\leq$24 weeks). Given the variation among strata in women, and that the FIT placebo population is considered to have an atypically low incidence of CV events, the increase in risk for women is felt to not be of concern.

In summary, CV SAE incidence rates in patients enrolled in VIOXX trials appear to be roughly consistent with what would be expected in the general population, and there is no clear evidence of consistently elevated adjusted risk compared to placebo controls from PROSCAR and FOSAMAX trials. There are necessarily a number of limitations to this study, including potential misclassification of events, possible biases associated with the use of historical controls, and the inclusion of all patients (including those treated with placebo and NSAID comparators) from the VIOXX program in the incidence rate calculations.

Based on these results, it is recommended that there be no change in the conduct of trials of VIOXX at this time. An analysis of CV SAE event rates in patients treated with VIOXX compared to those treated with VIOXX placebo/comparators is recommended when the trial databases are unblinded.

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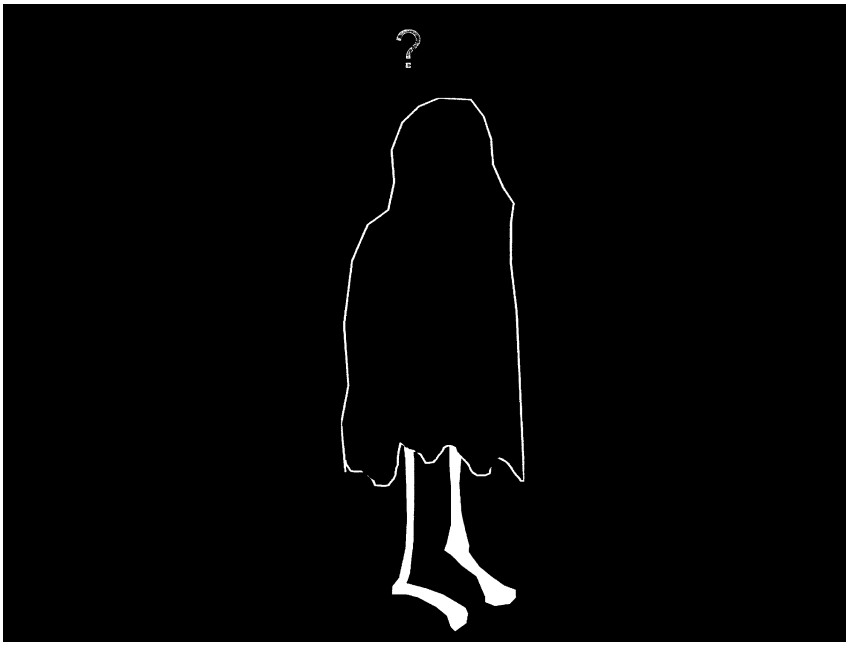

EXHIBITS

The following exhibits were obtained by the Committee on Finance pursuant to its investigation of the Food and Drug Administration's approval of Vioxx.

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 1

COX-2 OUTcomes Study

**MK-0966 (COX-2 INHIBITOR) CONSULTANTS' MEETING
PHASE III MONITORING OF GI CLINICAL EVENTS
and DESIGN OF A GI OUTCOMES MEGA-TRIAL**

September 28, 1996

MEETING MINUTES

The morning session of the meeting covered the Phase III Monitoring of GI Clinical Events; the afternoon session covered the Design of a GI Outcomes Mega-Trial. A list of the consultants is provided in Attachment 1 and a list of other attendees is provided in Attachment 2. Attachment 3 contains a copy of the agenda for the meeting.

PHASE III MONITORING OF GI CLINICAL EVENTS

Dr. Watson made opening remarks and provided an overview of the objectives (Attachment 4) of the meeting. Dr. Daniels presented the clinical background for the COX-2 program including the ongoing and planned clinical trials (overheads in Attachment 5) and facilitated discussion of the NSAID class label warning. Dr. Watson then presented the MK-0965 Phase III GI Clinical Event Monitoring Plan (overheads in Attachment 6). Productive discussion from the meeting is summarized below.

Clinically Significant NSAID-Related Events (Perforations, Ulcers, UGI Bleeding)

The consultants agreed that the basis for the primary hypothesis should be the collection of perforations, ulcers and bleeding (PUBs) from upper-GI sources. They approved of the criteria set forth to establish the "certainty" of these events, but suggested that the need for transfusion be added as a criterion for severity of bleeding. The consultants suggested that Clinically Significant Upper GI Bleeding should be defined according to "severity" in addition to "certainty" criteria. They also suggested that a sub-analysis of ulcers be performed related to severity (e.g., bleeding ulcers as a subset of all ulcers). Discussion of monitoring for esophageal and lower GI events pointed out that, while adding power to the analysis, this practice would also add to the misclassification of events leading to "noise" in the data. It was decided that these events would not be included in the PUB events. Similar discussion led to agreement that ulcer with obstruction would not be counted as a distinct event since these are expected to be rare and would be counted as an ulcer.

Dr. Spector suggested an additional category of reproducible hematocrit drops of ≥6 percentage points to broaden the collection of bleeding events. Since hematology testing is routine in all Phase III studies, the data would be readily available, and comparison to screening (pretreatment) values would be possible. Dr. Daniels noted that the protocols do have procedures for re-evaluation of hematocrit values triggered by a drop of 5 percentage points, and include the suggestion to perform stool guaiac testing. While the

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consultants agreed to the additional category, they emphasized that it should be considered separately from the PUB categories because attribution of these events to NSAIDs will be less certain, and because they represent a different set of GI bleeding events than upper GI bleeding as defined in the plan. The consultants felt that the strongest evidence of a class difference for MK-0966 will be obtained using the PUB category for the primary analysis.

UGI NSAID-Related Symptoms

In considering the second category of events in the plan, pre-selected NSAID-related GI events, the consultants suggested that symptoms should be collected actively by using a checklist rather than passively by mapping spontaneously reported events into several defined categories. The consultants thought that a checklist would be viewed as a more rigorous method of collecting these types of events, providing hard evidence that the patient was asked about the symptom(s). Prof. Langman also felt that regulators might view the data more favorably if efforts were made to use a defined symptom checklist. Discussion noted that a checklist was likely to increase the incidence of the named events which could be detrimental to the ultimate label language. Prof. Langman pointed out that definitions of symptoms are not internationally uniform and are subjectively determined by individuals. Dr. Spector pointed out that attempts had been made to validate GI symptom questionnaires in a pilot fashion in the 7-day endoscopy study, and in an ibuprofen study, with negative results. The former study produced an inconsistent result for the questionnaire; the latter study barely distinguished ibuprofen from placebo. It is known that there is no consistent relationship between symptoms and structural lesions. In the absence of a validated GI symptom checklist, MRL felt that the usual open-ended method of collection of spontaneous events would be best. Dr. Simon also noted that the decision to collect spontaneously reported information on a selected set of symptoms was prompted by the methods used in the nabumetone and meloxicam clinical trials. Since it is not expected that there will be a significant difference demonstrated for MK-0966 versus comparators based on analysis of symptoms, it was decided that no hypothesis related to symptoms would be stated, but a descriptive analysis would be performed. The consultants suggested that perhaps several more terms could be added to the pre-specified list of symptoms.

Dr. Griffin questioned whether the use of H_2-receptor antagonists or antisecretory drugs would be allowed during the study. The patients will not be allowed to use concomitant H_2-receptor antagonists, except as prescribed for an adverse event. The consultants sought clarification on the medical history of eligible patients and were advised that the enrollment will be stratified for prior history of GI complications. The exclusion from enrollment of patients with a history of the use of antisecretory medications will be at the discretion of the investigators.

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Data Analysis

The consultants agreed to the proposal to analyze the number of patients having events rather that the numbers of events. The primary analysis will analyze PUBs together since the total number is expected to be small. Consensus was reached that the PUBs and UGI symptom events would not be combined because the expected small number of PUBs would be overwhelmed by the much larger number of symptoms. The consultants agreed that there was no need to analyze the population of patients who discontinued due to significant GI events because they would all be represented in the other analyses.

The power of the primary analysis of PUBs was acknowledged to be small (there is about 50% power to detect the amount of difference in the expected event rates between an NSAID and placebo at a two-sided alpha level of 0.05). However, such an analysis will need to be done for regulatory purposes. The consultants agreed that to commit to many sub-analyses within the PUB category would most likely present many negative results due to small numbers which would then have to be qualified. Discussions concerning the analysis methods confirmed that what was implied by a "pooled analysis" was in fact a "meta-analysis" , and that the analysis would include a factor accounting for "study".

Consensus was reached that the endoscopy studies should be included in the monitoring plan and the meta-analysis, but information from protocol-scheduled endoscopies would be excluded. The plan as presented would have asked the endoscopist to identify whether a performed endoscopy was medically necessary. Various other methods of having investigators account for the timing of endoscopies relative to symptom onset and findings were discussed and found to be unreliable and operationally difficult. Since the likelihood of a significant clinical event being discovered on a scheduled endoscopy visit is low, and that a small number of such events would have little influence on the outcome of the analysis, it was agreed that a window of time around scheduled endoscopies would be defined and events occurring or discovered inside the window would be excluded from the meta-analysis.

Study Procedures

The consultants agreed to the plan to use an external review board to evaluate the investigator narratives, case report forms, adverse event reports and supporting documentation for PUB events. The review board will conduct these evaluations blinded to treatment. There was agreement that it would be important that the review board agree with the criteria set forth for PUBs in the monitoring plan. MRL must provide operating procedures for the functions of the review board. The board must be completely informed of the guidance given to investigators in the protocols, procedure manuals, and investigator meetings regarding medical evaluations of patients having significant GI events. The consultants agreed that it would be impossible to mandate standard work-ups by investigators, but that guidelines are desirable. The operational procedures for the external review board will also be added to the Phase III GI Event Monitoring Plan.

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Phase III Monitoring of GI Clinical Events
September 28, 1996

Discussion of Innovative NSAID-Induced Symptom Study Design

MRL raised the topic of how NSAID-related symptoms could be better studied. Drs. Bombardier and Strom were in agreement that it should be possible to plan a study of NSAID symptoms using a series of "N of one" studies. Under such a plan, patients with prior NSAID-related GI side effects, and the NSAID with which they experience the problem, would be identified for study. The subjects would then be randomized to a series of treatments including acetaminophen, the NSAID causing trouble previously, another active non-selective NSAID, and a Merck selective COX-2 inhibitor. Patients would be treated for approximately 2 weeks on each medication with adequate washouts (drug dependent) between treatments. Data regarding GI symptoms and treatment preferences would be gathered. The statistical analysis would be based on comparisons of the COX-2 selective agent vs. each of the other treatments, on an individual basis. This trial design is called an "n of 1" study because one is randomly allocating the drugs within the individual as opposed to randomly allocating drugs within groups of people. This type of design is ideally suited to the study of drug side-effects. Dr. Bombardier noted that some trials have been published using similar designs. Dr. Strom said that it has been found that 20-30% of patients report consistent GI symptoms on a given NSAID. Dr. Silverman's suggestion that as a more conservative approach the paradigm could be piloted without Merck study drug followed by a definitive study was favorably received.

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DESIGN OF A GI OUTCOMES MEGA-TRIAL

Dr. Musliner opened the afternoon session for discussion of a GI outcomes mega-trial. The overheads are in Attachment 7.

Overall Design

A variety of design options were discussed. Drs. Strom and Bombardier strongly favored an observational type study, approximating a more "real world" situation, to demonstrate the effect of MK-0966 on clinically important outcomes (e.g., hospitalization for GI bleed). Dr. Strom was concerned that in the absence of such a study, Merck might be susceptible to criticism for not testing the drug as it will be used in an uncontrolled setting. Dr. Strom suggested a double-blind, MK-0966 versus comparator design, where patients are given study medication then questioned at the end of a year as to whether they were hospitalized. Although Prof. Langman noted that the rate of hospitalizations would be very low, Dr. Strom thought that it represented the most important outcome and if we could not differentiate MK-0966 from NSAIDs in terms of hospitalization for bleeding, then other distinctions made would be less important. Dr. Bombardier agreed in general but noted that the cost of working-up GI symptoms were very important in the overall outcome of OA and RA and suggested collecting data to this effect. While many agreed that this sort of study had certain attractions, it was highly unlikely that a study with very limited monitoring would be allowable since MK-0966 is not an approved drug. Dr. Spector agreed that we could not conduct this type of a study during this phase (IIIb) of development and stated that we needed to gain interim data, including clinically important data on PUBs, in a more controlled setting. While Dr. Strom argued that we would get the intermediate data from the endoscopy and Phase III trials, Dr. Spector reminded the attendees that this was not a *fait accompli* and the GI Outcomes Study would provide a safety net in the event that data were not definitive. Dr. Spector further commented that the purpose of the GI Outcomes Study was to obtain scientific and medical data to establish MK-0966 as much safer than NSAIDs. He noted that the health economic outcome data, would be secondary to the clinical safety data collected.

When the consultants were questioned whether a comparator design would best support the goals of the program, Prof. Langman replied that he would not be fully confident MK-0966 were safe [enough to eliminate the NSAID class warning] solely on the basis of a comparative trial. Dr. Nies reiterated that data from the Outcomes Study would be used in combination with the endoscopy and Phase III studies to distinguish MK-0966 from NSAIDs and support elimination of the class warning label. Prof. Langman agreed that if all data were favorable, the argument would be stronger.

Number/Type of Comparative Agents

Dr. Strom suggested that MK-0966 be compared against drugs perceived to be the safest (e.g., acetaminophen and ibuprofen). Prof. Langman noted that we could not state that MK-0966 is as safe as placebo if we do not have a comparison study to placebo. Noting the difficulties with such a design in an OA population, Prof. Langman was of the opinion that data showing superior safety against several comparators would be stronger

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than data versus only one comparative agent. The consultants favored an acetaminophen arm in the study as a method for obtaining surrogate background safety endpoint rates. It was agreed that although the dropout rate would be high, dropouts due to lack of efficacy would be an important endpoint. The use of rescue therapy such as tramadol and other local measures (e.g., exercise) were recommended to enhance retention. Acetaminophen use as rescue therapy in a study of this design, was not recommended because of the potential for toxicity (due to high doses) in the acetaminophen arm. Dr. Silverman and Mr. Khanna questioned the advisability of an acetaminophen arm, because the findings could highlight favorable properties of acetaminophen.

Mr. Khanna noted that in the U.S., naproxen, ibuprofen and diclofenac currently hold 50 % of the NSAID market share and estimated this to be a constant over the next several years. Internationally, diclofenac holds the largest market share. Everyone agreed not to include nabumetone since off-label doses may be required to reach equivalent efficacy and an extremely large trial might be needed. The consultants' preference was for a single NSAID comparator to be studied in parallel with acetaminophen. It was, however, concluded that ibuprofen (due to it's perceived favorable safety profile) and diclofenac (because of its common use internationally) could be included in the NSAID comparator arm. A definitive conclusion concerning the acetaminophen arm was not reached. Everyone agreed that the study should be double-blind and that switching of NSAIDs during the study should not be allowed.

When questioned about doses of the comparator agents, the consultants suggested that dose titration be considered in order to closer approximate real world OA treatment practices and guidelines. However, the majority of Merck attendees felt that MK-0966, 25 mg, should be compared to fixed, equi-potent doses of the comparator agents. Dr. Griffin argued that equally efficacious doses are not necessarily known. She also questioned whether it would be ethical if titration were not allowed, as this is considered standard of care. Placing patients on near maximal doses of drug would not be consistent with current treatment guidelines that recommend progressing from low to high doses of an NSAID on an as needed basis.

Duration

Prof. Langman questioned why the study was being considered with a one year duration. Drs. Spector and Nies replied that the duration was mainly to show long-term data for regulatory purposes. In addition, it was noted that in animal studies, very large doses of MK-0966 appeared to be safe at three months but induced intestinal ulcerations at six and 12 months, even at lower doses. The reasons for this effect over time are not completely understood.

The drop out rate for the one year study was estimated by the consultants to be 40-70% even with the "typical" Merck efforts for increasing patient retention. They noted that drop outs would mainly be due to lack of efficacy.

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Use of Antiulcer Agents

Everyone agreed that patients regularly taking antiulcer agents (e.g., misoprostol, H_2 blockers, proton pump inhibitors, etc.) at baseline should be excluded from the study. It was agreed that the use of such medications during the study could not be disallowed and the need for these agents should be considered a secondary endpoint. Prof. Langman cautioned that indiscriminate use, especially of over the counter antiulcer medications, would need to be minimized. There was also a question as to how patients who start on antiulcer medications for preventive measures (i.e., without cause) would be analyzed. Dr. Guess was concerned that use of such agents during the study could compromise the primary outcome (PUBs).

Intention-to-Treat (ITT) vs. Per-Protocol Analysis

Whether patients should be followed in the study after discontinuing therapy was discussed (ITT approach). Dr. Griffin was a proponent for this approach stating that a per-protocol analysis (only analyzing data on patients while they are in the study on treatment) would be biased due to the likely high dropout rate and potential for an endpoint to occur shortly after discontinuation of treatment. Dr. Spector suggested following patients for four weeks after discontinuing therapy. Dr. Guess noted that regulatory agencies prefer an ITT approach. A final consensus was not reached.

Endpoint Definition

There was discussion as how the endpoint definition might be broadened. Dr. Spector suggested inclusion of hematocrit decreases of six percentage points or more as an endpoint as this could be considered a clinically important change. Prof. Langman was concerned that this would dilute the PUB endpoints as the event rate for hematocrit decreases would be far greater than that for PUBs. Dr. Strom was concerned that depending on the timing for monitoring blood counts in relation to observation of the cause for the decrease (e.g., a patient may have a decreased hematocrit due to a bleeding ulcer but the lesion may no longer be apparent by the time the lab result is obtained).

Dr. Musliner raised the possibility of endoscoping patients who discontinue therapy for GI symptoms as a method for increasing detection of symptomatic ulcers. The consultants were not in favor of required endoscopies stating that in practice, symptomatic patients are first instructed to discontinue therapy to see if symptoms disappear before other invasive tests are considered. In addition, enrollment might be hindered if patients had to consent to endoscopy once they experienced GI symptoms that required therapy discontinuation.

As a compromise, the consultants agreed that decreases in hematocrit would be a better endpoint than required endoscopy findings. It was reasoned that a decrease of six percentage points from baseline or previous visit, confirmed by repeat analysis, could be considered a presumed bleed after obvious non-GI causes were ruled out (e.g., trauma, blood donation, other anemias, etc.). It was recommended that the same definitions and criteria should be used in the Phase III pooled monitoring of GI clinical events.

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Additional Outcomes Measures

The extent of capturing efficacy data was discussed. Dr. Griffin felt that efficacy data needed to be collected as there was not an agreement as to what fixed dose is considered efficacious. Some Merck attendees argued to minimize efficacy measurements since the trial would not be appropriately designed to study efficacy rigorously and would have the risk of not being able to demonstrate clear superiority to acetaminophen. Dr. Gruer suggested that collection of minimal efficacy data may be inconclusive and either no efficacy data be collected or more rigorous measures be employed.

Closing

Dr. Watson thanked the consultants and all participants for their informed contributions to the discussion.

Post-Meeting

An Executive Summary of the meeting (Attachment 8) was distributed to all invitees on October 16, 1996. A written transcript of the meeting will be distributed by the Epidemiology department.

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 2

MERCK
Research Laboratories

MEMORANDUM

DATE:	November 4, 1996	
TO:	See Distribution List	
FROM:	Suzanne Pryor-Tillotson	RY 32-561
	Tom Musliner	RY 32-557

SUBJECT: Minutes for the MK-0966 Consultants' Meeting to Discuss the Design of the GI Clinical Outcomes Megatrial

EXECUTIVE SUMMARY

Areas covered included general study design, patient population, endpoint definition, approach to use of antiulcer medications, use of low dose ASA, efficacy measurements, anticipated dropout rates and the broad approach to data analysis.

The consultants generally agreed that a positive megatrial using an NSAID comparator design, in conjunction with Phase III/endoscopy studies, could adequately support the distinction of MK-966 from NSAIDs. They accepted that there would be no placebo or acetaminophen control arm(s). They were not in favor of a washout period.

There was a consensus than the patient population be weighted towards the elderly (due to their higher risk for significant GI events) and that the population should consist of patients with OA of the knee or hip anticipated to require chronic NSAID therapy for at least one year. The consultants recommended avoiding a stringent OA diagnosis definition, to favor easier recruitment as well as generalizability of the data. They felt that patients with histories of documented symptomatic peptic ulcer disease or upper GI bleeds could be included in the study, at the investigators' discretion, if their disease was inactive for a specified period of time (yet to be determined). It was agreed that enrollment be stratified by history of prior peptic ulcer or bleed, to insure equal distribution of these higher risk patients between treatment groups.

The consultants did not contest our choice of ibuprofen and diclofenac as comparators when the rationale was explained. Some recommended that we start patients on lower doses of comparator NSAID and allow titration and switching of agents, to be more consistent with published guidelines for OA treatment, as well as to enhance patient retention. MRL representatives explained that these options were not feasible for logistical reasons and the potential for bias against MK-966 if doses of comparator NSAIDs are not equi-potent to MK-966. Several consultants still felt that options for switching comparators should be considered to enhance retention.

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The consultants generally agreed with an approach of increasing detection of PUB endpoints by recommending work-up (i.e. endoscopy) for patients with symptoms strongly suggestive of ulcers, even though this might dilute the numbers of more serious PUBs. They felt that decreases in hemoglobin should not be included in the primary endpoint, although they may be used as a possible trigger for further evaluation. They advised that lower GI bleeding not be included in the primary endpoint, but should be evaluated in an exploratory fashion. Routine stool hemoccult testing was not recommended. It was recommended that serum samples from baseline be archived for subsequent use in patients with PUBs for testing of *H. pylori* status. If deemed appropriate, serology could be performed on archived samples for all patients at some point during or after the study.

A tentative consensus was reached to disallow the use of low dose aspirin so as not to compromise the primary endpoint. However, further internal discussion of the risk of observing greater proportions of cardiovascular events in the MK-966 group (due to absence of an antiplatelet effect) with this approach requires further assessment and internal discussion.

The consultants agreed that regular use of antiulcer agents at baseline should be prohibited, although this may exclude some higher risk patients. Antiulcer medication use during the study was considered acceptable as a secondary endpoint, provided investigators are given guidelines for their use and for appropriate work-up (e.g. endoscopy) in patients with high risk clinical findings.

All consultants expressed concern over the likely high dropout rate in a one year study. Use of rescue medication beyond acetaminophen, such as tramadol or Tylenol #3, was considered reasonable for enhancing patient retention. Use of intraarticular steroids and other local treatments should also be allowed as rescue therapy. In addition to scheduled visits, frequent patient contact by phone was recommended as a tool for increasing retention. The consultants warned that despite such efforts dropout rates in a one year trial can be expected to be 40-50%.

The consultants felt that collection of some efficacy data would be necessary in order to properly interpret the safety data. At a minimum a global measure and a quality of life assessment should be used, in addition to assessment of discontinuations due to lack of efficacy.

There was a consensus that the primary analysis should be based on a "modified" intention-to-treat approach -- that is, analyzing PUBs occurring in all patients during the time they remained on blinded therapy plus a specified period (e.g. 2 or 4 weeks). A secondary analysis would be a true intention-to-treat approach, including all events occuring during the time between start of study drug and the scheduled study discontinuation for each patient who enters the study. It was recommended that all patients who discontinue blinded therapy be followed for the remainder of the one year duration, applying the same follow-up procedures as for patients remaining on blinded therapy.

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MK-0966 GI Clinical Outcomes Megatrial-- 10/24/96 Consultants Meeting

MEETING MINUTES

The meeting was conducted at the Newark, NJ Airport Marriott on October 24, 1996 and was attended by five consultants and Merck personnel representing Clinical, Regulatory and Biostatistics (see Attachment 1 for list of attendees). Comments are documented by category and are not necessarily representative of the order of discussion throughout the day.

COX-2 Clinical Program Overview

The session opened with a COX-2 clinical program overview presented by Dr. Daniels. Concerning the one week endoscopy study, Dr. Bjarnason questioned whether patients were free of lesions at baseline to which he received an affirmative response. To emphasize the favorable safety profile of MK-966, Dr. Spector reminded the attendees that the dose of MK-966 used in the endoscopy study was 10-20 times the intended clinical dose of 25 mg and stressed that if this multiple of a standard NSAID dose were used, patients would have suffered severe adverse consequences. Dr. Brandt questioned whether we had six month efficacy data on MK-966 and was told that such data was not yet available. He also asked whether we had information on the analgesic and anti-inflammatory doses of MK-966 and was told the formal dose ranging studies are ongoing.

The remainder of the meeting focused on plans for a GI Clinical Outcomes Megatrial. Dr. Musliner presented the purpose of the study and reviewed prior relevant NSAID megatrial studies, potential designs for this trial, and several tentative design conclusions based on earlier internal discussions and input from a previous consultants meetings.

The consultants had several comments concerning other megatrials. Dr. Brandt noted that the misoprostol study did not demonstrate comparable efficacy of NSAID therapies. Dr. Hawkey noted that the meloxicam PUB rates are based on ~1 month data and may reflect a carry-over effect from previous NSAIDs as there was no washout period. He also suggested that the PUB rates in the nabumetone study may be more apparent than real.

Following his presentation, Dr. Musliner asked the consultants for comments on several pre-meeting conclusions, to which responses follow. Only a few issues were accepted without question or discussion, further highlighting a wide variety of opinion for this megatrial and its' multitude of complexities. Everyone agreed that the study should be double-blinded and there would be no attempt to compensate for potential compliance bias associated with the use of a once a day drug (MK-966) versus comparators that will be dosed three times a day. Dr. Silverman noted that the extended duration of at least one year was intended to satisfy regulatory concerns that MK-966 may be shifting the time frame in which PUBs occur, rather than minimizing their occurrence. It was also accepted that nabumetone and meloxicam would not be comparative agents. Dr. Bjarnason commented that he felt meloxicam was not better than piroxicam (therefore not in the same category as a potentially "safer" drug like nabumetone).

General study design

Commenting on the overall design concept, the consultants generally agreed that a comparative design megatrial, in conjunction with Phase III and endoscopy studies, would adequately support the case for distinguishing MK-966 from NSAIDs. Dr. Sandler commented that he felt the

overall structure was fine but some of the details were troublesome. Dr. Hawkey noted that the argument for demonstrating a superior safety profile of MK-966 compared to NSAIDs would be quite convincing if we could show a significantly decreased relative risk compared to ibuprofen (which is generally perceived as safe). Dr. Musliner noted that we may not have enough power show significance versus ibuprofen alone but would be powered to show differences versus the combined ibuprofen and diclofenac arms.

With regard to a potential study design that would incorporate an acetaminophen arm, Dr. Brandt commented that it may be incorrect to assume that acetaminophen would not be as efficacious as NSAIDs since long term data do not exist. Dr. Musliner stated that published data on 2600 mg acetaminophen over a shorter period, showed high dropout rates for lack of efficacy. Dr. Hawkey questioned why we had abandoned the design incorporating an acetaminophen arm. Dr. Musliner explained that in part, data suggesting there would be high drop out rate with acetaminophen (particularly for a one year study) and the very large patient sample sizes that would be required to demonstrate "equivalency" led to the pre-meeting decision that a study with an acetaminophen arm would not be feasible.

Dr. Musliner asked the consultants whether a washout period prior to study start would be advisable. Although the consultants acknowledged that there exists potential for a carry-over effect from the previous NSAID, they agreed that there should be no washout due to the difficulties of keeping patients off drug for any length of time. Dr. Spector suggested a two week washout using acetaminophen, but this was not considered feasible by Dr. Hawkey and others who commented that patients would not be willing to abandon medication for even two weeks. Dr. Bjarnason agreed and also stated that two weeks was not long enough for silent ulcers to heal. Dr. Schnitzer suggested a separate analysis of the data with and without the first few weeks of the study to address potential carry-over effect. This was generally rejected because of the lack of published data on the period of time NSAIDs may exhibit a carry over effect for PUBs. Additionally, there was concern that this approach may exclude legitimate events in those patients randomized to the NSAID group, particularly first-time users likely to be at increased early risk. Although the consultants were not in favor of a washout period, further internal discussion may be necessary.

Patient population

Dr. Sandler questioned why the population was limited to OA when in practice, those with other pain syndromes would also be candidates for COX-2. Dr. Silverman explained that the population needs to be limited for purposes of regulatory registration and labeling. That being the case, Dr. Hawkey suggested that the definition of OA should be broad (e.g. should not require radiologic evidence of OA) in order to increase the generalizability of the data and allow for easier recruitment. He referenced a study, conducted in Nottingham, that found 25% of regular NSAID users to have definite OA based on radiologic criteria, while 30-40% had OA-like pain or other chronic pain syndromes. Dr. Schnitzer agreed that the OA population should be primarily defined by the need to be on an NSAID for at least one year. He agreed with Dr. Musliner to exclude back pain as a criterion for OA. Dr. Brandt preferred limiting OA to one joint but was reminded by Dr. Spector that the focus of the study was safety and not efficacy. It was agreed that the population would consist of patients with OA of the knee or hip, who require chronic

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NSAID therapy for at least one year. Further discussion concerning the definition of OA will be required.

NSAID comparators (formulation(s), dose, titration)

Dr. Musliner asked the consultants to comment on our choice of ibuprofen and diclofenac as comparative agents given the study would be powered to detect a 50% reduction in PUBs for the combined NSAID group. He noted that ibuprofen was chosen because of its wide usage and perceived favorable GI safety profile and diclofenac because of its common use and "reference status internationally. He also asked whether the consultants agreed with our decision to use fixed doses of MK-966 and comparator agents and prohibit switching of therapy during the study.

Drs. Schnitzer and Bjarnason felt that the formulation of NSAID used was not as problematic as the fact there would only be two choices and switching would not be allowed. The consultants expressed concern that if the study were to rigid and did not allow switching of NSAIDs or titration of doses as is common in clinical practice, it would be very difficult to keep patients in a one year study. Dr. Schnitzer stressed that the design of the study should be kept as flexible and simple as possible and therefore switching of NSAIDs and dose titration should be allowed. Dr. Musliner commented that this had been discussed at length internally and was not adopted for two main reasons. The first is due to the logistical difficulties associated with allowing switching of medications in a double-blind study. The second is the potential for bias that may result from comparing a fixed dose MK-966 to an NSAID whose dose may be limited by side effects unrelated to efficacy. He added that we would enhance patient retention by allowing liberal use of rescue medication. Dr. Brandt noted that we should also consider non-pharmacologic modalities.

Dr. Brandt expressed general concern that the doses chosen for comparative NSAIDs, specifically ibuprofen (800 mg t.i.d.) and diclofenac (50 mg t.i.d.), were too high. He stated that information from a survey he conducted, found the average dose of ibuprofen prescribed by physicians was ~1800 mg per day. Regardless of the approved doses in the label, Dr. Brandt indicated that use of lower doses was consistent with the American College of Rheumatology recommendations and is currently the philosophy of many practicing physicians. Dr. Nies acknowledged that there is change in progress with the approach to medicating patients but indicated that our dose selections were based on the scientific need to compare equi-potent doses of NSAID to MK-966. Dr. Brandt continued to express his concern that by the time the study is over, we may end up with data on comparative agents at doses that are no longer used and not relevant to general practice. Dr. Simon questioned whether patients would receive maximal benefit from a lower analgesic dose rather than a higher anti-inflammatory dose of NSAIDs. Dr. Brandt indicated that clearly some patients needed higher doses of NSAID to achieve optimal efficacy. Dr. Spector offered that the intention of the COX-2 program is to show that, in terms of safety in the GI tract, COX-2 is like placebo or acetaminophen. He noted that the movement to use lower doses of NSAIDs in clinical practice may be due to an increased awareness of NSAID gastropathy and suggested that if the GI safety profile of a drug was clean, the medical community would be more likely to use higher doses to achieve better efficacy. He added that in his experience, higher doses of NSAIDs offered better efficacy but could not be tolerated due to

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adverse GI and renal effects. Dr. Brandt took exception and noted that efficacy in OA is not necessarily dose dependent.

Dr. Schnitzer accepted the need to fix doses and not allow titration as necessary to meet regulatory and labeling needs but indicated that this design may not be a reflection of general practice where patients tend to take intermittent doses of medication. He acknowledged that the megatrial would not be able to address these real world issues which he suggested may best be suited for a Phase IV study. Dr. Brandt continued to insist that he would prefer to see a study with lower doses of comparative agents since GI toxicity is dose-related. He also added that in practice, lower doses of NSAIDs are used for other reasons, not just for safety concerns (e.g. efficacy not different at lower dose, HMO restricted formularies, price, etc.). Dr. Brandt further commented that prescribing practices of physicians do not necessarily match their intentions for treatment (i.e. prescribed dose is not related to whether the physician is trying to achieve an analgesic or anti-inflammatory dose). Dr. Schnitzer stated that OA is not a stable disease and some patients appear to do better with higher doses. Since it is not known which patients will do better with higher doses, there is a clinical perception that higher doses of NSAIDs are more efficacious. Dr. Schnitzer added that if GI safety was demonstrated with a drug, dose would not be an issue.

Exclusion criteria/concomitant medications

In general, the consultants agreed that patients with histories of documented symptomatic peptic ulcer disease (PUD) or upper GI bleeds can be included in the study if their disease has been inactive for a specified period of time. Dr. Bjarnason suggested patients should not have had an ulcer within two years or a GI bleed within five years of study start. He would be reluctant to allow into the study, patients with a history of bleeding and perforation. Due to the restriction on antiulcer medications at baseline, it was felt that some of the high risk patients would naturally be excluded because their physicians would not allow them to be on NSAIDs without a protective agent. Although the decision to enter a patient will be based on investigator judgment, Dr. Hawkey suggested that a specified period of time for a patient to be without PUD be defined in the protocol. Definition of this time period will require further discussion internally. It was agreed that enrollment be stratified by history of PUD to insure equal distribution between treatment groups.

Dr. Musliner asked the consultants whether they thought it was reasonable to set the minimum age of the study at 65 to enhance the likelihood of PUB events. Dr. Brandt suggested the minimum age should be set at 45 and Dr. Hawkey preferred 55 since few patients below this age have OA. Dr. Spector suggested a forced distribution such that one-quarter of the patients would be between 55 and 65 and three-quarters of the patients would be older than 65. Dr. Hawkey felt this may naturally happen and was not in favor of forced distribution. A tentative consensus was reached that the minimum age will be set at 55 and there may be a requirement for a certain percentage of patients to be greater than 65 years old.

There was discussion as to whether *Helicobacter pylori* status should be determined in patients at study start. It was also questioned whether *H. pylori* should be eradicated before allowing patients to enter the study. Dr. Bjarnason noted that certain guidelines suggest treating *H. pylori*

in patients with a history of GI bleed who are on NSAIDs. Dr. Hawkey disagreed and felt that *H. pylori* positive patients do not require intervention for eradication just because they are on NSAIDs. He noted that NSAIDs cause ulcers regardless of *H. pylori* status. It was agreed that serum samples from baseline would be archived. All patients who have an endpoint will be tested for *H. pylori* status at the time of the event and positive results will be confirmed by a second measure such as a C13 breath test. Serology could be performed on archive samples for everyone at some point during or after the study.

Dr. Musliner asked the consultants to comment on whether low dose (enteric coated) aspirin used for cardiovascular effects, intraarticular corticosteroids and anticoagulants should be allowed during the study. Concerning low dose aspirin, Dr. Musliner expressed concerns that if regular aspirin users were excluded from the study, many potential participants may be lost as aspirin is widely used, especially in the older population we are targeting. Additionally, he expressed concerns that if low dose aspirin use is not allowed, there will be a risk of showing larger numbers of cardiovascular events in the MK-966 group relative to the NSAID comparator group, since MK-966 does not have an antiplatelet effect while dual COX inhibitors do.

Dr. Brandt referenced a study he recently completed in Indiana with 465 patients over the age of 65. He found that 25% of those patients were regular aspirin users, presumably for cardiovascular protection. He felt that low dose aspirin should be allowed and stated that if this were an exclusion, patient recruitment would be significantly hindered. Dr. Sandler agreed. Drs. Hawkey and Schnitzer felt aspirin should not be allowed in the study as there is no dose low enough that is not associated with increased risk for the primary endpoints in the megatrial. They felt we would have to accept that recruitment may be more difficult. Dr. Brandt questioned whether exclusion of aspirin in all the studies would end up as a restriction in the label. Dr. Nies responded by commenting that in smaller studies, we intend to evaluate whether MK-966 alters the effect of aspirin on platelets, and in at least one larger trial, patients will be allowed to take low dose aspirin to gain experience on adverse events in patients on MK-966 and aspirin. A tentative consensus was reached to exclude aspirin use from the study so as not to compromise the primary endpoint. However, further internal discussion of the risks of this approach will be necessary.

Everyone agreed that intraarticular steroids and topical capsaicin cream should be allowed as rescue therapy during the study (particularly since pain will not be an efficacy measurement) and anticoagulants should not be allowed at entry or during the study.

Use of antiulcer medications

Dr. Musliner proposed that patients who require antiulcer drugs (e.g. H2 antagonists, proton pump inhibitors, sucralfate, etc.) on a regular basis within one month of screening, would be excluded from the study . Use of antacid medications at baseline and during the study, would be allowed. Everyone agreed that regular use of antiulcer agents at baseline (other than antacids) should be prohibited and acknowledged that this restriction would therefore exclude presumably higher risk patients from the study population (hence lowering the anticipated rates for PUBs). Dr. Musliner proposed that prescribed use of such drugs during the study should be allowed and captured as a secondary endpoint. Dr. Hawkey suggested that use of antiulcer medications during the study only be allowed in conjunction with appropriate work-up (e.g. endoscopy). Dr. Schnitzer agreed and felt that this requirement would not hinder recruitment since most patients

would accept the need for a work-up if they were experiencing significant GI symptoms; perhaps 20% of patients would refuse endoscopy. There was a consensus that guidelines be provided to investigators for triggering endoscopic work-up and that this should be limited to high risk settings (e.g. patients with persistent and/or dosing-related dyspepsia; cases of substantial and verified decreases in hemoglobin, etc.). However, Dr. Schnitzer cautioned that an aggressive approach to ulcer detection will inevitably lead to higher rates for both MK-966 and NSAID comparators. Given the absence of a placebo or acetaminophen control, he expressed concern as to how the higher rates would be perceived for a drug that is purported to have a very good GI safety profile.

Dr. Sandler noted that symptomatic patients who are not found to have an ulcer by endoscopy, may still use antiulcer medications for symptoms. Dr. Bjarnason agreed that H2 blockers are freely used in the ~30 % of NSAID users who experience dyspepsia. It was acknowledged that there would be increased "noise" associated with this approach, but it was generally accepted that the advantages of increasing detection rates of symptomatic peptic ulcers would outweigh the disadvantages, due to the increase in study power that would result. It was also generally agreed that the need for an endoscopy would be left to the clinical judgment of the investigator when there is suspicion of an ulcer, although guideline recommendations would be provided. Dr. Hawkey particularly recommended limiting the indiscriminate use of H2 blockers, as data exist that suggest suppression of the rate of NSAID associated complications and potential ulcer healing effects with these medications.

Patient Retention

All consultants expressed concern over the likely high dropout rate in a one year study. Dr. Schnitzer estimated that only 40-50% of patients would complete the one year study. Dr. Sandler suggested that we seek to recruit patients who have been stable on NSAIDs for a long period of time and perhaps this would decrease the dropout rate. Dr. Spector questioned whether we could decrease the dropout rate by conducting part of the study in Europe and part in the U.S. at large centers of excellence. Dr. Hawkey felt that this type of study would be easier to do in Europe since there is more control over the primary physician prescribers, less independent medical practice, and patients tend to comply with their physician's recommendation more than their U.S. counterparts. Dr. Schnitzer is of the opinion that only a portion of the total study population could be recruited in the U.S. He noted that there are only 40-50 centers in the U.S. that would be able to recruit more than a hundred patients each. He agreed that at least half the study should be conducted in places like England and Scandinavia.

Dr. Hawkey felt it was reasonable to conduct study visits every three months (and perhaps at one month after study start) but recommended that patients be contacted by telephone at least monthly to keep them interested in the study and enhance patient retention and compliance.

Use of rescue medication beyond acetaminophen, such as tramadol or Tylenol #3, was considered a reasonable method for further enhancing patient retention. Dr. Musliner suggested a uniform approach to use of rescue (e.g. start with acetaminophen, followed by tramadol, etc.) since its use may affect the efficacy measurements.. He further suggested that rescue medication could be distributed to the patient at the beginning of the study so they feel they have more control over their OA pain control. Dr. Schnitzer felt these agents would help for acute

exacerbations but could not be used chronically and estimated that use of rescue medications would increase the retention rate 5-10%. Dr. Schnitzer thought that a standardization of rescue medication would not be necessary and would only further complicate the protocol. He strongly suggested that the protocol be as simple as possible to insure consistency between sites and to help keep patients in the study.

Dr. Brandt warned that despite best efforts to keep patients interested and to allow flexibility in the protocol, we should not underestimate the difficulties in keeping OA patients on one drug for a year.

Dr. Hawkey stated that in addition to the efficacy data from Phase III studies, it would be important to measure efficacy in this study to enable assessment of toxicity/safety in relation to efficacy. He suggested this be done in only a subgroup of the population using global scores and quality of life questionnaires. He further commented that this could be a simple assessment in ~5% of the population at baseline and one other timepoint. Dr. Schnitzer agreed and noted that the best measurement of efficacy may be whether a patient remains on drug for one year (e.g. a completer analysis). Dr. Brandt felt efficacy measures need to be more comprehensive including an x-ray assessment and pain outcome measure. He believes that these assessments represent the core measurements recommended in the current guidelines for clinical trials in OA. Dr. Friedman cautioned that the efficacy measures should not be too stringent considering the proposal to broaden the definition of OA. Dr. Musliner noted that x-rays and pain assessment are being collected in the other studies and therefore may not be necessary in this megatrial. Given that no therapy will completely treat OA, Dr. Ehrich expressed concern that efficacy measurements may be confounded due to use of rescue medications and high drop-out rates. Further discussion will be required to determine what efficacy data will be collected.

Endpoint definition

Dr. Hawkey felt strongly the we should actively seek out endpoints. As discussed previously, he suggested performing endoscopies on all patients who require treatment with full-dose antiulcer medications during the study (prior to their prescribed use), as a method for increasing detection of symptomatic ulcers.

Dr. Musliner asked the consultants if they felt it was reasonable to include significant decreases in hematocrit (e.g. six percentage points) in the primary endpoint definition or (preferably) as a secondary endpoint. All consultants agreed that this should not be a primary endpoint. Dr. Bjarnason was strongly against including hematocrit decreases as an endpoint since he felt such measurements in general are not obtained in clinical practice, are variable, and do not necessarily represent a serious outcome of the magnitude of a PUB. Dr. Hawkey felt that significant hematocrit decreases should be included as secondary endpoints since there is evidence that NSAIDs cause lower GI bleeding. While Dr. Bjarnason agreed that NSAIDs effect the lower GI tract, he argued that hematocrit measurements are a poor tool for studying this effect.

Drs. Brandt and Bjarnason further suggested that the primary endpoint should include only GI bleeds and perforations as these are the more serious and meaningful outcomes which would be diluted if symptomatic ulcers were included. Dr. Spector felt that it would be important to include symptomatic ulcers in the endpoint definition as they represent a significant event which

may lead to more serious sequelae (i.e. bleeding and/or perforation) and practically, the study size would be unreasonable if symptomatic ulcers were excluded from the endpoint definition.

Dr. Schnitzer felt that the endpoint definitions were reasonable and practical. He suggested if a patient presents with a clinical picture suspicious for an ulcer (including substantial drops in hematocrit, confirmed by repeat measurement), then further evaluation (i.e. endoscopy) would be warranted. If an ulcer is found on further evaluation, it should be included as a primary endpoint. Dr. Hawkey commented that he felt uneasy including heme positive stools as a trigger for further evaluation because of the potential for lower GI source. Dr. Musliner noted that another aspect of this aggressive approach is the potential that between-group differences in these events could persuade a safety committee to recommend stopping the trial prematurely (i.e. before sufficient data are available to present a convincing result for more severe PUBs).

As NSAIDs have been associated with the development of lower GI lesions and, to a poorly defined extent, increased risk for lower GI bleeding, Dr. Musliner questioned whether data on lower GI bleeds should be captured in addition to PUBs and if they should be included as a secondary endpoint. Dr. Hawkey thought it would be interesting to capture data on lower GI bleeding but not necessarily as an endpoint. He agreed with Dr. Musliner that patients found to have lower GI bleeding would be allowed to continue in the study on blinded therapy if considered acceptable by the investigator. Decreases in hemoglobin may be helpful in screening for lower GI bleeding although Dr. Hawkey commented that frank rectal bleeding can occur without a significant drop in hemoglobin.

Consensus was reached that significant clinical events suggestive of an ulcer should trigger further work-up (specific guideline yet to be decided). Lower GI bleeding will not be included as a primary endpoint but will be evaluated in an exploratory fashion. Stool hemoccult testing will not be performed routinely (except at baseline) and if performed during the trial at the investigator's initiative will not alone mandate upper GI evaluation.

Data Analysis

Two approaches for analyzing primary endpoint data were discussed. Dr. Capizzi pointed out that both approaches should be considered intention-to-treat. Dr. Oppenheimer suggested the primary analysis be based on a "modified" intention-to-treat approach, analyzing all patients during the time they remained on blinded therapy plus a specified period of time (e.g. 2-4 weeks) following discontinuation of therapy. A secondary analysis would be a true intention-to-treat approach, including all events occuring during the time between start of study drug and the scheduled study discontinuation for each patient who enters the study. The consultants and Merck attendees agreed with this approach.

There was a consensus that all patients who discontinue blinded therapy should be followed in the study for the remainder of the one year duration, applying the same follow-up procedures as for patients who remain on blinded therapy (e.g. same frequency and intensity). Dr. Silverman agreed and was of the opinion that regulators may want to know what happens to patients who discontinue therapy before reaching an endpoint. It was questioned whether patients would be followed in the study after reaching a primary endpoint since in the analysis, only the first event would be captured. Further discussion is required to define how patients who achieve a primary endpoint will or will not be followed in the study.

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There was discussion concerning the confounding factors associated with this secondary (intention-to-treat) analysis. Of concern was the high likelihood that patients who discontinue blinded therapy would start on a variety of more or less GI toxic NSAIDs as well as other concomitant medication making the subsequent interpretation of any endpoint reached during that time difficult to interpret. Dr. Spector and others suggested defining clear rules in the protocol for what happens to a patient who discontinues blinded therapy. These rules may outline a standard drug regimen based on the reasons a patient discontinued study therapy. For example, if a patient discontinued due to lack of efficacy, they may be switched to naproxen for a period of time before another defined drug if the OA was not controlled. This would be one approach for attempting to control some of the confounding factors associated with a true intention-to-treat analysis in this study. This area will require further internal consideration.

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 3

MERCK
Research Laboratories

MEMORANDUM

DATE: November 21, 1996

TO: B. Friedman, A. Nies, R. Spector

CC B. Gertz, J. Bolognese, B. Daniels, E. Ehrich, H. Guess, D. Khanna, J. McIntyre, B. Morrison, R. Silverman, S. Simpson, T. Simon, D. Watson

FROM: T. Musliner

SUBJECT: **Anticipated consequences of NSAID antiplatelet effects on cardiovascular events and effects of excluding low-dose aspirin use in the Cox-2 GI Outcomes Megatrial**

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1. Background -- prophylactic use of low-dose aspirin and risk of cardiovascular events

The largest clinical trial testing aspirin for cardiovascular (CV) primary prevention was the U.S. Physician's Health Study, in which 22,071 men 40 to 84 years of age were randomized to 325 mg aspirin q.o.d. vs. placebo[1]. The aspirin arm was terminated prematurely after ~5 years of follow-up, upon recommendation of the Data Monitoring Board. There was a 44% reduction in the risk of first myocardial infarction (MI) (RR=0.56, 95% CI 0.45-0.70; p<0.00001). A slightly increased risk of stroke in the aspirin group did not achieve statistical significance, although for hemorrhagic stroke alone the RR was 2.14 (95% CI 0.96-4.77, p=0.06). There was no significant difference in total CV mortality (RR=0.96, 95% CI 0.60-1.54; p=0.87). A reduction in risk for fatal MI (10 vs. 28, RR=0.31, 95% CI 0.14-0.68, p=0.004) was balanced by trends toward increased risk of sudden death (22 vs. 12, RR=1.96, 95% CI 0.91-4.22, p=0.09), stroke and other CV death. Fifty nine percent of the participants were ≥50 years of age at baseline and reduction in risk for MI in association with aspirin use was only apparent in patients above this age cut-off (p value in trend in RR with increasing age = 0.02; RR for participants <50 was 1.12).

The only other large randomized trial of aspirin in primary prevention of CV disease was the 6-year British Doctor's Trial in 5139 men 50 to 79 years of age[2]. The dose of aspirin was 500 mg/day. No significant reductions in total mortality, MIs or strokes were observed, however, the confidence intervals were wide. There was a trend towards greater numbers of disabling strokes in the aspirin-treated patients. There were significantly fewer TIAs in the aspirin-treated group. A meta-analysis of the U.S. and British studies[3] concluded that a 33% reduction in the risk of a first nonfatal MI (p<0.0002) could be anticipated with low-dose aspirin prophylaxis. The role of aspirin in primary prevention of stroke and death from vascular causes was considered inconclusive. There are no good clinical trial data on the use of still lower doses of aspirin for primary prevention, which might have a more favorable risk-

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benefit ratio. A randomized trial of lower dose aspirin within the Women's Health Study is ongoing.[4]

A number of studies have evaluated use of aspirin and other antiplatelet agents for secondary prevention in patients with a history of MI, stroke, transient ischemic attacks (TIAs) or unstable angina. A summary report of a meta-analysis of such trials was published in 1988 by the Antiplatelet Trialists' Collaboration group[5]. Twenty five randomized trials were included in the meta-analysis, involving ~29,000 patients treated and followed for ≥1 year, 3,000 of whom had died. Overall, there was a 15% odds reduction in vascular mortality, a 30% reduction in risk for non-fatal vascular events (stroke or MI) and a 25% reduction (SD 3%, $p<0.0001$) in risk for combined fatal and non-fatal CV events. Risk reductions associated with different types of antiplatelet therapy (e.g., 900-1,500 mg/day aspirin, 300-325 mg/day aspirin, sulphinpyrazone, aspirin + dipyridamole) were similar in magnitude. There were no significant differences in efficacy in patients with histories of cerebral vs. cardiac disease. Reductions in risk for non-fatal strokes and MIs were comparable in magnitude. No apparent effect was observed on non-CV mortality, with a slight tendency toward fewer non-CV deaths among patients receiving active antiplatelet therapy.

A subsequent overview of 145 randomized trials of "prolonged" antiplatelet therapy vs. control and 29 randomized comparisons between different antiplatelet regimens was published by the Antiplatelet Trialists' Collaboration group in 1994[6]. The analyzed trials included ~70,000 "high risk" patients (secondary prevention) and ~30,000 "low risk" patients (primary prevention); the comparison trials of different antiplatelet regimens involved ~10,000 high risk patients. Average duration of therapy was ~2 years. Highly significant reductions in CV events of approximately 25% were observed in the following four categories of patients: (a) acute MI (~20,000 patients), (b) prior history of MI (~20,000 patients), (c) prior history of stroke or TIA (~10,000 patients), and (d) other relevant history predisposing to CV events (unstable angina, stable angina, vascular surgery, angioplasty, atrial fibrillation, valvular disease, peripheral vascular disease, etc.). The observed reductions were separately statistically significant for subgroups of middle age and old age, men and women, hypertensive and normotensive patients, and diabetics and non-diabetics. For high risk patients taken together, there were reductions of approximately one third in non-fatal MI, one third in non-fatal stroke, and one sixth in CV death. As in the earlier meta-analysis, there was no suggestion of increase in non-CV deaths. Medium dose aspirin (75-325 mg/day) was the most widely tested and there was no evidence that higher dose regimens were more effective. Among the low risk primary prevention population, there was also a significant one third reduction in non-fatal MI, however, there was no demonstrable benefit in terms of vascular mortality and a non-significant increase in stroke accompanied the benefit. The absolute reduction in CV events was small in the primary prevention population (<1 per 1000 patients per year). In contrast, much larger absolute benefits have been demonstrated for patients at high or intermediate risk for vascular events. Low-dose aspirin is now considered standard therapy in such settings in the absence of contraindications to its use. The Antiplatelet Trialists' Collaboration has also published compelling analyses demonstrating benefit of aspirin therapy in patients at risk for vascular occlusion[7] and in patients in whom thromboprophylaxis is indicated[8].

2. Estimates of GI complications attributable to chronic therapy with low-dose aspirin

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It is well established that anti-inflammatory doses of aspirin are associated with an increased risk of PUBs that is as great or greater than that associated with standard NSAIDs. The GI toxicity of low-dose aspirin, however, is somewhat less well defined. In the Physicians Health Study, the incidence of GI discomfort was 26.1 vs. 25.6% in the aspirin vs. placebo groups, a nonsignificant excess (p=0.45). For all GI symptoms except ulcer, the figures were 34.8 vs. 34.2% respectively, again not significant. There were 169 participants with peptic ulcer in the aspirin group vs. 138 in the placebo group (RR=1.22, 95% CI 0.98-1.53, p=0.08). Among these ulcer patients, there were 38 vs. 22, respectively, with some degree of associated hemorrhage (RR=1.77, 95% CI 1.07-2.94, p=0.04). For a broad spectrum of terms related to bleeding (including easy bruising, hematemesis, melena, non-specific GI bleeding, epistaxis, other bleeding) there were 2979 in the aspirin group and 2248 in the placebo group (RR=1.32, 95% CI 1.25-1.40, p<0.00001). For transfusion, there were 48 in the aspirin group and 28 in the placebo group (RR=1.71, 95% CI 1.09-2.69, p=0.02). One death from GI hemorrhage was reported, occurring in a patient allocated to aspirin.

Stalnikowiccz-Darvasi (1994) published an overview of the risk of GI bleeding with low-dose (<325 mg/day) in placebo-controlled clinical trials of CV benefit in a variety of populations (primary prevention, secondary prevention, TIAs, CABG patency and prevention of emboli in atrial fibrillation)[9]. None of the studies were specifically designed to quantitate the risk of GI bleeding associated with low-dose aspirin usage. Mean age of patients ranged from 55 to 75 years and the daily aspirin dose varied between 75 and 325 mg. Although buffered aspirin was used in one study, enteric-coated aspirin was not used in these trials. The findings were heavily influenced by data from the Physician's Health Study, which accounted for approximately 75% of all patients. There were 485 (3.5%) and 322 (2.2%) patients in the low-dose aspirin and placebo groups, respectively, who experienced bleeding from the GI tract. This difference was statistically significant (p<0.001), with an overall odds ratio of 1.52, 95% CI 1.32-1.75. There was no correlation between the probability of bleeding and the duration of treatment.

Studies of low-dose aspirin for the prevention of pregnancy-induced hypertensive disease have not consistently demonstrated any increased risk for maternal or neonatal GI bleeding complications[10,11].

There is little doubt that when used in antiinflamatory doses, enteric-coated aspirin preparations offer some, but not complete protection against GI toxicity. For example, in an endoscopy study of Lanza et al.,[12] clinically meaningful damage was observed in 93% of patients taking plain aspirin (4 g/day) compared to 20-27% of patients taking Ecotrin at the same total dosage b.i.d. or q.i.d. Significantly less GI bleeding with antiinflammatory doses of enteric-coated vs. buffered aspirin has been documented in Cr-51 labeled erythrocyte studies.[13] Information quantifying the GI toxicity of lower dose enteric-coated aspirin is limited. In a short-term endoscopic study in healthy volunteers, gastric toxicity from 300 mg aspirin daily was virtually eliminated by enteric coating.[14] However, a Cr-51 labeled erythrocyte study comparing 325 mg/day plain aspirin with the same dose of enteric-coated aspirin showed significantly increased GI blood loss for the former compared to the latter, but the enteric-coated aspirin values were still significantly increased compared to control.[15] In a 12-month, double-blind, randomized, placebo-controlled study of 400 subjects 70 years of age or older without pre-existing vascular disease, 100 mg/day enteric-coated aspirin showed a trend towards higher GI toxicity. An 18% incidence of GI symptoms was observed in the

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enteric-coated aspirin group versus 13% in the placebo group. There were 6 (3%) clinically evident GI bleeds (1 hospitalization) in the aspirin group vs. none in the placebo group. The aspirin group showed a significant decrease in mean hemoglobin levels (0.33 g/dL) during the 12-month study compared to the placebo group (0.11 g/dL, $p<0.05$).[16]

In the Dutch TIA Trial, 30 mg of aspirin/day was compared with 283 mg/day (both non-enteric coated) in a randomized, controlled trial in 3131 patients who had had a TIA or minor stroke. The 30 mg dose was no less effective than the 283 mg dose in prevention of vascular events, and was accompanied by slightly fewer major bleeding complications (40 vs. 53 over the mean follow-up of 2.6 years, 95% CI 0.51-1.16) and significantly fewer reports of minor bleeding (49 vs. 84, 95% CI 0.41-0.83).[17]

There is data that suggests that still lower doses of aspirin may inhibit thromboxane-dependent platelet function without causing gastric mucosal injury. Lee et al.[18] observed that doses of aspirin below 30 mg in normal volunteers did not reduce gastric juice PGE_2 but still significantly reduced serum thromboxane B_2 in a dose dependent manner. However, doses such as 3 to 10 mg/day which this study suggested may still confer CV protection without risk of GI mucosal damage have not been studied in clinical trials.

3. Incidence rates of CV events and estimates of treatment group differences likely to be observed in a megatrial of a Cox-2 inhibitor vs. NSAID comparator(s)

The attached memo from Doug Watson provides estimates of CV disease incidence rates in different populations. Rates of CHD have declined substantially over the past 2-3 decades, consequently the data were drawn only from relatively recent epidemiologic studies. Event rates differ markedly by study population, gender, race, and age. Consequently, one can only roughly estimate CV event rates for the anticipated study population of the planned GI outcomes trial.

The table below lists estimates of the distribution of vascular events between the two treatment groups in a hypothetical GI outcomes megatrial involving 10,000 continuing patients followed for one year. Figures are provided for different assumed CV event rates. Assumptions underlying these numbers include the following: (a) Patients treated with standard NSAIDs will experience antiplatelet effects and resultant CV protection similar to that produced by aspirin. (There are good theoretical arguments, as well as limited clinical data to support this assumption.[19]) (b) The degree of reduction in fatal and non-fatal CV events in the NSAID group will be comparable to that observed with aspirin treatment (i.e. 25% – see above). (c) Patients treated with the selective Cox-2 inhibitor will experience neither a reduction nor an increase in CV events associated with this therapy. (d) Equal numbers of patients will be treated with NSAIDs and Cox-2 inhibitor over the course of the study. Some of these assumptions involve gross oversimplification, but are adopted for the sake of simplicity and because greater sources of error are likely to be introduced by other factors in any case. The corresponding p-values for the listed numbers derive from a simple Fisher's Exact Test (2-tail).

Rate of Vascular Events (%)	Cox-2 Selective Inhibitor Group	NSAID Group	p-value
	Expected Events	Expected Events	

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0.5	25	19	0.450
1.0	50	37	0.196
2.0	100	75	0.067
3.0	150	112	0.020
4.0	200	150	0.004
5.0	250	187	0.002

The rate of vascular events observed will be highly dependent on the characteristics of the patient population randomized. Based on the goals of the study and the experience of prior megatrials in which PUBs were evaluated in arthritic populations, it can be anticipated that there will be a predominance of females (~60-75%) and elderly patients. (It is intended to recruit primarily elderly patients into the planned megatrial in any case, in order to guarantee a reasonably high PUBs rate.) Although different approaches are possible, it is perhaps simplest and most fruitful to look at event rates in those of the epidemiologic studies where the patient population approximates the likely distribution (age and gender) anticipated for the outcomes trial. References 5, 7, and 11 in Doug Watson's memo represent 3 such epidemiologic studies, for which the annual incidence of total CV disease events (see Table 6 in the attached memo) ranged from 2.6 to 6.8%. The lower estimate may be conservative because it derives from the Leisure World study where the population consisted of a fairly well-to-do retirement community and because TIAs were not included as events. The higher estimate may exceed rates likely to be observed in the megatrial, since the study from which this figure derives focused on elderly patients (75-85 years of age), although TIAs were again not included. None of these studies counted peripheral vascular disease events, which from another study occurred at a rate of 0.34% in males 54-74 years of age without overt CHD.

4. **Conclusions and Options:**

If patients are allowed to use low-dose aspirin in an MK-966 vs. NSAID comparator design study, the published data suggest that the "background" PUBs rate in the selective Cox-2 inhibitor group can be anticipated to be ~1.5 fold higher than if aspirin use were not permitted. Since the GI effects of low-dose aspirin (particularly if an enteric-coated formulation is used) are predominantly attributable to its antiplatelet effect (rather than any local effect) it is likely that GI risk will be increased more in the Cox-2 inhibitor group than in the NSAID group, because platelet function will already be impaired in the latter group. It is of interest that aspirin use for CV prophylaxis was not permitted in the nabumetone megatrial[20]. This may have contributed to the very low (extrapolated) annual rate of PUBs observed in that trial, a rate which was in fact lower than that reported in many aspirin prophylaxis trials.

If aspirin prophylaxis is not permitted, there is a substantial chance that significantly higher rates of CV AE events (MIs, angina, strokes, TIAs, etc.) will be observed in the selective Cox-2 inhibitor group compared to the standard NSAID group, as summarized in the preceding section. While one could argue that the differences are not unexpected due to the absence of antiplatelet effect for the selective Cox-2 inhibitor, it would create a negative aspect to the

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results and leave open the question (reasonable or unreasonable) whether the drug might in some other way be contributing to such events.

The following options are listed as potential ways to deal with these risks; none of them appear ideal:

- Prohibit use of low-dose aspirin and accept the risk of observing significant differences in CV event rates. One could attempt to minimize between-group differences by excluding patients at high risk (i.e. with prior MI, angina, stroke, TIA, atrial fibrillation, valvular heart disease, peripheral vascular disease, etc.). Since occult atherosclerotic CV disease will still be common in an elderly population and since aspirin therapy is effective in "primary prevention," the risk of observing significant between-group differences in rates of these events will remain. This approach would also make recruitment more difficult.
- Allow low-dose aspirin therapy but restrict to "high risk" patients and use the lowest possible dose of an enteric-coated formulation. By minimizing the proportion of the patient population receiving prophylaxis and using the safest form, the increase in PUB rates within the total population would be low and anticipated differences in CV events between the treatment groups would be reduced (but not eliminated, since the entire NSAID group vs. a portion of the Cox-2 inhibitor group would be receiving antiplatelet prophylaxis).
- Consider placing all patients on extremely low doses of aspirin (e.g. 3-10 mg, enteric-coated formulation) with the aim of reducing CV risk without increasing risk for PUBs. Such an approach would itself need to be viewed as experimental, since clinical studies of efficacy at such doses for CV prevention or risk for GI toxicity are lacking. One could not be certain that the background rate of PUBs in both groups would not be slightly increased by even these extremely low aspirin doses.
- Allowing an alternative (non-aspirin) antiplatelet agent would not appear to offer any definite advantage compared to low-dose enteric-coated aspirin.
- Reconsider the possibility of a placebo-controlled (rather than NSAID comparator) study design, using an elderly population not absolutely requiring NSAIDs, with a co-primary cognitive function endpoint. Use of low-dose enteric-coated aspirin would not be a problem in such a study. Since the aspirin protective effect would be randomly distributed between the groups, the increased risk for observing a between-group difference in CV events would be eliminated. The background GI event rate would be slightly increased, but this would not interfere with demonstrating equivalency between the selective Cox-2 inhibitor and placebo, under "real-world" conditions where a portion of patients are taking low-dose aspirin.

Tom Musliner
594-4150

Attachment
ASAMEMI.doc

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 4

To: Simon, Thomas; Ehrich, Elliot W.; Morrison, Briggs; Reicin, Alise S.
From: Daniels, Brian F.
Cc
Bcc:
Date: 1997-02-26 04:44:12
Subject: RE: GI OUTCOMES TRIAL PROTOCOL

Alise,
I have left hard copy with comments on your desk.
150 mg of diflofenac is upper limit or OA. In fact ome labels indicate it's for acute use at this dose only.
I would throw in the hand you have nothing to lose
One month prohibition for steriod you are not evaluating efficacy with respect to a study joint. There is no need for a 3 month wait

Ahhh...ASA I feel that you are using an inflated estimate of the rate of PUBs with 75 mg of ASA. What ever the rate it is always lower than the doses of NSAID we are using. It is clear to me that the program wil be severly hurt if the megatrial shows a win in PUBs and a loss in MI/CVA. That is what we are setting up by not allowing ASA. And I a sure no one wants to hear thepractical concerns of significantly inhibiited patent enrollment.

From: Reicin, Alise S.
To: Simon, Thomas; Daniels, Brian F.; Ehrich, Elliot W.; Morrison, Briggs
Subject: RE: GI OUTCOMES TRIAL PROTOCOL
Date: Tuesday, February 25, 1997 10:39PM

Brigge:
Thanks for your input here are some answers;
1. My impression is that the doses of ibuprofen and diclofenac are felt to be equipotent. in fact diclofenac is approved in doses up to 200 mg for RA. The label is a little unclear about OA but implies that 100-150 is the suggested range. BRIAN and ELLIOT-am I correct?

2. We will alow acetominophen users maybe I should make that explicitly clear.
3. I discussed this with Brian, Elliot and a consultant- the feeling was that hand OA is unlikely to require chronic NSAIDS, and back "OA" is too diverse a group. Your idea about the X'ray is interesting. Theres still some discussion about wether we should loosen the criteria to "clinical diagnosis of OA". The criteria I used are modified ACR criteria.

4. Beth felt we should try to get patients at a somewhat stable baseline. Remember all we want to show with efficacy here is that patients on 966 don't get much worse. They should be comparable to NSAIDS. Remeber patients can always be rescreened after a month-Do you all allow rescreening in the phase III OA studies? In the asthma studies if patient didn't meet entry cirterion, they could be rescreened at a different time-but we were explicit in the protocol that they needed to have a different baseline number on the second try,

5.Low Dose Aspirin- I HEAR YOU! This is a no win situation! The relative risk of even low dose aspirin may be as high as 2-4 fold. Yet, the possiblity of increased CV events is of great concern- (I just can't wait to be the one to present those results to senior management!). What about the idea of excluding high risk CV patients- ie those that have already had an MI, CABG, or PTCA.? This may decrease the CV event rate so that a difference between the two groups would not be evident. The only problem would be -Would we be able to recruit any patients?

6. I am waiting for GI input on this one.
7.
8. Good idea-we probably can cut it out of the two week visit. Maybe leave it in the 6 week visit since some studies suggest risk of bleeding is increased in the first month of therapy.
9.No data on the MEDCO card-its my untested hypothessis
13. ECG- I think that for sure we would want a baseline ECG on file before patients enter the study- esp given our discussion of aspirin above. Maybe you are correct that we don't need to repeat it at V8- But remember this

study is on a nonmarketed drug.

Thanks for taking the time to read the protocol.

From: Morrison, Briggs
To: Simon, Thomas; Daniels, Brian F.; Ehrich, Elliot W.; Reicin, Alise S.
Subject: RE: GI OUTCOMES TRIAL PROTOCOL
Date: Tuesday, February 25, 1997 8:23AM

Quick comments - read it late last night

1. Dose of MK0966 and diclofenac are the maximum doses, dose of ibuprefen is a intermediate dose. Why?
2. Are you allowing acetaminophen users as we do in Phase III? (I would)
3. Why limit OA to knee and hip. Would allow any OA that requires therapy. Would also minimize radiograph criteria to "x-ray consistent with OA".
4. Why do you prohibit steroid injection prior to coming into study but allow once in study? Could end up with someone who never had injection before getting one 2 weeks into study and that is OK, whereas someone who had one 1 week before (and may not need another for months) is excluded.
5. Would allow low dose aspirin - I know this has been discussed to death, but real world is everyone is on it, so why exclude AND without COX-1 inhibition you will get more thrombotic events and kill drug.
6.With regrads to H-2, omperazle, etc would allow intermittent users to enter study (as we do in Phase III) and use same algorithm of antacids etc for any need to INCREASE use.
7. Do not specify temperature method (otic, oral both fine)
8. Ideally would limit blood work to that which the investigator feels is necessary to follow pts. If you do want to specify, keep CBCs to a minimum (3, 6, 9, 12 months at most). By doing frequent CBCs you will see decrease in Hct due to fluid retention and this will precipitate a GI work-up and you will end up with "true-true and unrelated" endpoints.
9. MEDCO card clever -is there any data to support the hypothesis that this minimizes OTC use?
10. Certainly can use Likert sacles instead of VAS.
11. A lot of weights and vital signs. Again, might want to leave to investigator discretion what they want to do.
12. Visit 9.0 is a "post therapy" visit not a "poststudy" visit.
13. Why ECG at v8? In fact, why ECG at all?
bwm

From: Reicin, Alise S.
To: Simon, Thomas; Daniels, Brian F.; Ehrich, Elliot W.; Morrison, Briggs
Subject: GI OUTCOMES TRIAL PROTOCOL
Date: Sunday, February 23, 1997 11:59PM
Priority: High

Attached is a preliminary draft of the GIOT protocol. You can see throughout I have written comments and questions. I would really appreciate the groups input.
Please forward this on to Ken-I'm in Boston and he is not on my E-mail list.
Tom-feel free to show is to your group. Have a look at the algorithm in the Appendix. Do you think this looks ok? Should we just not allow some of these meds?

To all-remember there will be 10-12,000 patients- any ideas on how to decrease the amount of data collected is very important.

Thanks in advance.

Alise

P.S. Beth asked me to put together a list of 10-12 potential names for heads of the steering comittee. We want the person to be academic and well connected-ideally this person should play a major role in helping to recruit other investigators. Beth thought we should include epidemeologists similar in caliber to Steve Cummings in this list. Some of you have given me names already. Think about it. I'll be touching base again with you this week-sorry to be a pain.<<File Attachment: GIOPROT1.DOC>>

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 5

MK-0966 (VIOXX™) Project Team Minutes: May 12, 1998
Executive Summary

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To: MK-0966 (VIOXX™) Project Team Members

From: Suzanne M. Pemrick, Ph.D.

Date: June 9, 1998

Subject: MK-0966 (VIOXX™) Project Team Minutes for May 12, 1998

EXECUTIVE SUMMARY

- **Critical Issues**
  - **-- Overview of discussions from 4/30 early RA clinical development FDA meeting**
    Among the concerns/recommendations expressed by the FDA were: 1) include swollen joint count as an endpoint; 2) extend placebo arm to 12 weeks; 3) demonstrate the 50 mg dose is at the therapeutic plateau; 4) explore higher doses, because of concern over "dosage creep". The FDA supported their previous draft guidance regarding GI safety issues.

  - **-- Important recommendations by the 5/98 Board of Scientific Advisors**
    1) Obtain clinical data at a higher dose range; 2) Schedule a renal consultants' meeting; 3) Obtain additional preclinical information on the effects of COX-2 inhibition on bone metabolism/healing of fractures; 4) Determine if there are pulmonary effects of VIOXX™ within the asthmatic subgroup of patients; 5) Undertake additional studies of atherosclerosis in animal models; 6) Begin from this point onward to systematically collect data on cardiovascular (CV) events in all clinical trials for VIOXX™ and MK-0663.

- **Safety Assessment -**
  - **-- 106 Week Rat Carcinogenicity Studies - Post-mortem findings in the WMA study**
    The was no increased incidence of tumors in treated groups.

- **Clinical Research**
  - **--Update on Results from the Phase III Dental Pain Studies (#066 & #071)**
    In both studies, 50 mg MK-0966 is comparable to 400 mg ibuprofen in terms of onset and peak effect, but with a longer duration of action. The minimal dose required to give maximal analgesic efficacy is 100 mg.

  - **--Outcomes Research**
    Acting on the recommendation of the Board of Scientific Advisors (see above), Alan Nies has asked Doug Watson to Chair an Adjudication Committee for CV events.

I. Administrative Items:

A. Review of the Minutes from the April 13, 1998 PT Meeting

Minutes Accepted.

II. CRITICAL ISSUES

A. Review the Project Team Key WMA Milestones (*see attachment 1 of Agenda*)

---Frozen File status
--- CSR status

Milestones

- Conversion of the last mini doc study (#065) to the CRISP data base will be delayed. Clin. Pharm. anticipates the delay for #065 will not impact upon the last Clin. Pharm. frozen file nor the ISOS tables.

Complete File Target Dates

- Between now and the beginning of June, there are 8 complete file deadlines.

CSR Status

- As of 5/11, there are 17 approved CSRs and 16 CSRs in L&R. There is a backlog in L&R, due to the number of clean reference copies being received/day to review.

B. Update on feedback from January's Team-Building Event

---Maureen McNamara asked for volunteers from various departments to form small groups to look at issues #2 & #3, at right.

Continual Communication and Positive Feedback

- After the last PT meeting, the Chairs sent out a program update. *Last week, Alan Nies and Beth Seidenberg received a memo from Ed Scolnick commenting positively on the performance of this Project Team!*

Feedback from brainstorming sessions at Team Building Event.

1. Need for constant communication between departments and the sharing of information
2. Importance of Work/Life balance issues to success of Team
3. Expectation of encouragement, incentives, rewards and recognition.

C. Review discussions from 4/30 early RA clinical development FDA meeting

The meeting included clinical representatives from the reviewing division of the FDA. Below are Agency recommendations and/or concerns expressed at the meeting.

Primary Efficacy Endpoints

- Prefer ACR 20
- Will accept the 4 endpoints (3/4 positive), but want swollen joint count included.

Study design and duration issues
- Grudgingly accept "flare" design because no established alternative exists
- Recommend extending placebo arm to 12 weeks

---*The Agency indicated their intent to review the NDA carefully to verify that the data demonstrate the 50 mg dose is at the therapeutic plateau.*

Dose
- Unable to provide definitive end of Phase II discussion because dose ranging information unavailable at this time
- Recommend exploring higher doses, because of concern over "dosage creep"
- Must demonstrate efficacy plateau.

---**GI Events Analysis**
- **Accept description in label**
- **No not support removal of GI Warning even if results are most favorable**
- **Definitive support of removal of GI Warning would require GI Outcomes Study**

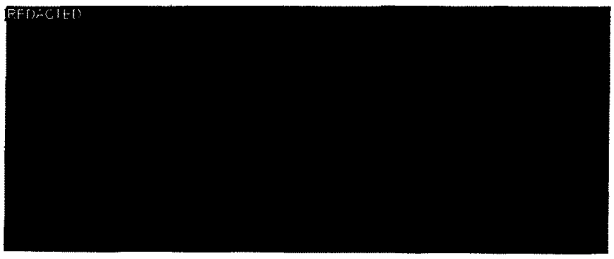
GI Safety Issues
- Support previous draft guidance
- Accept 3 month endoscopy studies as sufficient to describe in label, but not sufficient to remove NSAID GI warning
- Recommend a placebo arm in the study, because "RA stomachs different from OA stomachs"

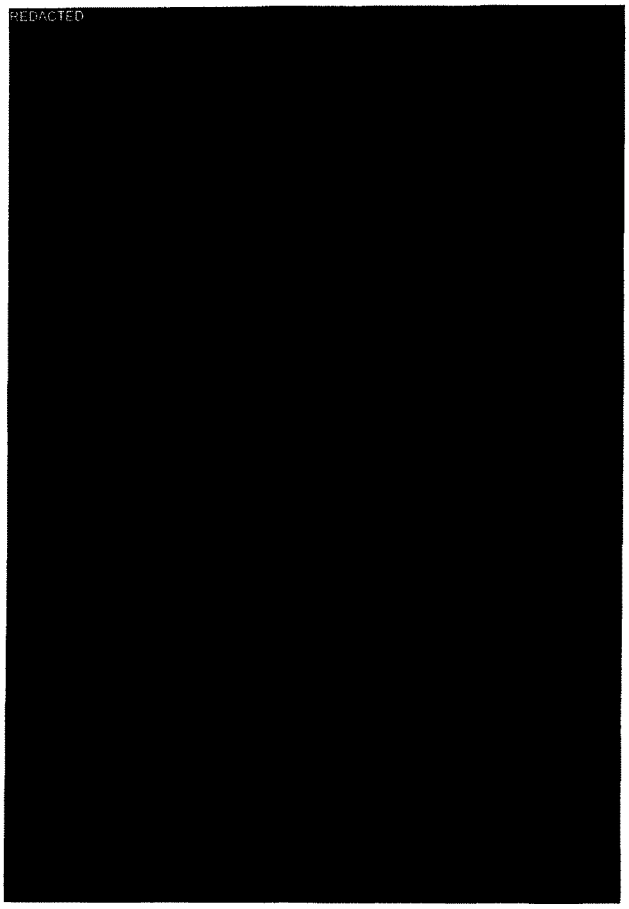
--- **Other Issues (see attachment #1)**
- Concomitant medication Use
- Pediatric Use
- Patient exposure - conform to ICH Guidelines

---*Will the RA CDS need to be revised as a result of the 4/30/98 meeting with the FDA?*

There will be important but not major changes
- Increase in the number of endpoints
- Extend placebo arm of efficacy study to 12 weeks
- Addition of placebo group to endoscopy study.

However, the overall structure of the RA program will remain intact.

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F. Update on the Commercialization Team Activities

---Plans/deliverables for 7/31 interim stage review with HHPAC.

The **interim stage review** at the end of July will be fairly extensive. The Team will begin to work on the background package in June. Deliverables will be:

- **Phase III data** (including pooled data, endoscopy study results)
- **CDP/CDSP study/strategy** with any changes based on upcoming Phase III data

- **Dose selection input to MMD**

[redacted]

- **Competition update**
- **Sales forcast update**
- **RA Section** describing the Phase III RA program and the WMA timing
- **Updated NPV (net present value) for OA, RA and Analgesia combined**
- **Alzheimer's Section** summarizing the Phase III Program and timing for the WMA filing, updated resources for the Phase V Program and an NPV.

G. Review of VIOXX™ presentation at the 5/98 Board of Scientific Advisors Meeting.

Alan Nies presented all data available on VIOXX™ at the time of the meeting, along with all of the potential problems (e.g., effects on renal function, ulcer healing, bone and prostacyclin metabolism, etc). The consultants considered the data, and the potential problems, and offered the following suggestions for future studies (postfiling):

- **Obtain clinical data at a higher dose range.** Gradually over time the drug may be prescribed at higher dose ranges in an attempt to achieve maximal efficacy. It would be conceivable, therefore, to see AEs as a result of high doses of VIOXX™ inhibiting COX-2 activity to a greater extent than normally observed with NSAIDs. This recommendation is too late to change the VIOXX™ program, but may change the RA program for the back-up compound, MK-0663 (***Note, a similar concern was expressed by the FDA at the 4/30 meeting for the RA program***).
- **Schedule a renal consultants' meeting,** to learn more about monitoring procedures, and diagnostic indications in the postmarketing surveillance of VIOXX™ patients for incidence of interstitial nephritis.
- **Obtain additional preclinical information on the effects of COX-2 inhibition on bone metabolism.** Dr. Bone suggested a preclinical emphasis on studying whether or not COX-2 inhibition alters fracture healing. A similar approach was undertaken with fosamax; therefore, the animal model is in house.
- **Determine if it is possible to combine VIOXX™ and steroid treatment in animal models, and if feasible pursue this research direction.**
- **Determine if there are pulmonary effects of VIOXX™ treatment within the asthmatic subgroup of patients.** Background: COX-2 is highly induced in the lungs of asthmatics. It is not known whether inhibiting COX-2 activity would lead to adverse pulmonary events, have no effects, or be beneficial, in this patient subgroup.
- **Undertake additional studies of atherosclerosis in animal models (e.g., ApoE**

"knockout" mice) to determine whether or not inhibition of COX-2 activity influences progression of the disease.

- **Begin from this point onward to systematically collect data on CV events in all clinical trials (for VIOXX™ and MK-0663) utilizing predefined endpoints for MCI (myocardial infarction), stroke, TIA (transient ischemic attack), unstable angina, etc.** To accomplish this task, an adjudication committee should be established and follow a formal plan. Alan Nies has asked Doug Watson to head this adjudication committee for CV events. The committee's guidelines for operation would be similar to the adjudication procedures for PUBs. Discussions are in progress regarding the draft protocol for this analysis. The plan should begin immediately; perhaps, with the Alzheimer's trial. Background: The consultants were in two ideological camps on this subject: 1) Since atherosclerosis is an inflammatory disease, patients should benefit from inhibition of COX-2 activity; 2) Based upon data on PGI metabolism obtained for VIOXX™, it is conceivable that VIOXX™ could disturb the [endothelium-platelet] interaction to favor platelet aggregation.

III. **SAFETY ASSESSMENT/MERCK FROSST**

A. Status of the 106 wk rat carcinogenicity studies:

---Post-mortem findings in the WMA study (2,5, and 8 mpk)

- The study, histological evaluation and statistical analysis have been completed.
- **There is no increased incidence of tumors in treated groups.**
- At 8 mpk, there was an effect of VIOXX™ on survival.

----Low dose study (0.2, 0.5, and 1 mpk/d)

This study is in the 68 DW, and there are no tumor related effects. This study continues only to define the no effect level for intestinal ulcers.

B. Status of the 105 wk mouse carcinogenicity studies

---WMA study-(5, 10, 20 & 30 mpk)

- ***The no effect level for GI effects is 5 mpk***

For both this study and the 60 mpk group from the high dose study, histological evaluations are completed, but the statistical analyses have not been done. There are no trends in the incidence of any tumor type, with one exception. In the lower dose study (,5-,0-,20-,and 30-mpk), at 30 mpk for female mice, there was a higher incidence of harderian gland tumors. However, at twice this dose, there

	was no increased incidence of harderian gland tumors. This suggests that the higher incidence at 30 mpk represents biological variability.
---Low dose study (0.3, 1, & 3 mpk)	This study will be terminated upon approval by senior level management. ***Post Meeting note: This study has been terminated.***
C. Studies to assess renal effects of COX-2 inhibitors. **---Results from the study with Meloxicam in dogs at 0.02, 0.1 and 0.5 mpk..** • ***The study will be completed in 3 weeks***	The results of the 2nd study under these conditions indicate: • At 0.02- and 0.1-mpk, little or no inhibition of either COX-1 or COX-2; • At 0.5 mpk, 70 to 80% inhibition of COX-2, and 10 to 15% inhibition of COX-1.
• **Upon completion of the study, the entire results section will be intact for the paper comparing renal function effects with VIOXX™ *versus* celecoxib, indomethacin, and Meloxicam.**	Currently, it is being decided whether or not to do the renal function study at 2 doses: 0.25- and 0.5-mpk. It is felt that at the higher dose, there will be effects on urinary sodium and water retention, plus possible effects upon the GFRs.
D. Status of the 2-wk study with VIOXX™ to determine synovial fluid drug levels in dogs.	The samples were collected on May 7th and 8th, and there was good sample recovery. Data will be available in 3 days.
E. Review and approval of WMA documentation	The pharmacodynamics section is behind schedule because of modifications modifications as a consequence of the preclinical consultants' meeting. This section will be ready in a few weeks.
F. Plans/timing for studies to evaluate wound healing and response to injury with analogs of	**Study Plans** A study was completed last week in dogs, which looked at different procedures for producing ulcers in the pyloric portion of the stomach. Histological evaluation has been completed: the best procedure

VIOXX™

---Alan Nies pointed out the following:
⇒the study should look at a standard NSAID
⇒The Board of Scientific Advisors was very interested in this type of study.

produces a lesion of 5-(L) x 7-(W) x 0.5-mm (D) mm. This procedure will be tested for reproducibility. The wound healing study will begin in June for the three analogs: L-748,706; L-72,860; L-783,003, and ibuprofen. Dose selection for the COX-2 inhibitors will be based upon *ex vivo* COX-1 and COX-2 inhibition studies which provide:

- a dose that gives level of inhibition equivalent to the clinical trials
- dose of maximal inhibition
- non-selective dose with respect to COX-1 and COX-2 inhibition

Study Timing

- Most of the data with the analogs will be available by July. Celecoxib and VIOXX™ will be evaluated in a separated study after the results of the analog study have been evaluated.

VII. REGULATORY AFFAIRS

A. Update on activities to further discussions with the FDA in follow-up to 3/24 FDA advisory meeting (on arthritis guidelines)

For an overview of the 3/24 FDA advisory meeting see the April Minutes of the VIOXX™ PT Meeting. Briefly, the purpose of the meeting was to discuss safety assessment issues which distinguish COX-2 from non-specific NSAIDs.

Update

- Conversations are underway with both the GI and Arthritis Divisions at the FDA in an attempt to get both divisions involved in working out guidelines for evaluation of GI toxicity.
- Discussions are ongoing with Merck management in terms of the best way to proceed.

[redacted]

C. FDA feedback on the VIOXX™ tradename.

--Possible outcomes at the FDA of response

Background

- FDA approves tradenames as part of the NDA process
- Regulatory had made a request to the nomenclature committee at the FDA for an unofficial early review of the chosen tradename.

letter described at right
- ⇒ **Issue may return to nomenclature committee with decision postponed until after filing**
- ⇒ **FDA may decide at this time to override the nomenclature committee**
- ⇒ **FDA may opt for more discussion**

Update
- The committee responded with concern that the tradename "VIOXX" might be confused in the marketplace with other drugs with a similar name.
- In a response letter, trademark staff at Merck documented their exhaustive search of data bases to avoid precisely this concern.
- This response letter is under internal review.

IV. CLINICAL PHARMACOLOGY/DRUG METABOLISM

In general, all ongoing studies are on schedule. For an update on current studies see **attachment #2.**

A. Review results from the gastric biopsy study (#062)

VIOXX™ is associated with no change in the PGE_2 or $PGF_{2\alpha}$ production assessed in gastric biopsy specimens. Naproxen causes approximately 70% reductions in both PGs.

V. CLINICAL RESEARCH/CBARDS/ EPIDEMIOLOGY

See attachment #3 for extensive update on this section (*e.g., OA, RA, Analgesia*). Items below represent additional data, or data highlighted at the PT Meeting.

GI Studies

A. Update on status of frozen files for the endoscopy studies (#044/045)

#044
- Frozen file occurred first week in May

#045
- Frozen file on target for June 1

Osteoarthritis Studies

B. Plans to address hypertension AEs reported in Protocol #034

---Timing for a consultants/meeting

⇒ The three outside consultants are: Andrew Welton; Art Weaver; Mike Weber. Questions are being prepared for the consultants, and will be

circulated to various members of this PT. The date of the consultants meeting will be set in the near future.

C. Update on Phase III Ibuprofen comparator studies (#033,#040)

Study Design

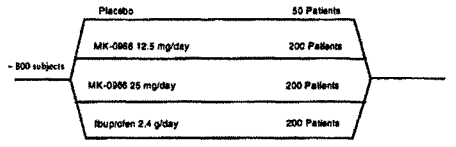
--See also Attachment #4

Ibuprofen Protocols

- Active comparator-controlled, parallel-group, 6-week, triple-blind studies, to assess the safety and efficacy of VIOXX *vs* ibuprofen in patients with OA of the knee or hip
- Protocol 033
  - 66 sites U.S and 734 allocated patients
- Protocol 040-
  - 50 sites non-US and 809 allocated patients

2

Study Schematic
Protocol 040-Non U.S. /Protocol 033-U.S.



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Study Hypotheses

1. MK 0966 will demonstrate comparable clinical efficacy to ibuprofen in the treatment of osteoarthritis of the knee and hip
   - Pain Walking on a Flat Surface
   - Patient Assesment of Response to Therapy
   - Investigator Assessment of Disease Status
2. MK-0966 will be safe and well tolerated

1

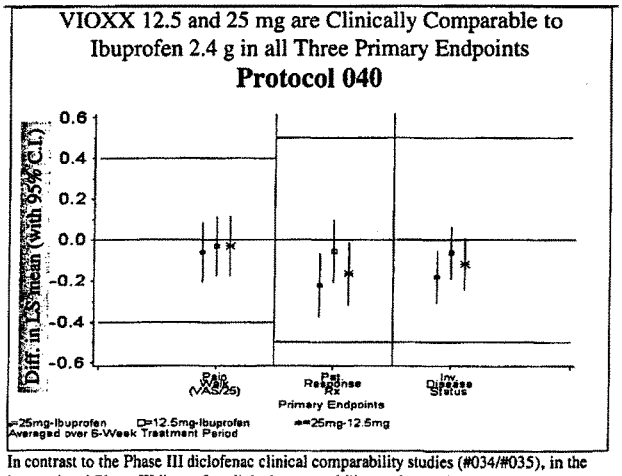
Study Objectives

1. Show 25 mg MK-0966 efficacy = ibuprofen 800 tid
2. Confirm safety and tolerability
3. Show 12.5 & 25 mg MK-0966 efficacy > placebo
4. Explore efficacy & safety in acetaminophen users
5. Compare efficacy and safety of 25 vs 12.5 mg MK-0966
6. MK vs ibuprofen in GI AEs.

1

Results

For a restatement of the definition of clinical comparability see Attachments #4a and #4b



In contrast to the Phase III diclofenac clinical comparability studies (#034/#035), in the international Phase III ibuprofen clinical comparability study (#040), for 2 primary endpoints (Patient Response to Therapy, Investigator's Assessment of Disease Status), 25

mg VIOXX™ is statistically superior to 2.4 gm ibuprofen. However, as the graph above shows, all treatment groups are clinically comparable.

Discontinuations due to Lack of Efficacy (*see also* Attachment #4c)

⇒ All treatment groups are significantly ($p < 0.05$) better than the placebo group

Discontinuations due to AEs (*see also* Attachment #4c)

⇒ For the U.S. study, the incidence of AEs is similar to the placebo group for all treatment groups.
⇒ For the International study, compared to the placebo group, the incidence of AEs is significantly ($p < 0.05$) greater in the ibuprofen group. The incidence of AEs among the 25 mg VIOXX™ treatment group is ***significantly lower*** ($p < 0.05$) than the ibuprofen treatment group.

For the Clinical AE Summary see *Attachments #4d and #4e*

Edema and Fluid Retention (*see also* Attachment #4f)

- The 25 mg VIOXX™ and the ibuprofen treatment groups have significantly ($p < 0.05$) more lower extremity edema/fluid retention than either the placebo or 12.5 mg VIOXX™ treatment groups.

Hypertension (*see also* Attachment 43g)

- Compared with the placebo group, there is no significant difference ($p \geq 0.05$) among all treatment groups.

Blood Pressure Predefined Limits of Change (*see also* Attachment #4h)

- No significant change in the diastolic pressure
- Compared to the placebo group, there is a significant increase in the systolic pressure for all treatment groups (both studies). For #033, the change from baseline systolic pressure for the 12.5 mg VIOXX™ treatment group is significantly less than for the ibuprofen treatment group.

NSAID Type AEs - Compared to the Placebo Treatment Group (*see also* Attachment #4i)

- For the US Study, the incidence among all treatment groups is similar
- For the International Study, the 25 mg VIOXX™ and the ibuprofen treatment groups have a significantly ($p < 0.05$) higher incidence.

Laboratory AEs (*see also* Attachment 43j)

The ibuprofen treatment groups consistently demonstrated greater decreases in hemoglobin and hematocrit with respect to both
⇒ predefined limits of change
⇒ mean changes over time

Overall Preliminary Conclusions

- ***VIOXX 12.5 mg once daily is comparable to Ibuprofen 800 mg TID***
- ***VIOXX 12.5 is not different from 25 mg***
  - Evaluate subpopulations: age, weight severity
- ***VIOXX is generally safe and well tolerated***
  - Similar renal vascular effects as Ibuprofen
  - More NSAID-type AEs for 25 mg VIOXX and Ibuprofen c/w placebo in one study only
  - Fewer Hemoglobin and Hematocrit Changes

1

D. Octogenarian study (#058)	The study is on target
Phase IV Studies	
E. Plans for Bone Metabolism Study (#083) ***---Current enrollment***	• 55 patients screened • 1 patient randomized
Rheumatoid Arthritis studies	
F. Status of synovial fluid prostaglandin studies ***---Timing for FPI in Italy (#049) and US (#081)***	**#081** • FPI occurred in Alabama • There is an additional site - at NYU **#049** • Set for FPI • Have drug supplies
Analgesia Studies	
G. Results from the Phase III Dental Pain Studies (#066 & #071))	**Previous Data:** **⇒ Protocol #004 - 50=250=500=400 mg ibuprofen** ***---Numbers in each treatment group were small. Therefore, study was not powered to do between***

treatment comparisons

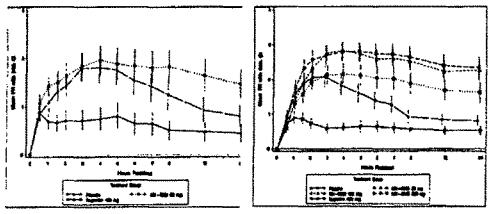
⇒ **Protocol #027 - 7.5< 25< 50=100=550 Nap Na+**
---Dose ranging study with old formulation

⇒ **Protocol #051 - 12.5< 25 ≤ 50=550 Nap Na+**
---Repeat dose ranging study with new formultation

Protocol #066 - placebo, 50 mg VIOXX™, 400 mg ibuprofen

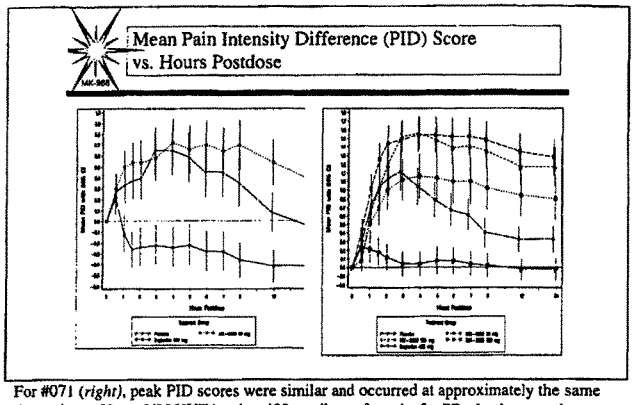
Protocol #071 - placebo, 50-,100-, 200-mg VIOXX™, 400 mg ibuprofen

Mean Pain Relief (PR) Score vs. Hours Postdose



For #061, peak PR occurred at approximately the same timepoint for both 50 mg VIOXX™ and 400 mg ibuprofen. In both experiments, compared with ibuprofen, PR lasted longer at the 50 mg VIOXX™ dose.

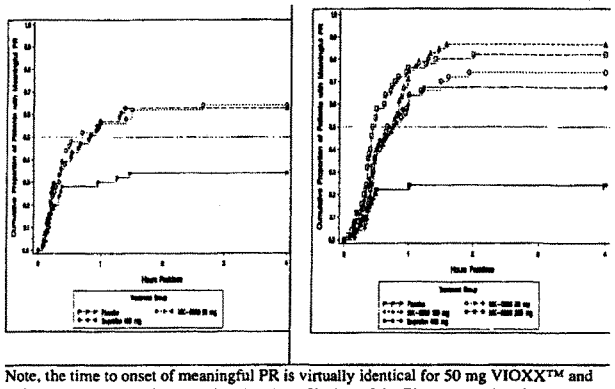
At the high VIOXX™ doses (100 & 200 mg) the peak PR scores were higher compared with the 400 mg ibuprofen group. At the 50 mg dose, PR scores are similar in both experiments and comparable to PR scores for the ibuprofen group.



For #071 *(right)*, peak PID scores were similar and occurred at approximately the same timepoint at 50 mg VIOXX™ and at 400 mg ibuprofen. As for PR, the therapeutic benefit, here expressed as PID, lasted longer for 50 mg VIOXX™ than for 400 mg ibuprofen. However, at 100- and 200-mg VIOXX™ the peak PID score was higher than for either 50 mg VIOX™ or for 400 mg ibuprofen.

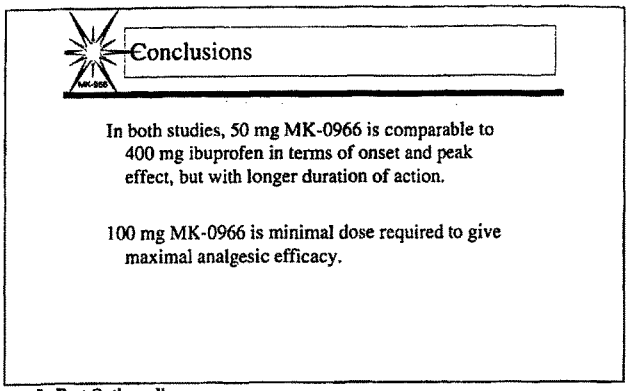
Patient's Global Evaluation at 8 Hours of Study Medication
(See Attachment #5a)

Time to Onset



Note, the time to onset of meaningful PR is virtually identical for 50 mg VIOXX™ and 400 mg ibuprofen. It is reassuring that these Kaplan-Meier Plots comparing the treatments of interest are reproducible between the two studies.

For an analysis of the Time to Rescue Medication see *Attachment 5b*
The duration of therapeutic benefit is clearly better for 50 mg VIOXX™ than for 400 mg ibuprofen. There is a need, therefore, for additional statistical analyses to determine the dosing regimen for acute analgesia.



In both studies, 50 mg MK-0966 is comparable to 400 mg ibuprofen in terms of onset and peak effect, but with longer duration of action.

100 mg MK-0966 is minimal dose required to give maximal analgesic efficacy.

I. Post Orthopedic Surgery Study #1 (#072)
---LPO

- LPO occurred May 1st
- Last patient submitted for review is May 15th
- Study is on target for frozen file

N. Status of the pilot (prn dosing) post orthopedic surgery study (#080)

---Despite the problems described at right, this study will continue to enroll patients until July. At that time, there will be sufficient data from the first study to make a decision regarding this study.

Current Status

- As of yesterday, May 11th. SCIREX, the CRO who had contracted to do the entire study, indicated that their surgeons in Texas will not be enrolling any patients into the study. This is because of their concern of having surgical patients concomitantly using anticoagulants and non-steroidals. There is no doubt that this decision, on the part of SCIREX, will delay the study.
- Two additional sites are ready to enroll as soon as they finish #072, the Post Orthopedic Study #1.

Background

- The FDA indicated that if the first study (#072) was definitive then this study could be a Phase IV commitment.
- The general opinion is that if the first study is not definitive, the situation will not be helped by the second study.

Alzheimer's Program

P. Status of the Alzheimer's Disease Prevention Trial-#078

---Feedback from 4/13 investigators' meeting

- FPI occurred 4/24
- Waiting for IRB approval on 3 additional sites
- Protocol Amendment was issued 5/8.
- Protocol will have to be amended again to include collection of data on CV events, and review by an adjudication committee (***See Critical Issues, Section G***).

Q. Plans/timing for an Alzheimer's Treatment Trial

- The study will start in 3Q98
- The study will be a fairly typical Alzheimer's trial (placebo controlled, parallel group design, 48 week duration)
- Several novel designs are being considered as an add-on at the end of the trial

Colon Cancer Studies

R. Plans/timing for consultants' meeting

In preparation for the forthcoming consultants' meeting, there was an additional meeting on April 28th, with 2 consultants (Dr. Robert Besselier from Henry Ford Hospital and Dr. John Barrett from Dartmouth Univ. Medical Center), principal investigators in a number of studies examining NSAIDs as chemopreventive agents for colonic adenoma recurrence. The consultants were generally supportive of the protocol design.

The date of the consultants meeting is still pending, but will probably occur in July or August.

A draft protocol will be presented to the consultants in June, in order to insure issuing of R-88s, and adequate drug supplies for initiation of this polyp prevention trial in 4Q98

VII OUTCOMES RESEARCH For general update, see **Attachment #3**

A. Update on GI AE

- The amendment to Protocol #069 is being

adjudication committee activities.	circulated for approval • Update on case review packages ---total number received - 40 ---number forwarded to adjudication committee - 23 • There will be another adjudication committee meeting tomorrow. It is anticipated that another 10 case review packages will be received at this time • Two additional meetings are scheduled - June: 2nd and 23rd.
B. Status of the GI Symptom Questionnaire Study (#077)	Enrollment has been poor for two reasons: ---patients do not want to be without effective OA treatment for 3 weeks ---patients do not want to be exposed to NSAIDs because of the risk of GI upset. Therefore, Telerex has a contract to provide advertising in an attempt to boost enrollment.
VIII. DRUG DEVELOPMENT SUB-TEAM (DDST)	**See Update in Attachment #3**
A. Update on Sub-Team activities	• A strategy is in place to cope with or without a tradename on the tablets.
B. Update on market container stability studies for tablets and suspensions	• **The manufacturing site stability study will initiate this week approximately 1 month ahead of schedule!**
C. CMC timelines/WMA document production	The first drafts for the bulk and the tablet went out to the first list of reviewers
IX. COMPETITION **B. Comments on recent meetings attended by MRL personnel**	
---Pharmacology	Alan Nies attended a symposium arranged by Phil Needleman of Searle. Alan Nies presented Phase II

Society Meeting

data on VIOXX™; Phil Needleman presented information on COX-2, and Phase III data on celecoxib.

- **Summary of Phase III data on celecoxib**
  ---Searle claims all 3 doses are equally efficacious in the treatment of OA. And a dose response was not apparent in the 100 to 400 mg bid range in the RA studies. Therefores, it is uncertain that Searle has identified a sub-effective dose.

The following is a summary of Phase III data on celecoxib

⇒ 2 OA Studies (placebo controlled, 3 months duration)
---50-, 100-, 200-mg CELEBRA™ bid vs. 500-mg Naproxen bid

⇒ 2 RA Studies (placebo controlled, 3 months duration)
---100-, 200-, 400-mg CELEBRA™ bid vs. 500-mg Naproxen bid

⇒ Subsets of patients from the OA and RA studies received endoscopies at the beginning and end of the 3 month treatment period.

⇒ Searle's Phase III results showed
---equivalency grossly (i.e., without statistical analysis) to Naproxen
---incidence of ulcers (from the 3 month endoscopy trials) just slightly greater than placebo (4 vs. 6%) and much less than Naproxen (20%)

⇒ Provided no comparability data, other than the general statement.

---Abstract of Poster presentation by Smith Kline Beecham [*J Inv Med 46(3): 227A (1998)*]

- Looked at the effects of CELEBRA™, Nabumetone, and indomethacin in the dog. The same doses were tested for all 3 drugs (3-10-,30-μmol/kg)
- All 3 drugs were effective on rat paw edema.
- Unlike Nabumetone which had no urinary effects celecoxib and indomethacin reduced
  urine flow
  urinary Na^+ excretion
  renal plasma flow
  GFR
- These results corroborate the findings of SAFETY ASSESSMENT in similar studies

---William Harvey Research Conference (4/22-24)

- Good coverage of a number of topics - nothing particularly new was presented on clinical or preclinical research
- Approximately 75% of the attendees were from Merck
- Good prelude to the October conference in Canada

X. Marketing

A. Update on 4/22 HHMC discussions

---The next meeting will be 5/22.

Items presented

- Clinical Development Strategy on Alzheimer's Disease Prevention/Treatment
- FDA Arthritis Advisory Committee Meeting
- Searle/Pfizer activity in US
- Identify the pricing issues which will be ***key*** to development of WW pricing strategy
- ATC plan and positive preliminary feedback from WHO on separate classification of VOIX from other NSAIDs. This will help with reimbursement, regulatory acceptance and promotion.
- Test preliminary concepts for the VIOXX™ branding.

[redacted]

C Review of publication/symposia plans for roll-out of phase III data.

The publication plan is currently under revision, and will be circulated to the PT shortly.

---Upcoming symposia/meetings

- The next meeting is the Pan American League against Rheumatism in Montreal in June. Merck is sponsoring a closed symposium chaired by Dr. Bellamy from Canada.
- The Arthritis Foundation is sponsoring a joint parade on 5/31. There will be a Merck team.

D. Review of key marketing assumptions in the Alzheimer's SOI

---Timing for final SOI

The SOI will be in final form by the end of May.

A number of the assumptions have been changed based upon the FDA meetings and the timing of Searle's trial.

XI. CDP/CDSP

A. Status of Nabumetone pilot study (#082):

- As of 5/11, there are 184 screened patients, and 121 patients, *the target number*, enrolled in the study. About 20 patients have dropped out (as early discontinuations), the vast majority of which were due to lack of efficacy.
- The data from this study will be available mid-June.

B. Plans/timing for large CDP Nabumetone studies

The protocol will be finalized after the results are in from the pilot study, and presented to CDOC on 6/23. The current target for FPI is August for the first study and September for the second study

XI. JAPAN

See attachment #6 for update

Key dates*		
Phase IIa Open Pilot Study in OA	Initiation (FPI) Completion (LPO)	A-11/96 A-9/97
Phase IIa Open Pilot Study in RA	Initiation (FPI) Completion (LPO)	A-11/96 T-6/98
Phase IIb DRF Study in OA	Initiation (FPI)	T-8/98
Phase IIa Open Pilot Study in Postoperative Dental Pain (PDP)	Initiation (FPI)	T-7/98
Double-blind Study in Familial Adenomatous Polyposis (FAP)	Initiation (FPI)	T-7/98

* No change in timelines since last month!

XIII. PROJECT PLANNING AND MANAGEMENT

A. Gantt chart of program milestones	This was attached to the Agenda for this Meeting.
B. Arrowwood Reminder	Arrowwood discussions of 1998 objectives and accomplishments will begin in June, continue in July and be finalized in August.
C. Next VIOXX™ Project Team Meeting	***The next meeting will be June 9, 1998 from 9:00 a.m. to 12:00 noon in RY84-20/BL-2554/MT/WHS3A55 video conference rooms.***

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 6

PROPOSAL TO GENERATE G.I. OUTCOMES DATA ON VIOXX

HH-PAC
6/12/98

I. Executive Summary

A. Overview

The primary development and marketing goal is to establish VIOXX, a specific COX-2 inhibitor, as a new preferred class of anti-inflammatory therapy, with a superior GI toxicity profile and with efficacy comparable to NSAIDs. The development program is designed to demonstrate that VIOXX is the best in this new class.

It has recently been reported that the major competitor for VIOXX, celecoxib from Searle/ Pfizer, will be releasing its WMA/ NDA at the end of July, 1998, approximately 4.5 months ahead of the WMA/ NDA release for VIOXX (T-12/98). While celecoxib will likely be the first to gain approval from regulatory agencies in this new class of compounds, specific COX-2 inhibitors, several key factors are different in the development program with VIOXX. Our present understanding of the difference in the GI safety programs include the following: 1) 6 month endoscopy study data with VIOXX vs. 3 month data with celecoxib, 2) pooled GI clinical event analysis from Phase III trials 6-12 months in duration with VIOXX vs. a similar pooled GI clinical event analysis from shorter duration Phase III trials with celecoxib, and 3) data with VIOXX from an intestinal permeability study and from a ^{51}Cr red blood cell loss study demonstrating less GI mucosal damage (including small bowel) vs. ibuprofen.

Prior Milestones and Recent Developments

One year ago, at the VIOXX Stage II Review, serious consideration was given to a double-blind G.I. Outcomes Study designed to demonstrate that VIOXX will result in fewer significant GI events (PUBs) compared to NSAIDs supporting the removal of the GI warning from the label. The study was canceled later in the 1997 year due to several factors including: 1) cost and resources, 2) lack of endorsement by the FDA, and 3) patent issues. Since the HH-PAC review for VIOXX last year, several developments have occurred which has prompted the Commercialization Team to re-evaluate the need for a double-blind G.I. Outcomes Study. First, at two recent meetings, the 1998 FDA Arthritis Advisory Board Meeting and the European Regulatory Consultants Meeting, strong recommendations were made that GI outcomes data would be necessary to remove the GI warning from the label. Second, it has been recently reported that Searle/ Pfizer is planning to initiate a large-scale, 8,000 patient Double-Blind G.I. Outcomes Trial with celecoxib in September, 1998, with data

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available in 1999. Searle has reported that they will carry the standard NSAID GI warning in the initial label at launch, with the GI outcomes study supporting removal of the warning from the label.

Alternatives Considered

The Commercialization Team has evaluated four alternatives with the primary objective of removal of the GI warning from the label within a timeframe to be competitive with that of Searle/ Pfizer: 1) **a simple, double-blind G.I. outcomes study with OA and RA patients***, 2) a simple, double-blind G.I. outcomes study with OA patients only, 3) an open label prospective cohort post-marketing surveillance study, and 4) a retrospective cohort post-marketing surveillance study. A comparative summary of the study descriptions, benefits and risks, probability of removal of the GI label warning if the study data are robust, and grant and drug supply costs is shown in Table 1 below.

* **CST Recommendation.** Please note the timing proposed for an accelerated double-blind GI outcomes study might allow completion before the currently scheduled RA WMA (Target filing date 1Q01T). This is discussed in the Clinical and Regulatory Affairs (Sections II.C. and II.E).

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Table 1. Summary of Proposed Studies to Generate Outcomes Data Vs. Competition

Brief Description of Study	Timeline	Risks/ Benefits	Anticipated Label Changes	Regulatory POS to Obtain Label Change (if Data are Robust)	Objectives/ Outcomes of Study	Cost of Study
Searle/ Pfizer: • Design: 1 year randomized double blind GI outcomes study w/ 8000 OA and RA patients • Comparators: celecoxib, naproxen 1000 mg/d, diclofenac 150 mg/d, ibuprofen- 2400 mg/day • Endpoints: significant GI events	• FPI - 9/98 • Results - 1999	• Under powered according to Merck hypotheses/ estimates	• Removal of GI warning in Label • Description of study in Clin Pharm section of label	• 95% • 95%	• Elimination of the NSAID GI warning from the label • Publication in leading medical journal	
CST RECOMMENDATION: **G.I. Outcomes Study (OA + RA Patients):** • **Design: 1 year randomized double blind controlled study w/ 10,500^ OA and RA patients** • **Comparators: VIOXX 25 mg, diclofenac 150 mg/d, ibuprofen 2400 mg/d** • **Endpoints: incidence of PUBs - perforations, symptomatic peptic ulcers and upper GI bleeding**	• **FPI - 12/98** • **LPI - 9/99*** • **LPO - 3Q00** • **Results - 4Q00** * **The Team will investigate novel methods to decrease the recruitment time. If feasible methods are found the timelines will be changed accordingly.**	• **Gold Standard** • **Most likely of alternatives to result in removal of GI warning in label and in publication in leading medical journal** • **Remain competitive with Searle (Searle's initial WMA filing and GI Outcomes Study will include RA patients)** • **Incorporation of RA pts (a non-indicated population and dosage in the initial registration) may engender concern from regulatory agencies to label changes until RA indication is obtained w/ VIOXX**	• **Removal of GI warning in Label** • **Description of study in Clin Pharm section of label**	• **95%** • **95%**	• **Elimination of the NSAID GI warning from the label** • **Publication in leading medical journal**	• **Clinical Grant Total - $55.5 million (includes $26.3 million in investigator grants, $5.0 million in central lab costs, $24.2 million in CRO costs)** • **Drug Supply Cost Total - $12.7 million (includes $4.4 million in comparator drug costs, $7.0 million in package/ label costs, and $1.3 million in contract labor costs)** • **Total drug supply cost between 6-7/98 - $2.5 million* (ordering supplies on risk so as not to impact study start date of 12/98T)**

[redacted]

^Note: Sample size for the study will be adjusted after evaluation of the pooled clinical GI event data from Phase III trials (HH-PAC Review - 7/31/98 T)

MRK-ABL0000162

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 7

New file for CSS - Informed Consent

generic - for local IRBs approved by L Siarell

Patient Informed Consent

Study Title: A Double-Blind, Randomized, Stratified, Parallel-Group Study to Assess the Incidence of PUBs During Chronic Treatment with MK-0966 or Naproxen in Patients with Rheumatoid Arthritis

Protocol No.: Protocol 088

Sponsor: Merck & Co., Inc.

Investigator:

Address:

Telephone:

You are being asked to participate in a drug research study. However, before you give your consent to be a volunteer, we want you to read the following and ask as many questions as necessary to be sure that you understand what your participation will involve.

You understand that you cannot be participating in another research study involving an investigational drug or be taking another investigational drug while participating in this study.

Nature and Purpose of the Study

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen (Advil®, Motrin®) and naproxen (Aleve®), are widely used for relieving pain and inflammation. Side effects, particularly in the stomach and intestines, are common with existing NSAIDS. MK-0966 is an investigational drug being developed by Merck & Co., Inc. for the relief of pain and for the treatment of inflammatory diseases such as rheumatoid arthritis. An investigational drug is one which has not been approved by the U.S. Food and Drug Administration (FDA). MK-0966 is being studied to see if it is as effective and causes fewer side effects than existing NSAIDs.

The purpose of this study is to assess the rate of stomach Perforations, Ulcers, or Bleeds (PUBs) in patients being treated chronically (for a long time) with either MK-0966 or Naproxen. Approximately 7,000 male and female volunteers will participate in this study worldwide. Your participation in this study may last for approximately 1 to 2 years, but may also be as little as 6 months. You will receive one of the following treatments throughout the study:

- 50 mg of MK-0966 daily
- 1000 mg of naproxen daily (500 mg twice a day)

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The type of treatment you will receive will be determined on a randomized basis (by chance, like the toss of a coin).

Due to the differing appearance of the study medications, you will be asked to take a combination of an active medication, which will be either MK-0966 or Naproxen, and a placebo (inactive medication). The drugs will be packaged in such a way that neither you nor the staff at the clinic can tell which medication you are taking during the course of the study, to reduce the chance of influencing the results. However, the information is available if needed in the event of an emergency. The study staff will provide you with detailed instructions on how and when to take your study medication.

During the course of the study, you will be informed of any significant new findings which may relate to your willingness to participate or to continue your participation in this study.

Entry Requirements

You must satisfy the following entry criteria to enter this study:

- You must be at least 50 years of age, or be at least 40-49 years of age and taking chronic oral corticosteroids; you must also have been diagnosed by a physician as having rheumatoid arthritis for which you will need to take non-steroidal anti-inflammatory therapy for at least 1 year.
- Female patients must have a negative serum (blood) pregnancy test at the prestudy visit and agree to remain abstinent, use oral birth control pills or double-barrier method of contraception (partner using condom and patient using diaphragm, contraceptive sponge, or IUD) beginning at least 7 days prior to treatment and continuing until 14 days after the End-of-Study Visit or Discontinuation Visit. Women who are postmenopausal or have had a hysterectomy or tubal ligation will not need a pregnancy test. (Postmenopausal is defined as no menses for the previous 1 year). If the last menses are within 18 months, a blood test will be done to make sure you are postmenopausal.
- Except rheumatoid arthritis, you are judged to be in otherwise general reasonable health, based on medical history, physical examination, and laboratory screening tests, enabling you to complete the trial.
- You are able to understand and complete the study questionnaires.
- You understand the study procedures and agree to participate in the study by giving written informed consent.

You may not enter this study if you meet any of the following criteria:

- You have a history of other inflammatory arthritis, such as lupus.
- You have a history of stomach, bile duct, or small intestine surgery that causes malabsorption.
- You have uncontrolled hypertension (high blood pressure).

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- You have a history of stroke or temporary stroke-like symptoms of stroke within the last 2 years.
- You have active hepatitis/liver disease.
- You have a history of cancer.
- You are currently a user (including "recreational use") of any illicit drugs, or have a history of drug or alcohol abuse within the past 5 years.
- You are allergic to acetaminophen, or have sensitivity to aspirin, naproxen, and other NSAIDs.
- You are obese and demonstrate significant health problems stemming from your obesity.
- You have a history of esophagus (food pipe) or stomach surgery.
- You have a history of inflammatory bowel disease.
- You have a history of a bleeding disorder.
- You have donated a unit of blood or plasma or participated in another clinical study with an investigational agent within the last 4 weeks.
- You have previously been enrolled in an MK-0966 clinical study.

In addition, there may be other reasons why you cannot participate which will be discussed with you by the Investigator or his/her staff.

Procedures to be followed during the Study

As was discussed with you during your initial telephone interview, you will be asked to report to the clinic for an initial Screening Visit. You will be assigned a screening (baseline) number and receive a physical examination, have vital signs (blood pressure, heart rate, breathing rate and temperature) measured, have an electrocardiogram performed (EKG, a recording of the electrical activity of the heart), provide an evaluation of your rheumatoid arthritis, and be interviewed by one of the research personnel who will take your medical history including any medications you are currently taking. In addition, blood will be drawn by venipuncture and urine will be collected for laboratory tests.

Venipuncture is a routine procedure that will be used for obtaining blood samples from you by inserting a needle into a vein in your arm and withdrawing a small sample of blood. Sterile, single-use needles will be used for each blood sample.

For the initial screening, the amount of blood drawn will be approximately 4 teaspoons (18 ml). Women of childbearing potential will have an additional 1-1/2 teaspoons (7 ml) of blood drawn for a serum pregnancy test. At subsequent visits, urine pregnancy tests will be performed. Postmenopausal women whose last menstrual period was within the last 18 months will have an additional 1-1/2 teaspoons (7 ml) of blood drawn for a test to make sure you are post-menopausal.

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MRK-MJ02446[illegible]

The initial blood and urine samples will be used to determine that you meet all of the study eligibility criteria.

Before leaving the clinic you will also be asked to provide names of two people who can assist us in reaching you in case the clinic staff cannot contact you directly. You will be also asked to grant written permission for the clinic staff to obtain copies of any medical records and/or reports should you be hospitalized for a stomach perforation, ulcer, or bleed. Lastly, you will be given three stool hemoccult cards (for detection of blood in the stool) with instructions on how to obtain samples and be scheduled for your next visit.

After the clinic has received and reviewed the results of your laboratory samples and determined that you are still eligible to continue in the study, you will be contacted and instructed to discontinue any non-steroidal anti-inflammatory (NSAID) medication you are taking and be reminded about your next clinic visit. You may continue to use other treatments for rheumatoid arthritis (such as gold, methotrexate, hydroxychloroquine [Plaquenil®], azathioprine [Imuran®], prednisone or other pain medications such as acetaminophen [Tylenol®]).

At the next clinic visit (Randomization Visit), which will take place within 10 days after the screening visit, you will be asked to return the stool hemoccult sample cards for processing. While the results of the hemoccult cards are being processed you will be asked to report any changes or corrections to your medical history and concomitant medications (any other medications that you are taking). All medications that are disallowed during the study will be reviewed at this time. You may receive a list of the "disallowed" medications. If the results of the 3 stool hemoccult cards are negative (no blood detected in the stool), you will continue with the remaining procedures for this visit. The procedures will include vital signs measurements, an assessment of your rheumatoid arthritis and plasma and blood samples will be collected as described earlier.

After all Randomization Visit procedures have been performed, you will be randomly assigned to a treatment group and receive study medication. You will need to take your study drug twice a day. Instructions for taking study medication will be reviewed and you will be scheduled for your next visit in 6 weeks. From this point on you will have two types of clinic contacts. In-clinic visits will be scheduled approximately every 4 months (Study Weeks 6, 17, 35, and 52) and telephone contacts will be scheduled in-between these clinic visits at Study Weeks 10, 26, and 43. Since the conclusion of this study is based on the number of patients with a confirmed stomach perforation, ulcer, or bleed, if the study continues past Week 52, you will continue to come into the clinic every 4 months and will be contacted by telelphone in between the in-clinic visits.

At each subsequent in-clinic visit, you will have your vital signs and weight measured, you will have blood and/or urine samples taken, an interim history and concomitant medications which you are taking will be reviewed, an assessment of your rheumatoid arthritis will be made at set intervals, unused study medication will be collected and new study medication will be dispensed.

As defined above, you will also be contacted by clinic personnel for "Phone Visits." During these phone calls you will be asked about your study compliance (how well you followed instructions) and other study-related questions. You will also be asked to report any changes in the medications you are taking.

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At the end of the study or if you discontinue the study, you will be asked to come in for your last clinic visit to have the final set of in-clinic procedures as described above. You will also receive instructions as to when treatment with NSAIDs may begin again. After this visit, you may still be contacted by telephone for additional follow-up information with regard to any adverse events you may have.

Prior Experience with Drug/Risks and Benefits

Previous studies with MK-0966 have been conducted in approximately 5500 individuals and it has been generally well tolerated.

Side effects considered possibly associated with the use of MK-0966 may include, but are not limited to headache, dry mouth, mouth sores, heartburn, loose stools, abdominal discomfort, nausea, acid reflux, vomiting, drowsiness, dizziness, blood in stools, shortness of breath, abnormal liver function, temporary stroke-like symptoms that go away, fluid retention with swelling, hypertension (high blood pressure), itching, upper respiratory infection, and virus-like symptoms.

The study medications may have other side effects and discomforts to you (or your unborn child) that are not yet known.

The most common side effects experienced by being treated with naproxen are flu-like symptoms, constipation, heartburn, abdominal pain or discomfort, nausea, indigestion, loose stools, mouth sores, headache, dizziness, drowsiness, lightheadedness, vertigo, itching, skin eruptions, bruising, sweating, purpura (purple discoloration of the skin), tinnitius (sensation of noise/ringing in your ears), hearing and visual disturbances, fluid retention with swelling, shortness of breath, palpitations (rapid heartbeat), dry mouth and thirst. Allergic reactions are also possible. Rarely these may be life threatening. Other less common side effects have been reported. The investigator or his/her staff will discuss these with you.

During the collection of blood samples, you may experience pain and/or bruising at the site on your arm where blood is taken. Fainting may occur during or shortly after having blood drawn. If you experience faintness, you should lie down immediately to avoid possible injury caused by falling, and notify study personnel. The approximate amount of blood drawn over the course of the study will be less than 10 tablespoons (approximately 140 ml).

The study drug must be taken only by the person for whom it was prescribed, and it must be kept out of the reach of children or persons of limited capacity to read or understand.

Pregnancy Risks

It is very important that you not become pregnant during this study. You are aware that abstinence from sexual activity is the only certain method to prevent pregnancy. If you are a female of childbearing potential and choose to be sexually active during the course of this study, you agree to use oral contraceptives, or double-barrier contraception (partner using condom and patient using diaphragm, contraceptive sponge, IUD, or spermicidal foam/jelly) throughout the study period, and to accept the risk that pregnancy could still result.

There is a slight risk that a pregnancy test could be inaccurate, thus exposing you to potential

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MRK-NJ0244670

loss of pregnancy as well as other unknown effects on a developing fetus. The effects of the study drug on a fetus are unknown. There may be other side effects and discomforts to you (and to the embryo or fetus, if you are to become pregnant), which are not yet known.

Potential Benefits

You may receive therapeutic or direct health benefit from participation in this study such as the reduction of your rheumatoid arthritis pain. Society may also benefit from the information obtained based on your response to study medication. It is possible that no therapeutic or other direct health benefit may result during or following your completion of the study.

Alternative Treatments

You understand that if your pain is not sufficiently relieved with the study medication, your doctor will provide you with an alternative pain medication such as acetaminophen, or other pain medications. Other medications used to treat rheumatoid arthritis are over-the-counter oral medications, such as aspirin and ibuprofen, as well as more powerful medications available as prescription products, however, use of these medications while you are taking study medication will require that you discontinue from the study. The study doctor or study personnel will discuss with you the risks associated with any alternative medication you may take. In no way will your decision not to participate affect your current or future treatment. The investigator will provide you with information regarding the side effects of alternative treatments.

Compensation for Medical Treatment

(Compensation, if any, provided by investigator/hospital).

If you suffer any adverse drug experience resulting directly from the Merck study drug, Merck & Co., Inc., will provide reimbursement for the reasonable costs of medical treatment to the extent such costs are not covered by your medical or hospital insurance or by third-party or governmental programs providing such coverage. No other form of compensation is available.

Confidentiality

Unless required by law, only the investigator, the sponsor, (Merck & Co., Inc.), their agents (Covance), and governmental regulatory agencies (US Food & Drug Administration and other governmental regulatory agencies in other countries) will have access to confidential data which identifies you by name. You will not be identified in any reports or publications resulting from the study.

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Parties to Contact

The investigator or his designate has answered all your questions. If you have additional questions during the course of this study about the research or your rights as a research subject, you may address them to _____ _____ at _____. In the event of a research-related injury or if any other problems arise, please contact _____ (IRB) at _____.

Voluntary Participation

Your participation in this study is voluntary. You may refuse to participate or may discontinue participation at any time during the entire duration of the study without penalty or loss of benefits to which you are otherwise entitled. If you stop your participation, you may receive a standard medication and no prejudice will be shown toward you for medical care or participation in future studies. In addition, your participation may be ended by the investigator or sponsor with out regard to your consent if you need additional medication, violate the study plan, experience a study-related injury or for administrative reasons. Any time your participation is terminated you shall go through the termination procedures—physical examination, blood, and urine tests for your own safety.

I have read this consent form. My questions have been answered. I voluntarily consent to participate. I will receive a signed copy of this consent form.

_____	_____
(Signature of Volunteer)	(Date)
_____	_____
(Signature of Person Obtaining Consent)	(Date)
_____	_____
(Signature of Investigator)	(Date)

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 8

To print: Select **File** and then **Print** in your browser pull-down menus.

TheStreet.com

Biotech/Pharmaceuticals

Vioxx's Victory Lacks Key Safety Recommendation

By Jesse Eisinger
Senior Writer
4/20/99 9:53 PM ET
URL: http://www.thestreet.com/stocks/biotech/738239.html

WASHINGTON -- Beaming **Merck** (MRK:NYSE) officials proclaimed victory after a **Food and Drug Administration** panel recommended approval of its would-be category-painkiller, **Vioxx**. Vioxx is a member of the new Cox-2 class of anti-inflammatory and painkilling drugs, the so-called superaspirins.

Edward Scolnick, Merck's head of research and development, opened a question-and-answer session after the meeting by doling out congratulations to various company employees who had a hand in developing Vioxx. And he projected bravado in the face of an imminent marketing battle with **Monsanto** (MTC:NYSE) and the hated **Pfizer** (PFE:NYSE), the firms which co-market the hit Cox-2, **Celebrex**.

"I don't think this has any disadvantages to Celebrex and has some advantages," he said. "We have a real once-a-day drug and they don't." Scolnick said that difference would be clinically meaningful to patients. The drug starts working faster than Celebrex as well. "Not. Too. Shabby," he said, smiling for emphasis.

Winning the recommendation for approval from the panel was never in doubt. The question was whether the panel would regard Vioxx as safer than the widely used nonsteroidal anti-inflammatory drugs, or NSAIDs, such as ibuprofen. The promise of the Cox-2s is that they will cause fewer gastrointestinal complications, such as ulcers, than chronic use of NSAIDs does.

On that issue, the panel wasn't so convinced, indicating that it would recommend the same safety profile for Vioxx as the one given to NSAIDs. Analysts say that doctors widely believe that the drug is safer, hence the panel's safety recommendation may not have much of an impact.

The panel recommended that the drug be approved to treat osteoarthritis and acute pain, but it stopped short of recommending the drug for approval in chronic pain treatment. Celebrex doesn't have approval for acute pain, but it is recommended for rheumatoid arthritis, a clearance Vioxx will not get immediately.

The FDA, which has to rule on approval by May 23 to hit its deadline, usually takes its panels' advice.

The panel had some concerns with Merck's argument that Vioxx is as benign as a sugar pill. The drug can cause, in high doses, fluid retention and high blood pressure. The fluid retention, called edema, was a central issue for the bulk of the meeting.

Scolnick proclaimed after the meeting that edema was not a significant problem. "We don't have an edema problem. I'll stake my reputation on it." Which, in his case, actually means something.

Wall Street may find the panel vote a bit disappointing because some analysts foresaw that Vioxx would get a better safety recommendation than Celebrex.

"The primary difference between this drug and Celebrex is that Merck got acute pain," says Ira Loss, an FDA analyst for **HSBC Securities**. (HSBC hasn't participated in any underwriting for Merck.) "The side-effect and safety issues were decided similarly to Celebrex. The company directed the Street to expect a comparable-to-placebo side-effect

profile."

The anticipated market reaction may only last for a short while, however. Merck desperately needs Vioxx to be a billion-dollar-a-year-plus drug and will fight like a cornered badger in the marketplace. Merck faces a potentially severe multi-billion-dollar hole in sales, as several products go off patent during the next couple of years. The company also faces intense competition to several of its major drugs, including its Drano for arteries **Zocor**. And several recent launches, such as hair-loss remedy **Propecia**, have been flops.

And so, Merck must make Vioxx into a major seller, or, in three years or so, Merck will have a hyphen attached to its name. Steve Tighe, analyst for **Merrill Lynch**, said that three years out, Vioxx and Celebrex "will be pretty close" in market share. (Merrill hasn't performed recent underwriting for Merck.) At peak, the Cox-2s will be a multi-billion dollar category, said Tighe. He projects Vioxx sales of around $250 million this year. Celebrex sales could reach over $1 billion in sales this year.

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November 18, 2004

Exhibit 9

To: Binkowitz, Bruce; Bolognese, James; Cook, Thomsa; Peszek, Izabella; Shapiro, Deborah; Zhang, Ji
From: Capizzi, Thomas
Cc
Bcc:
Date: 1999-04-22 17:29:11
Subject: FW: interaction

Fyi
Tom Capizzi
Sr. Director, Clinical Biostatistics
Merck Research Labs, 126 Lincoln Ave Rahway NJ 07065
732-594-4202; 732-594-6075 fax

From: Scott Zeger[SMTP:szeger@jhsph.edu]
Sent: Thursday, April 22, 1999 9:25 AM
To: tom_capizzi@merck.com
Cc: szeger@jhsph.edu
Subject: Re: interaction

Tom, I believe that Qian Li did come to appreciate that what probably happened was that the 044 placebo rate was higher by chance. She certainly acknowledged that:

1. Because 044 and 045 were randomized studies, the people in the control group in 044 were a priori, like the ones in the other treatment groups

2. That except for the placebo group, 044 and 045 were totally similar in the rates and that this similarity, because of the randomization is evidence that the two studies have comparable findings.

3. That the difference between the 044 and 045 placebo groups is not close to being statistically significant.

4. That it is in the public health interest to pool the data to better address the comparability of vioxx and placebo, if the evidence for an interaction is not strong.

She is concerned that there is an interaction. She is following the statistical dictum on never estimating a main effect in the presence of an interaction. She was willing to think about the information in the other treatment groups and the small numbers, but the testing rules ("p<0.10 is significant for an interaction") has her concerned.

I had her very close to buying the Merck position when Ed S. came up and nearly strangled her and her supervisor (who I do not know). That hurt badly. They were less willing to talk afterward.

I went up to her when the meeting broke up and made some peace but there may be some slightly hard feelings.

In summary, she was close to appreciating the Merck position. Keep harping the points above and she will understand, I think.

Good luck, Scott

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> Date: Wed, 21 Apr 1999 15:23:13 -0400
> From: "Capizzi, Thomas" <tom_capizzi@merck.com>
> Subject: Interaction
> To: "'zeger, scott'" <szeger@jhsph.edu>, "'Wittes, Janet'"
<janet@statcollab.com>
> MIME-version: 1.0
> Content-transfer-encoding: 7BIT
>
> Janet- Scott-
>
> We are trying to piece together the conversations that we and you had with
> the FDA statisticians yesterday. What was your feelings about these. I
> know that Qian Li did not back off her assertions. However did you detect
> any signals that her management may have agreed with our point of view?
>
> Thanks
>
> Tom
> Tom Capizzi
> Sr. Director, Clinical Biostatistics
> Merck Research Labs, 126 Lincoln Ave Rahway NJ 07065
> 732-594-4202; 732-594-6075 fax

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Exhibit 10

7.5. THROMBOEMBOLIC AND VASCULAR SAFETY

There is a theoretical concern that patients chronically treated with a COX-2 selective inhibitor may be at higher risk for thromboembolic cardiovascular adverse experiences than patients treated with COX-1/COX-2 inhibitors (conventional NSAIDs), due to the lack of effect of COX-1 inhibition on platelet function.

Most of the serious adverse events observed in this NDA were of the cardiovascular body system, including MI, unstable angina, CVA and TIA's. Of note, patients with a recent history of MI or unstable angina and with a TIA or CVA within 2 years prior to entry were excluded from the studies, although a significant percentage of the population had a preexisting cardiovascular condition, mostly hypertension (see Table 50 and 51). Additionally, patients taking low dose aspirin or other antiplatelet or anticoagulant medications were excluded from the studies.

Table 50. Baseline demographics and cardiovascular history in elderly and primary 6-week studies.

	Elderly OA Study	Primary 6-Week Studies
Total Number of Patient	341	2457
Mean Age (years)	83	65
% of Female Patients	64	75
% of Patients with Preexisting Cardiovascular Condition	75	60
% of Patients with Preexisting Hypertension	48	42
% of Patients with Preexisting Angina Pectoris	10	3
% of Patients with Preexisting Myocardial Infarction	11	2
Mean Creatinine Clearance (mL/min)	45	88

[P010; P029; P033; P040; P058]

Table 51. Secondary diagnoses (incidence ≥ 0.5 %) in 6 month OA studies (from Table E-16, original NDA).

	Placebo		Rfx 12.5 mg/d		Rfx 25 mg/d		Rfx 50 mg/d		Ibuprofen		Diclo	
Cardiovascular System	**183**	**(49.3)**	**295**	**(60.2)**	**482**	**(54.8)**	**202**	**(53.3)**	**291**	**(58.4)**	**205**	**(54.4)**
Hypertension	107	(28.8)	206	(42.0)	309	(35.2)	133	(35.1)	194	(39.0)	143	(37.9)
Venous insufficiency	4	(1.1)	19	(3.9)	22	(2.5)	3	(0.8)	27	(5.4)	4	(1.1)

Evaluation of deaths, cardiovascular serious non-fatal and of thromboembolic adverse events in this NDA does not seem to indicate a dose response relationship with rofecoxib (Tables 36. And 37).

Evaluation of CV thromboembolic events regardless of seriousness shows a numerically higher incidence of ischemic/thromboembolic events (angina, myocardial infarction, CVA, TIA) in patients taking rofecoxib when compared with patients taking placebo, but the exposure to placebo was less than the exposure to rofecoxib. In 6 weeks studies there was one event in the placebo group (0.2 %) and a total of 12 events (approximately 1 %) in the rofecoxib groups. In 6 month studies there were 3 events in placebo

(approximately 1%) and 23 (approximately1 %) in the total rofecoxib group, even though placebo patients were only exposed for up to 18 weeks. The data seem to suggest that in 6 –week studies, thromboembolic events are more frequent in patients receiving rofecoxib than placebo but do not show a clear dose response relationship with rofecoxib. There is a trend towards an increased incidence in longer trials, but it is always expected to have some increase in the incidence of adverse events with longer time of observation. The incidence of thromboembolic events with rofecoxib appears to be similar to comparator NSAIDs.

It is difficult to reach meaningful conclusions when the number of events is relatively small and the length of the exposure and doses of rofecoxib used were different among studies. Longer studies included only the 12.5 and 25 mg rofecoxib doses; exposure to the 50 mg dose was limited to 397 patients in 6 month studies and less than 60 patients in 6-month to 86 week studies.

In summary: With the available data, it is impossible to answer with complete certainty whether the risk of cardiovascular and thromboembolic events is increased in patients on rofecoxib. A larger database will be needed to answer this and other safety comparison questions.

Patients who need aspirin for cardiovascular reasons should not stop aspirin when taking rofecoxib. There is a potential concern of increasing the risk of GI bleeding events with the concomitant use of rofecoxib and aspirin but limited data are available from clinical studies with this combination.

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Table 52. Thromboembolic adverse events regardless of seriousness. All OA trials.

	6 week studies	6 month studies	6 month to 86 week plus 029-10 and 058-10
	N/n %	N/n %	N/n %
Placebo	1/412 (0.2%) Cerebrovascular accident	3/371 (0.8%) Acute myocardial infarction 2 Unstable angina	
Rofecoxib 5	0/149		
Rofecoxib 12.5	5/725 (0.7%) Myocardial infarction Cerebrovascular accident Coronary artery disease Ischemic heart disease Angina pectoris	7/490 (1.2%) Cerebrovascular accident Myocardial infarction 2 Angina pectoris 3 CAD Ischemic heart disease	7/550 (1.3%) Angina pectoris 3 CVA CAD Ischemic heart disease Transient ischemic attack
Rofecoxib 25	5/735 (0.8%) Myocardial infarction 2 Unstable angina 2 Angina pectoris	10/879 (1.0 %) Transient ischemic attack 3 Myocardial infarction 2 Angina pectoris 3 Coronary artery disease 2	6/547 (1.1%) Angina pectoris 2 CVA 1 Coronary artery disease Ischemic heart disease Myocardial infarction
Rofecoxib 50	1/97 (1.1%) Angina pectoris	4/379 (1.1%) Cerebrovascular accident 3 Transient ischemic attack	3/123 (2.4%) CVA Coronary artery occlusion Myocardial infarction
Rofecoxib 125	(1/74) (1.4%) Transient Ischemic Attack		
Ibuprofen 2400	(2/470) (0.4%) Cerebrovascular accident Angina pectoris	2/377 (0.5%) Angina pectoris 2	
Nabumetone 1500	0/115		1/92 (1.1%) Angina pectoris
Diclofenac 150		9/498 (1.8%) Cardiac arrest 2 Myocardial infarction 2 Angina pectoris 2 Coronary artery disease Unstable angina Cerebrovascular accident 2	6/439 (1.3%) Myocardial infarction Coronary artery occlusion Coronary artery disease 2 Angina pectoris 2

N/n = number of events/number of patients randomized.

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November 18, 2004

Exhibit 11

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 16 1999

TRANSMITTED VIA FACSIMILE

Ms. Ellen R. Westrick
Senior Director
Office of Medical/Legal
U.S. Human Health
Merck & Co., Inc.
P.O. Box 4, WP37C-116
West Point, PA 19486

Re: **NDA 20-560 Fosamax (alendronate sodium)**
NDA 21-042 Vioxx (rofecoxib)

MACMIS ID # 8086

Dear Ms. Westrick:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of promotional materials for Fosamax (alendronate sodium) and Vioxx (rofecoxib) that are lacking in fair balance or otherwise misleading. Reference is made to two direct-to-consumer (DTC) Broadcast Advertisements for Fosamax (MISC-FOS-8PR98), submitted under cover of Form FDA 2253 on June 9, 1999. Reference is also made to a DTC Print Ad for Vioxx, appearing in the July 7, 1999, issue of the *El Nuevo Dia*. The publication of these materials by Merck & Company, Inc. (Merck) violates the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. DDMAC requests that the use of the above referenced material and those containing the same or similar violations cease immediately.

Reminder Advertisements

Reminder advertisements call attention to the name of the drug product, but may not contain written, printed, or graphic matter containing representations or suggestions relating to the advertised drug product.

Fosamax : Broadcast Ad-Script #3 "Women"

This advertisement in its entirety makes a representation or suggestion about Fosamax. The pictorial presentation of an active, menopausal or postmenopausal woman swimming coupled with the statements, "I don't feel I have changed and I certainly don't want my life to change" and "Discover Fosamax" makes a representation or suggestion about the use of Fosamax.

Vioxx : DTC Print Ad

This advertisement in its entirety makes a representation about Vioxx. The pictorial presentation of a hand (an X-ray image with superimposed red markings at the joints) makes a representation or suggestion about the use of Vioxx.

Therefore, DDMAC considers both advertisements to be full product ads and in violation of the Act for the following reasons:

- they fail to provide adequate information regarding the product's approved indication and usage,
- they fail to include risk information,
- they fail to present a brief summary of necessary information related to side effects, contraindications, and effectiveness, or provide adequate provision for the dissemination of full product labeling in connection with the broadcast ad.

Fosamax : Broadcast Ad-Script #2 "No title"

DDMAC considers this ad to be a product specific ad, because the advertisement in its entirety clearly identifies Fosamax. Although this ad does not mention Fosamax directly, the statement, "But there is a medication with the power to rebuild bones and reduce the risk of fractures" implicates only Fosamax as the drug with both of these particular effects. Therefore, DDMAC considers this advertisement to be a full product ad and in violation of the Act for the following reasons:

- it fails to provide the name (proprietary and established) of the drug,
- it fails to provide adequate information regarding Fosamax's approved indication and usage,
- it fails to include risk information,
- it fails to present a brief summary of necessary information related to side effects, contraindications, and effectiveness, or provide adequate provision for the dissemination of full product labeling in connection with the broadcast ad.

Merck should immediately cease using these and all other promotional materials for Fosamax and Vioxx that contain the same or similar claims or presentations. Merck should submit a written response to DDMAC, on or before July 30, 1999, describing its intent and plans to comply with the above. In its letter to DDMAC, Merck should include a list of all promotional materials that were discontinued, and the discontinuation date.

Merck should direct its response to the undersigned by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-40; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds Merck that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS#8086, NDA 20-560, and NDA 21-042.

Sincerely,

Michael A. Misocky R.Ph., J.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

United States Senate
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Exhibit 12

CONFIDENTIAL

DATE: October 4, 1999

TO: Drs. David Bjorkman, James Neaton, Deborah Shapiro, Alan Silman, Roger Sturrock

FROM: Dr. Michael Weinblatt

SUBJECT: Interim Analysis of VIGOR - Unblinded Minutes

On October 3, 1999, the Data Safety and Monitoring Board of VIGOR convened by teleconference to discuss the first interim analysis of the VIGOR trial. Attendees were Drs. David Bjorkman, James Neaton, Deborah Shapiro (non-voting), Alan Silman, Roger Sturrock and Michael Weinblatt. The committee decided that they did not wish to have the identity of treatment groups A and B revealed at this time.

The primary and secondary endpoint data were reviewed and it was noted that not all the criteria for early termination were met. At the request of Merck Clinical which had reviewed these cases in a blinded fashion, attention was drawn to three patients with complicated events. Two of these patients in Group A were likely protocol violators with very early events (one may have begun prior to randomization); the other in Group B with a GI bleed had a duodenal arteriovenous malformation.

It was noted that at least some patients appear to have been taking other NSAIDs or COX-2 inhibitors concomitantly with study drug and concern was raised regarding the degree of protocol violation present in the database. Dr. Shapiro informed the group that the database was not yet sufficiently up-to-date to employ the rules for determination of protocol violation. She will provide an update when it is possible. The group also commented that the primary approach is the All-Patients-Randomized where the protocol violators would be included.

The narratives for patients that died were reviewed. Members noted the occurrence of three possible GI deaths in Group A and one in Group B, and there was some surprise at this difference compared to the decreased relative risk for complicated events for Group A compared to Group B. It was noted that the deaths were few and therefore comparisons are difficult, but members wish to continue to track deaths as they accumulate. Note was also taken of several pulmonary deaths some of which may be related to methotrexate use.

The occurrence of 3 humeral and 3 hip fractures in Group A and none in Group B (serious adverse experiences) was noted. It was also noted that diarrhea led to 18 discontinuations in Group A and 8 in Group B; this could possibly relate to drug effects described in a recent paper.

In the current report, counts were provided separately for serious adverse experiences and for adverse experience leading to study discontinuation. A request was made that counts

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be provided for the combination, ie, for serious adverse experiences or events that lead to study discontinuation. These counts will be provided in the next report.

Members voted 5 to 0 to continue the trial as designed.

The possibility of conducting an additional formal interim analysis was discussed and the committee decided that that should not occur. No formal analyses of endpoints should take place until the final stopping rules are met, ie, 120 PUBs, 40 complicated PUBs, or 6 months after last patient in whichever comes last. Presently, it appears that these targets will be met in January, 2000.

The committee will meet on November 17, 1999 in Boston to discuss the next report which will have an update of non-endpoint safety along with some efficacy results. Drs. Bjorkman, Shapiro, Silman, and Weinblatt will be present in Boston while Drs. Neaton and Sturrock will phone in.

Michael Weinblatt, MD

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CONFIDENTIAL

DATE: November 18, 1999

TO: Drs. David Bjorkman, James Neaton, Deborah Shapiro, Alan Silman, Roger Sturrock

FROM: Dr. Michael Weinblatt

SUBJECT: Interim Non-Endpoint Safety Analysis of VIGOR - Unblinded Minutes

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On November 17, 1999, the Data Safety and Monitoring Board of VIGOR convened to discuss the interim non-endpoint safety analysis of the VIGOR trial. Attending in Boston were Drs. Deborah Shapiro (non-voting), Alan Silman, and Michael Weinblatt. Participating by phone were Drs. David Bjorkman, James Neaton, and Roger Sturrock.

The focus of the discussions were the excess deaths and cardiovascular adverse experiences (AEs) in Group A compared to Group B. At the time of the first interim report (with a cutoff of September 2, 1999) there were 11 deaths in Group A and 6 in Group B. In the present analysis (with a cutoff of November 1, 1999), there were 5 additional deaths all in Group A. Of these 5 deaths, 4 were due to cardiovascular causes.

In the first report, there were 36 and 16 patients with serious cardiovascular AEs in Groups A and B, respectively, while in this analysis there were 52 and 29, respectively. Therefore an additional 16 and 13 patients in Groups A and B, respectively, have had serious cardiovascular AEs since the previous report.

In the first report, there were 32 and 17 patients with cardiovascular AEs that led to discontinuation in Groups A and B, respectively, while in this analysis there were 40 and 17, respectively. Therefore an additional 8 patients all in Group A discontinued due to cardiovascular AEs since the previous report. Please note that discontinuation information is not as current as the serious AE and death data.

The increase in systolic blood pressure in Group A (mean/median increase 4.0/2.5 mmHg) compared to little or no change in Group B was noted as was the increased occurrence of hypertension AEs in Group A.

Dr. Neaton had suggested several additional analyses that were performed prior to the meeting (these are attached for the benefit of the members attending by teleconference). A Cox model examined the occurrence of death, death or serious cardiovascular AE, and death or serious cardiovascular AE or cardiovascular AE leading to discontinuation. These were examined in the entire population and in those patients with a cardiovascular system secondary diagnosis (co-morbidity). The differences between the treatment groups were noted as being significant beyond the level of chance. However, it was also noted that there is no ability in this trial to distinguish between a potentially harmful effect of Treatment A and a cardiovascular protective effect of Treatment B due to its

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anti-platelet effects. It was also noted that while the trends are disconcerting, the numbers of events are small.

Members were concerned and want to follow up on these data more thoroughly and frequently but did not believe that the trial should be stopped at this time. It was decided that an additional non-endpoint safety analysis will be performed using a December 1 cutoff. The report will be sent to members during the week of December 13 and discussed at a teleconference on December 20, 1999 at 4:00 p.m. EST. The report will focus on deaths and cardiovascular AEs and will consist of counts tables and survival analyses (Cox model) with plots of the three outcomes suggested by Dr. Neaton above. These will be performed on the overall population and on several subgroups, ie, patients with and without cardiovascular system co-morbidities, with and without more significant cardiovascular system co-morbidities (as defined by Alise Reicin for another purpose) and those with and without hypertension as a co-morbidity. Since members cannot retain the previous reports, the prior incidences will be quoted for reference.

Michael Weinblatt, MD

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DATE: December 22, 1999

TO: Drs. David Bjorkman, James Neaton, Deborah Shapiro, Alan Silman, Roger Sturrock

FROM: Dr. Michael Weinblatt

SUBJECT: Cardiovascular Safety Analysis of VIGOR - Unblinded Minutes

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On December 20, 1999, the Data Safety and Monitoring Board of VIGOR convened by teleconference to discuss the interim cardiovascular safety analysis update for the VIGOR trial. Attendees were Drs. David Bjorkman, James Neaton, Deborah Shapiro (non-voting), Alan Silman, Roger Sturrock and Michael Weinblatt.

The purpose of this additional analysis was to update the experiences with deaths and cardiovascular adverse experiences. The members noted that the trends previously observed continued at this update. Examination of subgroup results showed the expected higher rate of events in higher risk patients in both treatment groups, very similar relative risks in all the groups examined, and consequently greater excess risks in the higher risk patients. Curiosity was expressed on the relationship of age with the analyzed events. Tables 1 to 3 attached shows the previous subgroup results along with two additional subgroups, age<70 and age≥70 years. Again, the differential treatment effect was similar for all subgroups, ie, none of the treatment by subgroup interaction effects were significant.

None of the members believed that the trial should be stopped based on these results and members expressed the belief that the differences may be due to a cardioprotective effect of Treatment B. However, all members believed that these results are important in evaluating the risks and benefits of Treatment A. Interest focused on the analysis plan for the serious vascular events. Dr. Shapiro explained that certain serious vascular events were being adjudicated in a blinded fashion by an committee external both to Merck and to the VIGOR trial. They are adjudicating events in VIGOR and all other VIOXX® studies. While the VIGOR Data Analysis Plan states that a data analysis plan would be developed for these events in both VIGOR and the VIOXX® program as a whole, this has not yet taken place. The DSMB agreed that it is important that this analysis plan be developed before the plan's authors are unblinded to the cardiovascular results. In order to accomplish this goal, Drs. Weinblatt and Shapiro drafted a letter (attached) addressed to Dr. Alise Reicin.

Members did not feel it appropriate to bring this issue to the Advisory Committee since we are not recommending a change to the trial conduct, simply that a prespecified plan be accomplished. Also since the vascular adjudication committee is not specific to VIGOR, this request seems to be outside the purview of the VIGOR Advisory Committee. *Post*

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Meeting Note: The letter was provided to Drs. Reicin and Capizzi on December 21, 1999. Dr. Reicin provided assurance that a plan will be developed before unblinding.

The Board next discussed concerns regarding the eventual publication of VIGOR results. It will be important that any report on gastrointestinal protection include a discussion of the cardiovascular results. After study unblinding, one or more members of the DSMB may be invited to join the Publications Committee. A letter may be written to the Executive Committee after unblinding noting the need for their careful review of the cardiovascular events. Dr. Shapiro will update the Board when such unblindings will take place.

Michael Weinblatt, MD

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Table 1
Summary of Analysis of Death

Subgroup	Trmt	N	Cases	PYR[1]	Rates[2]	Proportionality Assumption p-value	Relative Risk[3]		
							Estimate	95% CI	p-value
Overall	A	4051	17	2083	0.82	0.717	1.88	(0.84, 4.21)	0.127
	B	4031	9	2067	0.44				
History of any CVD	A	1856	12	948	1.27	0.778	2.91	(0.94, 9.01)	0.065
	B	1809	4	916	0.44				
No history of any CVD	A	2195	5	1135	0.44	.	1.01	(0.23, 4.41)	0.982
	B	2222	5	1151	0.43				
History of significant CVD	A	187	1	91	1.09	.	0.46	(0.01, 8.74)	0.498
	B	166	2	83	2.40				
No history of significant CVD	A	3864	16	1991	0.80	0.791	2.28	(0.94, 5.54)	0.069
	B	3865	7	1984	0.35				
History of Hypertension	A	1187	8	601	1.33	0.657	1.92	(0.58, 6.38)	0.287
	B	1138	4	573	0.70				
No history of any Hypertension	A	2864	9	1482	0.61	0.984	1.82	(0.61, 5.42)	0.285
	B	2893	5	1494	0.33				
Age 70+ years	A	508	6	247	2.43	.	1.56	(0.37, 7.53)	0.487
	B	546	4	257	1.56				
Age < 70 years	A	3543	11	1836	0.60	0.578	2.17	(0.75, 6.25)	0.151
	B	3485	5	1810	0.28				

[1]Patient-years at risk
[2]Per 100 PYR
[3]Relative risk of Treatment A with respect to Treatment B from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates and p-value is from discrete logrank distribution.

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Table 2

Summary of Analysis of Death or Serious Cardiovascular Adverse Events

Subgroup	Trmt	N	Cases	PYR[1]	Rates[2]	Proportionality Assumption p-value	Relative Risk[3]		
							Estimate	95% CI	p-value
Overall	A	4051	73	2076	3.52	0.304	2.07	(1.39, 3.10)	<0.001
	B	4031	35	2063	1.70				
History of any CVD	A	1856	51	943	5.41	0.484	2.06	(1.27, 3.35)	0.003
	B	1809	24	913	2.63				
No history of any CVD	A	2195	22	1133	1.94	0.341	2.03	(0.99, 4.19)	0.055
	B	2222	11	1150	0.96				
History of significant CVD	A	187	17	90	18.94	0.704	2.24	(0.93, 5.41)	0.072
	B	166	7	83	8.48				
No history of significant CVD	A	3864	56	1986	2.82	0.319	2.00	(1.27, 3.14)	0.003
	B	3865	28	1981	1.41				
History of Hypertension	A	1187	33	597	5.52	0.439	2.26	(1.21, 4.22)	0.011
	B	1138	14	572	2.45				
No history of any hypertension	A	2864	40	1479	2.70	0.522	1.92	(1.13, 3.26)	0.015
	B	2893	21	1492	1.41				
Age 70+ years	A	508	21	245	8.57	0.667	1.83	(0.90, 3.72)	0.095
	B	546	12	256	4.69				
Age < 70 years	A	3543	52	1831	2.84	0.171	2.23	(1.37, 3.65)	0.001
	B	3485	23	1807	1.27				

[1]Patient-years at risk
[2]Per 100 PYR
[3]Relative risk of Treatment A with respect to Treatment B from unstratified Cox model.

LEH 0114745

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Table 3
Summary of Analysis of Death or Serious Cardiovascular Adverse Events
or Cardiovascular Adverse Events Leading to Discontinuation

Subgroup	Trmt	N	Cases	PYR[1]	Rates[2]	Proportionality Assumption p-value	Relative Risk[3]		
							Estimate	95% CI	p-value
Overall	A	4051	100	2074	4.82	0.937	2.43	(1.69, 3.49)	<0.001
	B	4031	41	2063	1.99				
History of any CVD	A	1856	67	942	7.11	0.864	2.33	(1.50, 3.62)	<0.001
	B	1809	28	913	3.07				
No history of any CVD	A	2195	33	1132	2.91	0.914	2.58	(1.36, 4.90)	0.004
	B	2222	13	1150	1.13				
History of significant CVD	A	187	19	90	21.19	0.903	2.19	(0.96, 5.01)	0.062
	B	166	8	82	9.70				
No history of significant CVD	A	3864	81	1985	4.08	0.920	2.45	(1.64, 3.68)	<0.001
	B	3865	33	1981	1.67				
History of Hypertension	A	1187	44	596	7.38	0.771	2.64	(1.49, 4.68)	<0.001
	B	1138	16	572	2.80				
No history of any Hypertension	A	2864	56	1478	3.79	0.883	2.26	(1.41, 3.63)	<0.001
	B	2893	25	1492	1.68				
Age 70+ years	A	508	28	245	11.45	0.305	2.46	(1.25, 4.83)	0.009
	B	546	12	256	4.69				
Age < 70 years	A	3543	72	1830	3.94	0.701	2.45	(1.59, 3.77)	<0.001
	B	3485	29	1807	1.60				

[1]Patient-years at risk
[2]Per 100 PYR
[3]Relative risk of Treatment A with respect to Treatment B from unstratified Cox model.

Michael E. Weinblatt, M.D.
Director of Clinical Rheumatology
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115

December 20, 1999

Alise Reicin, M.D.
Director, Clinical Research
Merck Research Laboratories
P.O. Box 2000, RY33-656
Rahway, NJ 07065

Dear Dr. Reicin:

We are aware that the VIGOR trial is in its final stages. We are also aware that there is an adjudication committee reviewing serious vascular adverse experiences in the entire VIOXX® program. Due to the interest about COX 2 inhibitors and their potential role in vascular events, we recommend that an analysis plan be developed to analyze adjudicated serious vascular events in the VIGOR trial separately from any other planned analyses of these data. It will important that these events be adjudicated blinded.

Sincerely yours,

Michael Weinblatt, M.D.

cc: Deborah Shapiro, Thomas Capizzi

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 13

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 16 1999

TRANSMITTED VIA FACSIMILE

Ellen R. Westrick
Executive Director
Office of Medical/Legal
Merck & Co., Inc.
P.O. Box, WP37C-116
West Point, PA 19486

RE: **NDA 21-042**
Vioxx (rofecoxib) tablets
MACMIS ID #8410, 8506

Dear Ms. Westrick:

Reference is made to Merck & Co., Inc.'s (Merck) letters, dated November 30, 1999, and December 15, 1999, in response to letters from the Division of Drug Marketing, Advertising, and Communications (DDMAC) dated, November 12, 1999, and December 1, 1999. Our letters concerned the alleged dissemination of two "homemade" promotional pieces, entitled "TEN REASONS WHY VIOXX IS BETTER THAN CELEBREX," and "Vioxx vs. Celebrex Poem" distributed by or on behalf of Merck, that promoted Vioxx (rofecoxib) capsules in violation of the Federal Food, Drug and Cosmetic Act (Act) and its regulations. DDMAC requested that Merck investigate the extent to which these "homemade" pieces were used to promote Vioxx, and the number of health care professionals who received these pieces.

In your letter, you described that in both cases one sales representative distributed these "homemade" pieces in their respective geographic regions. Your letter also described Merck's policy for prohibiting dissemination of homemade materials by your sales force, and specified the corrective actions taken to ensure that this activity will not continue.

We have reviewed these promotional pieces and have determined that they are false or misleading because they contain misrepresentations of Vioxx's safety profile, unsubstantiated comparative claims, and are lacking in fair balance.

Misrepresentation of Safety Information

- You present claims that misrepresent the safety profile for Vioxx, including but not limited to, "VIOXX HAS ENDOSCOPY STUDIES SHOWING A SAFER THAN PLACEBO INCIDENCE RATE OF GASTRODUODENAL ULCERS." However, this claim is in direct contrast with the approved product labeling (PI) that states, "...the studies cannot rule out at

least some increase in the rate of endoscopic gastroduodenal ulcers when comparing Vioxx to placebo." Furthermore, this claim suggests that Vioxx is safer than placebo in regards to clinically significant gastroduodenal events. However, the PI states, "The correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established." Moreover, this claim minimizes the warning in the PI that states, "Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms...," and omits material fact in the PI which states, "Serious clinically significant upper GI bleeding has been observed in patients receiving VIOXX in controlled trials...." Therefore, we object to this claim because it minimizes the GI warning associated with Vioxx and is inconsistent with the data in the PI.

Unsubstantiated Comparative Claims

Promotional materials are false or misleading if they contain representations or suggestions that a drug's safety or effectiveness is comparable or superior to another drug when such has not been demonstrated by substantial evidence. Some examples of misleading comparative claims in your "homemade" promotional pieces include:

- In the Vioxx vs. Celebrex Poem you claim, "Your patients in pain – they give you their grief; A Cox-II is the answer for their pain relief." This claim makes a broad superiority claim comparing Vioxx to not only the class of NSAIDs, of which it is a member, but to all analgesic and anti-inflammatory therapies available for the management of pain. However, this global superiority claim has not been demonstrated by substantial evidence, and therefore, is false or misleading. Moreover, PI states that Vioxx is indicated, "For the management of acute pain in adults." (emphasis added). Therefore, this claim lacks important contextual information concerning Vioxx's approved indication, and consequently, is misleading.

- You also presents several unsubstantiated comparative claims to Celebrex (celecoxib), including but not limited to, "Vioxx of course – the answer again, It's stronger, lasts longer, is faster, and then its safer...." This claim suggests Vioxx is more efficacious and has a superior safety profile compared to Celebrex, when such has not been demonstrated by substantial evidence. Therefore, this unsubstantiated comparative claim is misleading.

Fair Balance

Overall, Merck's "homemade" promotional pieces are lacking in fair balance with respect to the content and presentation of risk information related to the use of Vioxx. In general, promotional materials must present information about the risks associated with the use of a drug with a prominence and readability reasonably comparable to that of claims for the drug.

- Although these pieces contain numerous claims for the efficacy and safety of Vioxx, you have not presented any risk information concerning the contraindications, warnings,

precautions, or adverse events associated with Vioxx's use. (emphasis added). Therefore, we consider these promotional pieces to be lacking in fair balance. Furthermore, these promotional pieces are in violation of the Act because the approved product labeling for Vioxx did not accompany them.

In addition, promotional materials must be submitted to the FDA, under Form FDA 2253, at the time of initial dissemination. However, our records indicate these promotional materials were not submitted at the time of initial use. This failure to submit promotional materials at the time of initial dissemination is in violation of the Act.

We have reviewed your response and actions taken in response to the dissemination of this violative promotional piece. We do not wish to comment your internal processes, however we do acknowledge your investigation and the corrective actions taken to prevent reoccurrence of this type of violative promotional activity. At this time, we have no further questions and consider this matter closed.

If you have any further questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or by written communication at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to the MACMIS # 8506 and 8410, in addition to the NDA number.

Sincerely,

/S/

Spencer Salis, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 14

respectively.

Elliot

From: Gresser, Michael
Sent: Sunday, January 09, 2000 9:02 PM
To: Ehrich, Elliot W.
Cc: Robertson, George; Turner, Mervyn
Subject: stroke outcomes

Hi Elliott,
Will the VIGOR study have the potential to provide any information regarding stroke outcomes? I guess I would not expect patients on Vioxx to have a lower incidence of stroke(actually if our worst fears concerning the prostacyclin business have any foundation in reality they could have a higher incidence, but let's put that aside for purposes of this query), but there is a chance that they might come out of the experience in better shape than patients who were not on Vioxx or NSAID therapy at the time of the event (the NSAID part is a complicating factor, because of the antithrombotic effect of Cox-1 inhibition, so that would have to be taken into account). I suppose one would have to obtain data from a similar population of patients not on Cox inhibitors. If enough strokes occurred in both groups, one might be able to detect a statistically significant difference in extent of impairment between the two groups. George Robertson was telling me about some recent reports on the effect of Cox inhibitors on ischemic injury, and I wondered whether one could tease anything out of some of the trials which are ongoing or already finished.
Best regards,
Mike

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 15

To: Shapiro, Deborah R.
From: Scolnick, Edward M.
Cc
Bcc:
Date: 2000-02-11 13:05:57
Subject: Talk

Deborah Please read this story. It is my understanding that you are the unblinded statistician in our Vigor study. In the last few days we are being pounded by stories like this. As with the key issue with aggrastat when Snappin and i had to make a decision as soon as you know what the answer is I would like a confidential meeting with you. This situation cannot simply follow the " book " ways of my knowing. Please let me know when I can talk to you confidentially. You can reach me when this time comes at work at home [redacted] by voice mail(private) or anywhere by email-I am the only one who isitens to my voice mail or email, Thanks I hope your lucky rabbit's foot is as good as it was with mevacor afcaps/ Ed scolnick

MTC's SEARLE: RECAPTURING MOMENTUM IN COX-2 INHIBITOR MARKET Part 1

07:09am EST 11-Feb-00 Salomon Smith Barney (HEUER 212-816-0232) MTC PNU PFE MRK

--SUMMARY:--Monsanto--Ag Biotech/Fertilizers

--EARNINGS PER SHARE----------

	FYE	1 Qtr	2 Qtr	3 Qtr	4 Qtr	Year
Actual	12/98 EPS	$0.32A	$0.43A	$0.13A	$0.05A	$0.93A
Previous	12/99 EPS	$0.20A	$0.53A	$0.09A	$0.18E	$1.00E
Current	12/99 EPS	$0.20A	$0.53A	$0.09A	$0.18A	$1.00A
Previous	12/00 EPS	$N/A	$N/A	$N/A	$N/A	$1.28E
Current	12/00 EPS	$N/A	$N/A	$N/A	$N/A	$1.28E
Previous	12/01 EPS	$N/A	$N/A	$N/A	$N/A	$1.70E
Current	12/01 EPS	$N/A	$N/A	$N/A	$N/A	$1.70E

Footnotes:

--FUNDAMENTALS----------

Current Rank.....:2H Prior:No Change Price (02/10/00).....:$41.25
P/E Ratio 12/99.....:41.3x Target Price...:$48.00 Prior:No Change
P/E Ratio 12/00.....:32.2x Proj.5yr EPS Grth....:20.0%
Return on Eqty 98....:N/A% Book Value/Shr(99)...:8.29
LT Debt-to-Capital(a)49.1% Dividend(99).....:$.12
Revenue (99).....:10743.00mil Yield.....:0.3%
Shares Outstanding...:648.1mil Convertible.....:No
Mkt. Capitalization.:26734.1mil Hedge Clause(s).....:#
Comments.....:(a) Data as of the most recently reported quarter.
Comments.....:

--OPINION----------

COX-2 INHIBITORS

In the red hot battle in the COX-2 inhibitor market, MRK's Vioxx stunned MTC (and marketing partner Pfizer) during the 2H99 after a May launch that was not nearly as spectacular as that of Celebrex. MRK's Vioxx steadily increased its share of U.S. COX-2 new prescriptions to 46% by year-end 1999. Vioxx beat MTC/PFE's Celebrex to a pain indication in the U.S.; Vioxx was the first COX-2 to be approved in Europe; and MRK drastically narrowed the gap between the sales of the two COX-2s overseas.

In 2000, we expect the momentum to shift back to MTC/PFE. We expect MTC to beat MRK with GI outcomes data expected to definitively demonstrate the superior GI profile of Celebrex vs NSAID and to secure FDA removal of the current NSAID GI warning on the label of Celebrex. MTC appears to be about six months ahead of MRK in achieving this very important label upgrade. We also expect MTC to beat MRK to market with the 2nd-generation COX-2s. MTC should launch injectable parecoxib and oral valdecoxib (that will be co-promoted with PFE) in late 2001 (NDA submission late 2000E); they should be a powerful combo for pain. (Oral valdecoxib also will be indicated for osteo-arthritis and RA; parecoxib is a pro-drug of valdecoxib.) We think the injectable paracoxib + oral valdecoxib combination can be a powerful duo for pain -- as was injectable and oral Toradol in the early 1990s before severe GI side effects crashed its sales.

	-- Sales, 1999 ($MM) --				
	1Q99	2Q99	3Q99	4Q99	Year
Celebrex US	279	294	363	454	1,390
Vioxx US	--	92	97	231	420
Celebrex Fx	--	24	34	52	110
Vioxx Fx	--	5	14	33	52
Celebrex WW	279	318	397	506	1,500
Vioxx WW	--	97	111	264	472

Vioxx Excels in 2H99
In the hot contest with Merck in the COX-2 inhibitor market, MRK's rofecoxib (VIOXX) unexpectedly excelled in the 2H99 by steadily taking U.S. market share of new presciptions away from MTC/PFE's celecoxib (CELEBREX). MRK surprised MTC by aggressively marketing Vioxx against Celebrex instead of against NSAIDs, and MRK initiated head-to-head clinical trials of Vioxx vs. Celebrex. MRK capitalized on Vioxx's faster onset of action vs. Celebrex (which produced a statistical advantage in efficacy in a head-to-head trial in dental pain). MRK (which is the largest US drug company in Europe) outmaneuvered MTC in Europe and won the first COX-2 approval. Both drugs used the mutual recognition process for approval in Europe: Vioxx was the first to be approved in June 1999 in the U.K.; Celebrex was approved in Dec 1999 in Sweden. But MRK paid a price for rushing by only getting an indication for osteoarthritis (OA) in Europe: Celebrex got indications for both osteoarthritis (OA) and rheumatorid arthritis (RA).

Vioxx is close in units, not cash sales
Vioxx is close to achieving half of new COX-2 scrips but far beind in achieving half of cash sales. A Celebrex new prescription generates much more cash than a Vioxx scrip due to Celebrex's rheumatoid arthritis (RA) claim (which Vioxx does not have) that generates more days of therapy at higher doses and more refills. Vioxx has a pain claim (that Celebrex

does not have), but Vioxx is taken for only 5 days for pain.

	Celebrex	Vioxx	
Days/scrip	32.0	29.2	+10%
Dollars/scrip	$82.31	$70.42	+17%
Refill/new ratio	2.07	1.64	+26%
$ value/new scrip	$170.38	$115.48	+48%

Celebrex Recaptures Momentum in 2000
Now the stage appears to be set for the momentum to shift back toward Celebrex in 2000. Based on the latest data available (week ended January 20) Celebrex had 54.1% of new scrips vs. 45.9% for Vioxx. In that week, the Celebrex market share of new scrips upticked by 0.1% -- the first uptick in share for Celebrex in a long time. Is this the beginning of a new trend?

Factors behind the improved Celebrex performance: (1) In January direct-to-consumer (DTC) advertising began for the brand Celebrex. (2) On February 1, promotion began for the new indication for Celebrex approved by FDA in late December: familial adenomatous polyposis (FAP) -- a rare form of colorectal cancer. Celebrex reduces the formation of polyps in the colon that can become become malignant -- creating colon cancer. The FAP dose for Celebrex at 800 mg/day is four times higher than the most popular dose for OA (200 mg) -- thereby reinforcing the very clean side-effect profile of the drug.

Now MTC/PFE seems to have at least a chance of preventing MRK's Vioxx from achieving more than a 50% share of all new scrips for COX-2s in the U.S. market -- a psychologically damaging event for MTC/PFE.

GI Outcome Studies & Removal of NSAID GI warning: The next growth surge for the COX-2s could come after the large scale GI outcomes studies are completed, and the results are presented and published. Both MTC and MRK are conducting trials that are designed to show an endoscopically

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BROKER: Salomon Smith Barney

:TICKER: MTC PNU PFE MRK PNU.XX PFE.XX MRK.XX

:SUBJECT: DRUG BIOT CHEM EARN USA

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Received by NewsEdge Insight: 02/11/2000 07:06:06

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 16

To: Distlerath, Linda; Slater, Eve; Frazier, Kenneth C.; Weiner, Jan D.; Basaman, Mary E.; Hirsch, Laurence J.
From: Reicin, Alise S.
Cc
Bcc:
Date: 2000-03-26 14:19:50
Subject: RE: VIGOR MATERIALS

---

1)I think you are correct that mainly we have seen an increase in the thrombotic events. DVTs do look increased on rofecoxib but I think of DVTs as thrombotic as well (venous instead of arterial) Remember however, it was a combined analysis. We have not looked at the CVAs in enough detail for me to be able to tell you if they were embolic or thrombotic but my general overview is that most were not embolic.

[redacted]

Alise

From: Hirsch, Laurence J.
Sent: Sunday, March 26, 2000 8:45 AM
To: Reicin, Alise S.; Distlerath, Linda; Slater, Eve; Frazier, Kenneth C.; Weiner, Jan D.; Basaman, Mary E.
Subject: FW: VIGOR MATERIALS
Importance: High
Sensitivity: Confidential

Per Brian's earlier email on the Q&A, he made a strong point about the fact that VIGOR had an average F/U of 9 months, and this probably explains why we detected the cardio protective effect. Do we want to add a sentence to the Key message about T/E events speaking to that? I realize it wasn't in the release, but it does help answer the question "why did you see this?" See the attached.

Alise, there are two things we still have questions about.
1. Were there really differences in thromboembolic events, or just thrombotic ones? What I saw in your presentation looked like MIs and CVAs but NOT DVTs or PEs were different between the two groups? THe difference in these two terms is important, I think.

[redacted]

Let's discuss this at 9:30. Thnx
Larry Hirsch, MD
MRL Public Affairs
WS 1A-13 (mail stop 1A-28)
Phone 908-423-4650
Fax 908-735-1191

From: Reicin, Alise S.
Sent: Saturday, March 25, 2000 10:00 PM
To: Slater, Eve; Distlerath, Linda; Basaman, Mary E.; Hirsch, Laurence J.
Subject: FW: VIGOR MATERIALS
Importance: High
Sensitivity: Confidential

I made some comments and suggested revisions on the Q&A document.

Alise

From: Basaman, Mary E.
Sent: Saturday, March 25, 2000 8:39 PM
To: Slater, Eve; Reicin, Alise S.; Frazier, Kenneth C.
Cc: Distlerath, Linda; Hirsch, Laurence J.; Weiner, Jan D.; Kaufman, Art; Reaves, Gregory; Skidmore, Janet; Jordan, Laura J.
Subject: VIGOR MATERIALS
Importance: High
Sensitivity: Confidential

Attached are:
* the final news release
* the key messages
* the Q&A.

[redacted]

<<File: news release.doc>><<File: KEY MESSAGES REVISED.doc>><<File: VIGOR Q&A.doc>>

Mary Elizabeth

Mary Elizabeth Basaman
USHH Public Affairs
Phone: (215) 652-5244
Fax: (215) 652-4283
mary_basaman@merck.com
Assistant: Deb Wambold, 652-7486

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 17

To: Gertz, Barry J.
From: Nies, Alan S.
Cc
Bcc:
Date: 2000-03-28 20:13:38
Subject: FW: Carlo Patrono on VIGOR

I think we should talk directly to Carlo. I presume he heard from Garret (confidentiality agreement???).
Alan

From: Reicin, Alise S.
Sent: Tuesday, March 28, 2000 2:54 PM
To: Nies, Alan S.; Gertz, Barry J.
Cc: Ehrich, Elliot W.; Daniels, Brian F.; Scolnick, Edward M.; Slater, Eve; Blois, David W.
Subject: FW: Carlo Patrono on VIGOR

I have attached a message from Martino re his discussions with Carlo Petrono. I think it would be worth walking through the data with Carlo. Do you think we should try and set up a teleconference?
Alise

From: Laurenzi, Martino
Sent: Tuesday, March 28, 2000 2:10 PM
To: Daniels, Brian F.; Ehrich, Elliot W.; Reicin, Alise S.
Cc: Chakhov, Iouri; de Jesus, Daniel G.; Guerra, Jorge G.; Hormbrey, Janet; Kylish, Gregory S.; McKinney, Errol S.; Moan, Andreas; Ruef, Tim; Salib, Atif; Schwartz, Jules; Yrivarren, Juan Luis
Subject: Carlo Patrono on VIGOR

Guys,

I met with Carlo Patrono last Saturday in Rome. He had already been informed by other sources about the results of VIGOR, and we had an interesting chat about it.

He said that he does not think that the CV effect that we observed can be attributed to naproxen for a couple of good reasons. First there is a weak pharmacological basis and no epidemiological evidence (Garcia Rodriguez & Patrono, Epidemiology, in press) for CV protection associated with conventional NSAIDs. Additionally the magnitude of the effect would not be plausible even if the comparator had been aspirin itself. In fact, in at least three different trials, aspirin has shown no effect on the primary prevention of stroke, while we have seen a 50% lower incidence of stroke in the naproxen arm of VIGOR; additionally, we have an overall reduction of the risk of CV events of 47% with naproxen, while aspirin has shown a reduction of cumulative CV risk of a magnitude between 15 and 18%. Aspirin data come from a primary prevention setting (similar to VIGOR) and include the Physicians Health Study, the Thrombosis Prevention Trial (Lancet 1998) and the Hypertension Optimal Treatment Trial (Lancet 1998).
Carlo also does not think that the CV effect can be explained by the inhibition of prostacyclin given that VIOXX inhibits only the COX-2 component of prostacyclin secretion, and he has conceptual difficulties in explaining how this could translate in an increase of the CV risk of the magnitude that we observed. His conclusion is that what we saw in VIGOR is to be attributed to a large extent to chance. He is curious about the 95% confidence interval around the 47% reduction in CV risk. He also pointed out that in CV disease DVT (deep venous thrombosis) is considered as a soft end-point which usually is not included in this type of analysis. He suggested that we carry out an analysis limited to nonfatal MI, nonfatal stroke and vascular death, i.e. the cluster typically used in the studies on platelet aggregation.

Food for thought, coming from the world's most respected and knowledgeable gourmet.

Best regards,

Martino Laurenzi
CROPS
(732) 594-2785
fax 594-6670
RY 33-318

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 18

To: Shapiro, Deborah R.; Scolnick, Edward M.
From: Reicin, Alise S.
Cc
Bcc:
Date: 2000-04-03 04:30:10
Subject: RE: Update to thromboembolic CVD cases VIGOR

One other piece of info to remember
In the Advantage study the rate of "thromboembolic" SAEs was identical in the two treatment groups. But there were 7 MIs in Treatment A and 1 MI in Treatment B and for CVAs there were 0 in treatment A and 4 in treatment B. The numbers are quite small and the adjudication of these events will be important, but it will be important to see which arm had the 7 MIs. LPO has been achieved for the study and they are cleaning the database now.
Alise

From: Scolnick, Edward M.
Sent: Saturday, April 01, 2000 9:01 AM
To: Shapiro, Deborah R.
Cc: Reicin, Alise S.
Subject: RE: Update to thromboembolic CVD cases VIGOR

Deborah This is really interesting. In fact the results are NOT surprising. All the low dose aspirin data says that low dose aspirin had beneficial effects on MIs but hardly clear on cerebral events. This data is perfectly in line with that. The prostacyclin /thromboxane hypothesis is further strengthened by this data.whether naproxen lowers in RA patients is the issue. Only more work will clarify this aspect/ Ed Scolnick

---

From: Shapiro, Deborah R.
Sent: Friday, March 31, 2000 12:26 PM
To: Slater, Eve; Nies, Alan S.; Scolnick, Edward M.; Reines, Scott A.; Gruer, Peter JK; Barr, Eliav; Williams, George (U.S.); Bain, Raymond P.; Oppenheimer, Leonard; Guess, Harry; Gertz, Barry J.; Daniels, Brian F.; Hostelley, Linda S; Reicin, Alise S.
Subject: RE: Update to thromboembolic CVD cases VIGOR

The breakout is below. The results are somewhat surprising. I'll work on a table that shows all adjudicated events by type of event. The adjudicated categories are:
Acute MI
Unstable angina pectoris
Sudden and/or unexplained death
Resuscitated cardiac arrest
Cardiac thrombus
Pulmonary embolism
Peripheral arterial thrombosis
Peripheral venous thrombosis
Ischemic CVA stroke with documentation
Ischemic CVA stroke w/o documentation
Cerebrovascular venous thrombosis
Transient ischemic attack

Adjudicated MIs in Vigor

TRMT	Frequency	Percent
Rofecoxib	16	80.0

Naproxen 4 20.0

Adjudicated CVAs in Vigor

TRMT	Frequency	Percent
Rofecoxib	6	46.2
Naproxen	7	53.8

Deborah
Dr. Deborah Shapiro
Director, Clinical Biostatistics
RY33-404
Phone: (732) 594-5612
Fax: (732) 594-6075

From: Reicin, Alise S.
Sent: Friday, March 31, 2000 11:57 AM
To: Slater, Eve; Nies, Alan S.; Scolnick, Edward M.; Reines, Scott A.; Gruer, Peter JK; Barr, Eliav; Williams, George (U.S.); Bain, Raymond P.; Oppenheimer, Leonard; Guess, Harry; Gertz, Barry J.; Daniels, Brian F.; Hostelley, Linda S; Shapiro, Deborah R.
Subject: RE: Update to thromboembolic CVD cases VIGOR

Deborah
How many MIs and CVAs in each group?
alise

From: Shapiro, Deborah R.
Sent: Friday, March 31, 2000 11:48 AM
To: Slater, Eve; Nies, Alan S.; Reicin, Alise S.; Scolnick, Edward M.; Reines, Scott A.; Gruer, Peter JK; Barr, Eliav; Williams, George (U.S.); Bain, Raymond P.; Oppenheimer, Leonard; Guess, Harry; Gertz, Barry J.; Daniels, Brian F.; Hostelley, Linda S
Subject: Update to thromboembolic CVD cases VIGOR
Importance: High

<<File: cvdadj.rtf.doc>>
Attached please find the updated results on the adjudicated thromboembolic events. There were 52 events in 50 patients. Let me know if you have any questions.
Deborah
Dr. Deborah Shapiro
Director, Clinical Biostatistics
RY33-404
Phone: (732) 594-5612
Fax: (732) 594-6075

From: Guess, Harry
Sent: Thursday, March 30, 2000 6:23 PM
To: Blois, David W.; Slater, Eve; Barr, Eliav; Shapiro, Deborah R.; Oppenheimer, Leonard; Reines, Scott A.; Reicin, Alise S.; Daniels, Brian F.; Bain, Raymond P.; Williams, George (U.S.); Hostelley, Linda S; Nies, Alan S.
Cc: Santanello, Nancy C.; Nelsen, Linda M.; Watson, Douglas J.; Holmes, Richard
Subject: FW: Vascular Event Adjudication Status
Importance: High

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
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Exhibit 19

V. Marketing Update

The preliminary VIGOR results offer further support to differentiate VIOXX® and the Coxibs as a new class, superior to traditional NSAIDs, based on long-term, endpoint driven, GI outcomes data. Marketing plans to use this data to achieve the following objectives: (1) continued broad reimbursement of VIOXX® by government authorities and managed care organizations, (2) expedited publication in a quality journal, and (3) modification of the NSAID GI warning in the US and addition of the data in ex-US labels. By demonstrating a significant reduction in the incidence of serious GI adverse events, these data support the Marketing strategy of displacing traditional NSAIDs as an acceptable treatment choice for chronic use.

The finding that naproxen was associated with a reduced incidence of serious thromboembolic adverse experiences compared to VIOXX® requires clear and consistent communication in order to be appropriately managed. The proactive communication of these findings, both internally and externally with investigators and opinion leaders has been well accepted. While initial press reports have been positive, a strong competitive response from Searle/Pfizer and other NSAID manufacturers is expected. Specific messages from Searle/Pfizer are expected in an attempt to convince the medical community that: (1) the cardiovascular findings in VIGOR can not be explained as a cardioprotective effect of naproxen, but are a result of a negative cardiovascular effect specific to the VIOXX® molecule (no class effect), (2) VIOXX® does not have an RA indication because of dose-dependent increases in side-effects, particularly cardiovascular and renal side-effects at the 50 mg dose, and (3) VIOXX®, unlike celecoxib, is not proven to be safe when given concomitantly with low-dose aspirin.

The following are the Marketing needs:

Secure a label statement that "VIOXX® can be used with low-dose aspirin"
There is an urgent Marketing need to obtain a label statement describing the ability to use VIOXX with low dose aspirin, similar to the wording in the current Celebrex label. As discussed in Section II of this background document, plans are to file three additional MRL and CDP studies (protocols 058, 085 and 090) with the VIGOR study to support this label change.

Rapid publication and communication at opinion leader events of phase III OA results demonstrating comparable incidence of thromboembolic events with VIOXX®, placebo, and NSAID comparators
The existing phase III data for VIOXX® is being evaluated and supports the explanation that the cardiovascular event rates from VIGOR represent a positive effect for naproxen and not a negative effect for VIOXX® 50mg.

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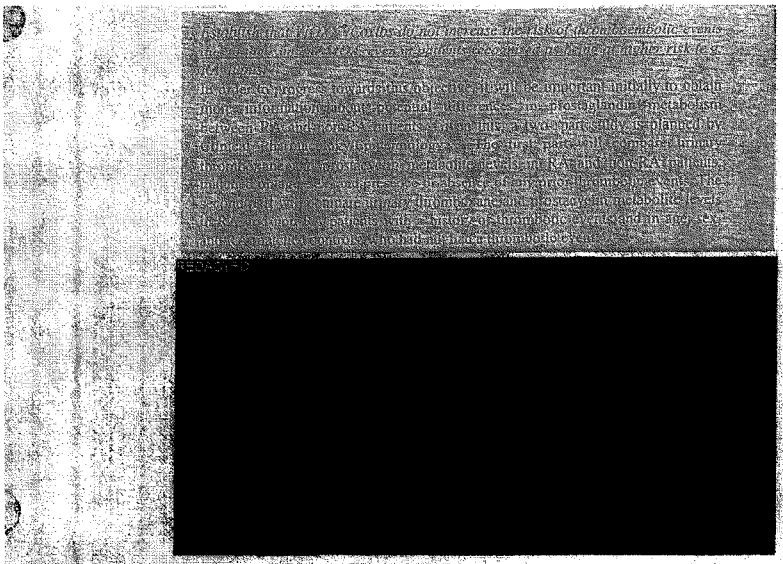
[redacted]

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"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 20

MERCK

MEMO

TO: Edward M. Scolnick **LOC:** WP26-215

FROM: Wendy L. Dixon **LOC:** WP39-425

SUBJECT: [redacted] **DATE:** 05/08/00

As you know, Pfizer/Searle have been executing a strategy of differentiating Celebrex on the basis of superior safety versus VIOXX®. The purpose of this memo is to describe briefly the messages that they are promoting to support their strategy and to describe the counter messages and activities that we are implementing to handle the challenge. Pfizer/Searle seem to be making three unfavorable comparisons between Celebrex and VIOXX®. They have been trying to convince physicians that:

1. Celebrex offers superior renal safety compared with VIOXX®; their detail pieces explicitly state that Celebrex does not have dose dependent edema or hypertension. Their advocates highlight the renal profile of VIOXX® at 50 mg and the dose-related increases in hypertension and edema; they also speculate that these 'unique' effects may be due to an active or toxic metabolite.

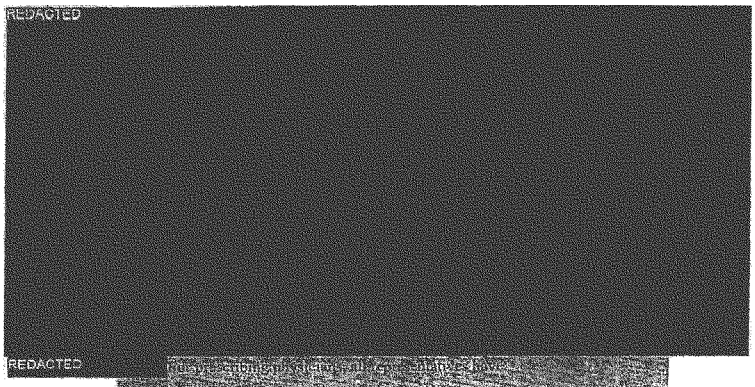
2. Celebrex can be safely used with aspirin; VIOXX® cannot.

3. In the VIOXX® GI Outcomes Study, VIOXX® caused thromboembolic events. In CLASS, Celebrex showed no increases in thromboembolic events or other cardiovascular adverse events. In Celebrex studies with RA patients there was no difference in the thromboembolic event rates between Celebrex treated and naproxen treated patients. The increase in thromboembolic events in the VIGOR is not a 'class effect' but rather a unique toxicity due to VIOXX® or a VIOXX® metabolite (consistent with statement 1).

[redacted]

[redacted]

REDACTED



REDACTED

Copies of the renal card, cardiovascular card, and the Rossat paper are attached. A copy of the renal slide set used in consultants' meetings is also attached.

For each of the public releases surrounding the VIOXX® GI Outcomes Trial or CLASS, the TBG developed and implemented a communication plan to insure all field personnel were fully informed of the appropriate issues.

REDACTED

For thought leaders, we have a number of activities underway and planned. The purpose of these activities is to provide advocates with the data they need to support Merck's position with prescribing physicians and in formulary decisions. The renal and cardiovascular issues have been and will continue to be discussed at our [illegible] VIOXX® Advisory Board meetings and in several faculty training meetings. [illegible] slide set from a consultants' meeting is attached. Important recurring scientific issues raised by our thought leaders include the role of prostacyclin in the VIOXX® thromboembolic events and the GI safety of the combination of aspirin and VIOXX®.

In addition, we have planned a series of consultants' meetings over the summer with high priority physicians to cover the data.

The following key activities are planned for the remainder of the year.

Date:	Event:
Late May	Digestive Disease Week,, including core scientific program, CME satellite symposium, and meetings with HSAs; speaker training teleconferences
June	National Gastroenterology consultants meeting, National Rheumatology consultants meeting, VIGOR Investigators Meeting, EULAR, National CV/Nephrology Consultants Meetings
June – September	Consultants meetings with high prescribing rheumatologists, orthopedic surgeons and primary care physicians
July – December	CME programs Audioconference CME programs

David mentioned that you are offering your help to develop additional messages in response to the competitive environment. A meeting is scheduled for Friday, May 19th at 11 am – 1 pm in Whitehouse Station, to get your input on these issues. A background package is attached.

Cc: David W. Anstice
Gregory Bell
Brian F. Daniels
Riad El-Dada
Douglas A. Greene
Margie McGlynn
Charlotte O. McKines
Errol McKinney
Alan S. Nies
Roger Perlmutter
Alise Reicin
Tim Ruef

United States Senate
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"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 21

Key Marketing Messages

HHPAC
May 17, 2000

Presentation Flow

- Current Selling Environment
- Competition Driven Messages and Market Impact
- VIOXX Key Messages
  - ✓ Sales representation
  - ✓ PIR (Professional Information Request)
  - ✓ Advocates/Opinion Leaders

Two Different Environments

Promotional Environment	Scientific Exchange Environment
• Target audience is prescribing physicians • Messages governed by the label for VIOXX • Merck representatives (Office Based Representative's and A&A Specialists) limited in what they can say by Medical/Legal Board • Personal promotion resources are primarily sales aids and M/L approved slide sets • Physician Information Requests used to respond to physician requests for information only	• Target audience is thought leaders • MRL physicians and other thought leaders conduct programs • Key venues for scientific exchange include consultants' meetings (market research), professional meetings and CME programs

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Representative Selling Environment: Access is Limited

- Two-thirds of physicians have policies that restrict representatives access
- As a result, 40% of details are delivered as stand-up discussions at the sample closet; 40% are sample drops only; and only 20% are delivered as "sit down" discussions (average 10 minutes)
- These restrictions are most common amongst PCPs, who account for two thirds of VIOXX prescriptions

Healthcare Strategies Group, Inc.

MRK-ABL0000924

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Representative Selling Environment: Merck Sales Force Face Many Intense Competitive Battles

Group A	Competition
Zocor, Cozaar, Maxalt, Vioxx	Lipitor, Pravachol, HMGs
(n=1700)	Diovan, Avapro, Alls
	Imitrex, Zomig, Elitriptan
	Celebrex
Group B	
Singulair, Fosamax, Vioxx	Serevent, Flovent, Advair
(n=1700)	Actonel, Evista,
	Celebrex
A&A Specialists	
(n=70)	Celebrex
HSA's	
(n=24)	Celebrex

MRK-ABL0000925

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Representative Selling Environment: Conclusion

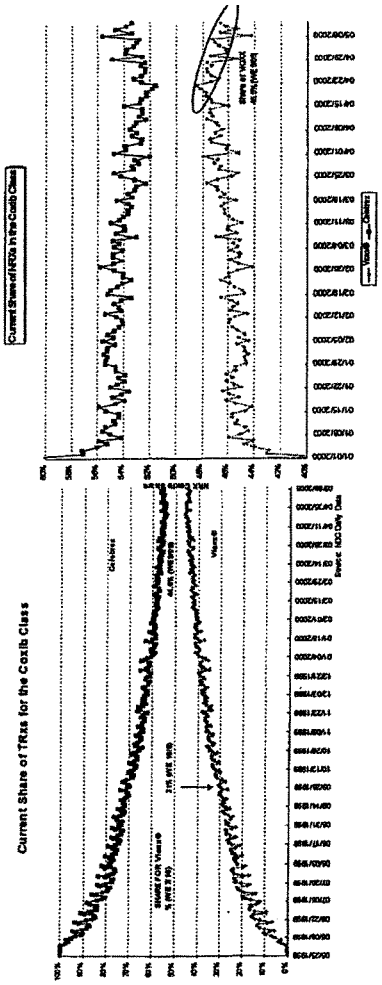
- Time with prescribing physician does not allow for long discussions
- Increasingly limited access, particularly among primary care physicians
- Entire Merck Sales Force facing intense competitive challenges
- Important to have clear, concise, focused messages adaptable to a variety of settings

MRK-ABL0000926

Competition Driven Messages

- "Celebrex offers superior renal safety; VIOXX has dose related increase in hypertension and edema."
- "Celebrex can be safely used with aspirin, VIOXX cannot."
- "The increase in thromboembolic events in VIGOR was not a mechanistic based effect, but rather a unique toxicity due to VIOXX, no increase in such events was found with CLASS."
- Messages aggressively disseminated via Consultants Meetings, analyst reports (Solomon Smith Barney) press releases, news stories (by Reuters) faxes signed by Searle/Pfizer MD's, sales reps.

Competitive Driven Messages: Impact on Market Share



♦ Note: Subsequent to the Reuters' news article, for the week-ended 5/5/00, NRX volume growth for the A&A Market and the Coxib class increased (vs. the previous week). However, NRX share for VIOXX® in the A&A market and Coxib class declined (.1) and (.9), respectively to 14.6% and 47.8%, respectively.

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Merck Response: Sales Representative Messages

- Renal
  - ✓ No change in serum creatinine in two 52 week OA trials
  - ✓ Small change in baseline BP on these trials
  - ✓ In nine OA trials, at therapeutic doses, incidence of edema and hypertension same as active NSAID comparators
  - ✓ Low discontinuation rates
- Aspirin
  - ✓ VIOXX does not affect antiplatelet effect of aspirin and is not a substitute for low dose aspirin
- Thromboembolic events
  - ✓ State the incidence rates for VIGOR and CLASS
  - ✓ CV event rate in nine OA trials is low and similar to comparator NSAIDs

MRK-ABL0000929

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Merck Response:
PIR: Professional Information Request

- Same day fax response from US MEDSA
  - ✓ Turnaround time is 10 minutes (can process 2,000 faxes/hour)
- Includes messages for physicians to respond to patient inquiries
- PIR summarizes CV findings in VIGOR and OA clinical trials:
  - ✓ VIOXX does not block platelet aggregation and therefore would not be expected to have similar effect as naproxen, a potent inhibitor of platelet aggregation
  - ✓ In nine OA trials, similar incidence of CV events for VIOXX, ibuprofen, diclofenac, and nabumetone.
  - ✓ VIOXX treated patients had discontinuation rate due to hypertension of 0.1% and lower extremity edema of 0.2% in the nine OA trials
  - ✓ Incidence of MI in CLASS for Celebrex was similar to VIOXX in VIGOR

MRK-ABL0000930

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Merck Response: Advocates/Opinion Leaders

- Renal
  - ✓ Changes in renal function are a class effect among NSAIDs
  - ✓ Review of safety databases for Celebrex and VIOXX show at therapeutic doses that both have dose related increases in edema and hypertension
- Aspirin
  - ✓ VIOXX does not have anti-platelet effects of aspirin and is therefore not a substitute for aspirin CV prophylaxis
  - ✓ VIOXX has been used safely in conjunction with aspirin in three separate trials

MRK-ABL0000931

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Merck Response: Advocates/Opinion Leaders

- Thromboembolic Events
  - ✓ Absolute MI rates between CLASS and VIGOR trials similar across all drugs except naprosyn
  - ✓ This suggests that the difference in event rates between naprosyn and VIOXX is an effect of naprosyn and not VIOXX
    - Naprosyn has never been studied at 1000mg for this length of time
    - Flurbiprofen, with potent anti-platelet effect similar to naprosyn, has shown ability to reduce CV events
  - ✓ Patients in VIGOR were not on aspirin. The difference in events between treatment groups become N.S. if patients needing aspirin but not taking it are excluded from the analysis
  - ✓ No correlation between HTN, edema, and MIs

MRK-ABL0000932

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Merck Response: Advocates/Opinion Leaders Core VIOXX® GI Outcomes Messages

- VIOXX was significantly safer than a traditional NSAID (naproxen) on all GI study endpoints.
  - ✓ VIOXX reduced the risk of symptomatic ulcers and complicated GI events (PUBs; the primary study endpoint) by 54%.
  - ✓ VIOXX cut the risk of complicated GI events (POBs) by 57%.
  - ✓ VIOXX reduced the risk of GI bleeding from anywhere in the upper or lower GI tract by 62%.
- VIOXX was associated with significantly fewer everyday GI nuisance symptoms than a traditional NSAID
- VIOXX demonstrated efficacy comparable to naproxen in RA patients

MRK-ABL0000933

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Merck Response: Advocates/Opinion Leaders Supporting CV Messages

- In the VIOXX GI Outcomes Trial, patients on naprosyn experienced a lower rate of MI (0.1%) than on VIOXX (0.5%). This result is not unexpected since naprosyn is a potent platelet inhibitor and none of the patients in the trial were on aspirin.
- In the VIOXX GI Outcomes Trial, the differences in MI between VIOXX and naprosyn are N.S. in patients who were not candidates for aspirin therapy.
- In CLASS, the rate of MI on Celenbrex (0.5%) was similar to VIOXX in VIGOR. Twenty-two percent of the patients in CLASS were on aspirin. Aspirin not allowed in VIGOR.
- In 9 OA trials, VIOXX demonstrated proven CV safety:
  - The incidence of thromboembolic events, including MI, was similar for VIOXX, comparator NSAIDs, and placebo.
  - Overall mortality and cardiovascular mortality with VIOXX was low and similar to comparator NSAIDs and placebo.
  - The incidence of hypertension and edema with VIOXX was low and similar to comparator NSAIDs.

MRK-ABL0000934

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Conclusions

- Recent competitive messages targeting VIOXX have impacted market share
- Merck response varies by audience:
  - ✓ Short, simple messages for high prescribing physicians
  - ✓ More sophisticated messages for opinion leaders/ advocates
- Key messages address physicians' concerns

MRK-ABL0000935

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CV Outcome Study

- At present, within Clinical Research there is no consensus as to hypothesis and design of such a trial.
  - Properly designed "non-inferiority" trial would need close to 50,000 patients
- At present, there is no compelling marketing need for such a study
  - Data would not be available during the critical period
  - The implied message is not favorable

MRK-ABL0000936

VIOXX® HH-PAC 5/17/00
Decisions Requested

- Approve plans, timing, incremental resources for new endoscopy study

	Y2000	Total	
– Cost (Clinical Grants):	New $	New $	FTEs
• GI Endoscopy	$ 1.5 M	$7.5 M	10

- Approve present and planned marketing messages concerning Renal and cardiovascular issues and VIGOR data.
- Approve decision not to initiate CV outcome study at present

CROPS resources are TBD.

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"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 22

To: Reicin, Alise S.
From: McGlynn, Margie
Cc Edward Scolnick
Bcc:
Date: 2000-05-25 18:38:38
Subject: VIGOR Analyst Reports

Alice, attached are 2 analyst reports which most clearly demonstrate the success of our efforts to defuse the CV risk issue for Vioxx. You played a major role in making this happen, along with Brian and I know many others supporting you in MRL. I wanted to personally thank you for all of your efforts and the tremendous support you provided for the marketing organization. Regards, Margie

Vioxx Reduces GI Side Effects Versus NSAIDS, Cardiac Events Not An Issue--Maintain BUY Rating and EPS Estimates

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Date:	05/24/2000	EPS:	1999A	2000E	2001E
Price:	74.63	1Q	0.54	0.63A	NE
52-Wk Range:	81 - 52	2Q	0.61	0.69	NE
Ann Dividend:	1.16	3Q	0.64	0.73	NE
Ann Div Yld:	1.55%	4Q	0.66	0.75	NE
Mkt Cap (mm):	179,455	FY(Dec.)	2.45	2.80	3.10
3-Yr Growth:	12%	FY P/EPS	30.5X	26.7X	24.1X
		CY EPS	2.45	2.80	3.10
Est. Changed	No	CY P/EPS	30.5X	26.7X	24.1X

Industry: PHARMACEUTICALS
Shares Outstanding(Mil.): 2404.6
Return On Equity (1999) : 41.0%

HIGHLIGHTS:
*After attending the presentation of VIGOR trial data at DDW in San Diego, we highlight the following key points:

*HIGHLY STATISTICALLY SIGNIFICANT RISK REDUCTION IN GI EVENTS WITH VIOXX...The VIGOR trial included 8,076 patients and compared Vioxx 50 mg. once daily (two-to-four times the daily dose) to Naproxen at 500 mg. twice daily in rheumatoid arthritis patients. The study assessed the incidence of serious GI events. Vioxx demonstrated a 54% reduction ($p<0.001$) in its primary endpoint (risk of perforations, obstruction, bleeding, and symptomatic ulcers). The rate of these events was 4.5 percent among patients taking Naproxen and 2.1 percent per year among patients taking Vioxx. Vioxx demonstrated a 57% reduction ($p=0.005$) in its secondary endpoint (complicated GI events, defined as perforation, obstructions, or major bleeds) when compared to naproxen, at a rate of 1.4 percent among the Naproxen patients and 0.6 percent for Vioxx. These results were highly statistically significant. Most patients remained in the study for nine months, and the analysis was done on an intent-to-treat basis.

*NO DIFFERENCE FROM CELEBREX IN CARDIO EVENTS...Responding directly to recent comparisons with Celebrex which questioned Vioxx's cardiovascular safety profile, the VIGOR data demonstrated that there was no difference in cardiovascular mortality and the incidence of strokes between the groups treated with naproxen and Vioxx. Significantly fewer heart attacks were seen in patients taking naproxen (0.1 percent) compared to the group taking Vioxx

(0.4 percent), which appears to be consistent with naproxen's ability to block platelet aggregation by inhibiting COX-1. In fact, 4 percent of the patients enrolled in VIGOR did meet the criteria for use of aspirin to prevent second cardiac events, but were not permitted to take aspirin in the trial. Therefore, among the remaining 96 percent of patients in VIGOR, there was no statistical difference in heart attack rates: 0.1 percent for naproxen, and 0.2 percent for Vioxx. Vioxx's 0.2 percent event rate was the same rate as reported for Celebrex in non-aspirin patients in the CLASS trial. In the Celebrex trial, the patients who were at risk were allowed to take aspirin. Moreover, in other completed OA trials, Vioxx demonstrated no difference in the incidence of cardiovascular events vs. ibuprofen and diclofenac, the same NSAIDs used in the Celebrex CLASS trial.

*DATA COULD SUPPORT A LABEL CHANGE FOR VIOXX. . .We believe that the VIGOR data should support a positive label change, tempering GI warnings dramatically, although we do not believe that the FDA would remove all GI warnings. MRK could file the data in 2Q00/3Q00, with a potential label change coming in approximately one year, which would boost Vioxx's already strong sales. Our model assumes Vioxx sales of $1.7 billion in 2000 and $2.4 billion in 2001.

*CELEBREX LABEL CHANGE COULD FACE GREATER HURDLES...The Celebrex data is less clear cut as CLASS did not reach statistical significance for one of its primary endpoints. Furthermore, the study appears to have been modified to exclude the first three days of treatment and results beyond six months. Therefore, we believe that the FDA's labeling change for Celebrex, may depend on the extent to which the agency believes that there is a class benefit for the COX-2 selective agents. PHA's Celebrex has already been consistently losing the market share battle with Vioxx. Clearly, the VIGOR trial results appear to be substantially more compelling.

*For a copy of the full VIGOR data, please call Barbara Ryan at 212-469-5226 or email patricia.eager@db.com.

Additional Information Available Upon Request

The following stock(s) is (are) optionable: Merck & Co. Inc..
There is a (are) convertible issue(s) outstanding on Merck & Co. Inc..
A member of the immediate family of an author of this comment has a long position in the shares of Merck & Co, Inc.
An author of this comment has a long position in the common shares of Merck & Co., Inc.
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BROKER: Deutsche Banc Alex. Brown

:TICKER: MRK MRK.XX PFE PFE.XX PHA PNU.BE

:SUBJECT: DRUG BIOT CONW USA
Vioxx Reduces GI Side Effects Versus NSAIDS, Cardiac Events Not An Issue--Maintain BUY Rating and EPS Estimates

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A member of the immediate family of an author of this comment has a long position in the shares of Merck & Co, Inc.
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BROKER: Deutsche Banc Alex. Brown

:TICKER: MRK MRK.XX PFE PFE.XX PHA PNU.BE

;SUBJECT: DRUG BIOT CONW USA
Margie

Margie McGlynn
Worldwide Human Health Marketing
908 423-6524
margie_mcglynn@merck.com

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 23

Gertz, Barry J.

To: Nies, Alan S.; Reicin, Alise S.
Subject: FW: aspirin

This is garret's response to my query that I sent to both of you on the clinical evidence for the need for >90% or >95% inhibition with aspirin or any other anti-platelet agent.
Barry

From: Garret FitzGerald[SMTP:garret@spirit.gcrc.upenn.edu]
Sent: Saturday, September 02, 2000 5:21 AM
To: barry_gertz@merck.com
Subject: Re: aspirin

thre is no comparative outcome data that im aware of , only evidence relating to platelet function and the degree of inhibition of capacity.

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
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Exhibit 24

10/18/00 Consultants Meeting

Relevant question - NSAIDs & Coxibs raise BP - in the long term what is the effect of this elevation
HOPE study?
periph edema ⟷ blood vessel wall ? can't get at it
T_xB_2 - peak trough etc map 95%. consultants when does it reverse

Rory allvasc - split into cardiac cerebro. periph test diff in RR between those groups of events

RC - misleading to emphasize asp indication since no signi heterogeneity
wouldn't have expected diff in RR based on APTrials
Robert Califf - did expect it
Konstam agrees w/ RC - RR not believably diff
Just CV + Just VIGOR

CV
RC-Myron signal may be something wrong
contraindicated in RA trade off in NNT
4 PUBs vs 1 MI is that a good trade
also ↑BP will eventually increase risk - long term
same worry though applies to other NSAIDs
Robert Califf must consider 15,000 GI bleed deaths/yr in US
Konstam either VIOXX ↑ risk or Naprxn ↓ risk - can't tell

They want BP in Advantage

instead of our blocks want to see RR in naproxen trials and w/i non naproxen trials found pbo data reassuring

RC - start & MA w/ 1dF naprx/not, RA vs non (but we really can't)

APTC +MI - mn comparison RR with naproxen + non

RC - observa data (GRH epi) not worthwhile

Robert Califf : answer not known but 50% protective naprx
35% chance
15% harm
to answer as a ACH need more input on GI
. data would go in label

Konstam : reasonably impressed w/ pbo data, possibl RA diff, dose issue - could that be driving prothrombotic effect more likely naprxn benefit but if ACM may not be persuaded

MWeinfeldt - component of prothrom in RA still seems possible, Alz coronary prone should have seen something so that is helpful

RC 50
35
15
Same opinion
to need clear benefit/risk in terms of severity
RC add relecoxib to Meta (drs - can't really do it)

MK - need more data supporting not prothrombotic ...
Celecoxib
Continue current studies long term (BP effects)

toRC - could BP explain VIGOR? No but no evidence
Napr + CV + is evidence BP ↑ CV ...

Cliff - add rigor to CV ascertainment

RC found Clin Pharm + also bleeding AEs compelling
look at asp bleeding rates ecchy etc.
diff seems must more assoc w/ comparator than
condition so not prothrombotic but need more
data to back it up

very high risk - aspir + Vioxx ? ~~NSAID~~ pbo

Cliff if endos shows Vioxx + asp wipes out GI
benefit then great drug but not for
high risk CV pts

RA high risk (to close asp + Vioxx, Naproxen) ⊖ PUBs 30% +

OA
very high CV all asp Vioxx ~~pbo~~ Naproxen pbo endpt GI but data on CV not powered

Repeat VIGOR w/ arthritec - won't stay on Celecoxib for CV - hypothesis of harm!

VIGOR™ CARDIOLOGY CONSULTANTS MEETING

Millennium Broadway Hotel
New York, New York
October 18, 2000

PARTICIPANT LIST

Consultants

Robert M. Califf, MD
Rory Collins, MD
Marvin A. Konstam, MD – T/C
Myron L. Weisfeldt, MD

Merck & Co., Inc.

Eliav Barr, MD
Christopher Brett
Lori Geissler
Barry Gertz, MD
Bonnie Goldmann, MD
Leonard Oppenheimer, MD
Alise S. Reicin, MD
Rick Sax, MD
Deborah Shapiro, MD
Bob Silverman
Ka Losano
Ned Braunstein

Scientific Therapeutics Information, Inc

Patricia Korshalla

Intro + letter, confirming Hotel + DI directions to Hotel to internal People
(Patti-e-mail to me- I send to all internal

Cardiovascular Consultants Meeting — When? Where? [illegible] ①

–? Relationship between sodium retention and hypertension

R.C. Post. Ph III / Prior to VIGOR ⇒ 2 propositions emerged

① COX-2 inhibitors alone might ↑ risk

② NSAID action vs COX-2 inhibitor might relatively ↓ risk

But no specific NSAID identified as unique at that time

What has Merck Done to investigate these

R.C. Hypertension

~ 3.5 mm Hg diff. in systolic [illegible] 50 vs [illegible]

~ 1 mm Hg diff. in diastolic [illegible] 50 vs [illegible]

Cleave – refers to HOPE study where reduction in BP was of similar magnitude and ↓ C-V events noted.

→ yet this was a 9 mo trial

[did C-V events occur more w/ pts on longer therapy]

R. Califf. Edema – if peripheral edema, is there edema in the arterial wall in location of plaque and thereby an increased risk.

– What studies have been done to assess what effect COX-2 inhibitors has on the endothelial wall of vessels

☆ Slides – mean change in BP for Vioxx in VIGOR versus the NSAID meta-analysis and Naproxen in VIGOR

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(2)

* Need slide of actual values, esp. range of TxB_2 inhibition w/ various NSAIDs

* Need slide comparing inhibition of plt. agg. w/ Naproxen and ASA – side by side

(* Did you ever get this information)

[Also – be careful on the 95-97% inhibiting plt COX (serum TxB₂) w/ ASA → could reflect assay LLOD]

* slide on wording of cardiovascular exclusions in protocol

(* Did (1) approve a waiver of study of CV events in Vigor study?)

[illegible] – misleading to provide estimate of effect in ASA only indicated group as there is heterogeneity of effect
– he feels the best estimate of effect is the overall estimate for all groups, and can't say that the absence of signif effect in the ASA not indicated group should → a reduced ~~sig~~ relative risk in the ASA non-indicated group.

* All 3 consultants felt that one cannot believe the RR are diff (based on our data) for the ASA ± indication

(– If they were, and knowing that Vioxx does not effect ASA's ability to prevent CV events, this would be damaging.)

(3)

MI - could reviewer suppress SC- MIs? We did not get calls at end study to know what rate of "silent MIs" were in each group.
(Discussion of "high rate" of 1/2 of adj. event in reference group - Cliff felt high rates were indicative, & RA - so not too surprising)

R.C. - why, if naproxen is anti-plt agent, is benefit in the MI category and not CVA
Cliff - also may have greater benefit on MI than stroke + CV death but Collins similar to BC in non-fatal MI and non-fatal stroke

[Risk - reduce the emphasis on MI - just subdivision and subdivision [redacted])

Based on Vigor Alone
Cliff - a signal vs no PDXID
Wenfeld - a contraindication in RA
Collins - a contraindication in RA
- A consensus can include for naproxen as anti-plt effect and other is balanced like APC7 data
- The increase in BP adds to the concern
- Protective effect of naproxen (yes)
- But no consensus evidence in short-term that Vigor is increasing risk
- only firm conclusion to vigor vs naproxen
- But he feels can't tell if Vigor or naproxen & risk

What scientific data/evidence to support these positions.

Continue Naproxen

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(4)

* [Alise: - slide for overlay of K-M plots ?
for OA II/III and VIGOR]

ADVANTAGE

Constance - notes difference in dose of Vioxx in ADVANTAGE
versus VIGOR

Collins — wants to know effect of BP at 25mg Vioxx
(He is very concerned about an ↑ BP.)
(He cautions about FDA very detailed
review of BP effects of Vioxx)

Meta-Analysis

± ASA ; sensitivity analyses - all too few events

Constance — need to pull out Naproxen from
the other NSAIDs, Emphasize the PCB-ctrl'd Meta Analysis

* Collins - compare ⇒ PCB vs Naproxen vs Non-Naproxen NSAID
for the Meta Analysis

Constance - Why is VIGOR different?
a) Beneficial effect of Naproxen (attractive)
b) Dose of Vioxx
c) Disease - specific:
Not enough PCB-ctrl'd data in RA.

No! * Is there any clinical trial or epi data supporting Naproxen effect?

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[Also – we may be able to show the Naproxen epi data for UKGPD]

[Also – event rate from Celebrex FDI for vs Naproxen]

[Kleinfeldt –] RA – in that population, Vioxx ↑ risks

[illegible] + [illegible] Columbia

[May need to have the NNT for bleed vs MI in RA patients – 1% specifically Real Bleeder if asked]

Collins – very skeptical of any epi observational data, even in RA pts, to show a difference in Naproxen vs other NSAIDs.

– Strongly encourage not to focus on point estimate in VIGOR but rather the CI (which would not be outside of an ASA effect)

What is interpretation of CV data?

Califf - 30% chance; 35% prothrombotic effect; 55% benefit of naproxen

* → Needs to have more data on Risk : Benefit

↓ GI events; relative ↑ CV events

Get longer-term data on the PCB-ctl'd trials.

Konstam - Still concerned that dose may be driving VIGOR results.

Non-RA population w/ too few events.

Whitfield - a component of prothrombotic - effect in RA population sufficient to manifest clinically

* All consultants stressed need to show PCB data as rigorously as possible.

Collins - agreed w/ general ? of explanation.

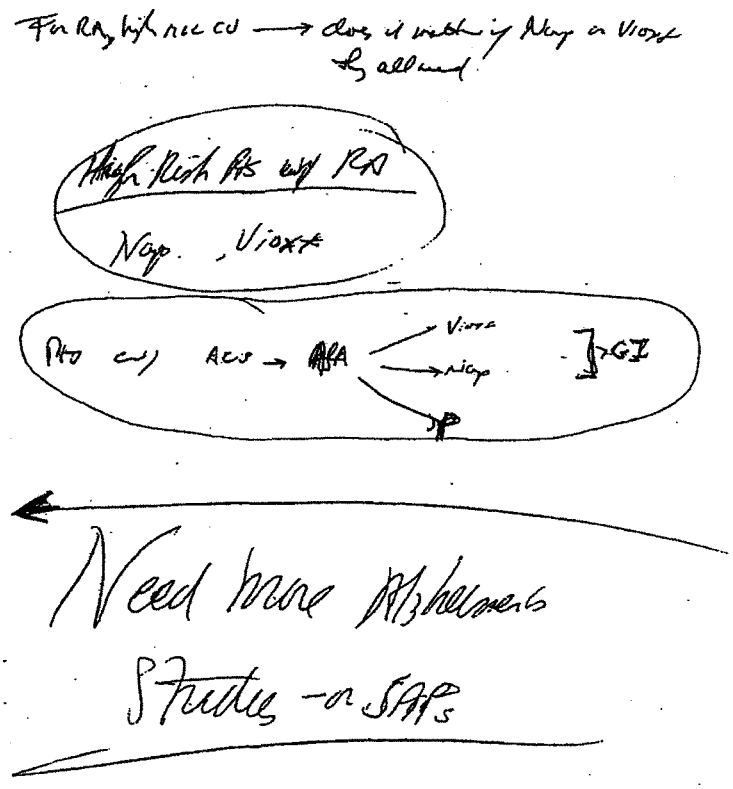
* Raise question of NSAIDs on origin of the CV events.

Fitzgerald → How long does steady-state anti-plt. effect last of naproxen?

Collins - Need more presentation on BP

Also Naproxen vs ASA on plt function + clinical bleeding

Highlight that it is the comparator not the condition



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PB Consultant Mtg
Crude Event Rates

Vigor 1.3 % rofecoxib
0.7 % Naproxen

(Physicians Health Study 0.7%) [redacted]

AD. Study 1.5 % rofecoxib
2.3 % placebo
But ASA was allowed

Explanations
- Play of chance - Patrono
  - P.H.S. 5 yr study to demonstrate sufficient events
  - ✓ Flurbiprofen – small 500 pt study (30 events)
  - ✓ indobufen – more selective for cox-1 vs cox-2; > 75% TxB2
    One placebo-ctld trial: 30 evnts, 71% ↓ RR.
    All other studies are underpowered comparison to ASA.

Hypertension Data → Demonstrate the dose dependence
Magnitude of Effect → ✓ Emphasize C.I. for APCT

✓ Could RA pop explain the larger magnitude of effect

? John – reduced likelihood of chance
given that MI/CVA/CV? all move
in same direction.
–(& Garret) data "compatible" w/ an
ASA-like effect BUT we don't know
for sure w/ clinical data

Cardiovascular Effects –

Anti-platelet Strategies

⇒ Hypertension as a CV Event – AEs; mean change;
2 sustained ↑;

Meta-analyses – handling of ASA-allowed trials
– What went wrong, Konstam article

Celb – CLASS p1253
Incidence of MI in either celecoxib
or NSAIDs was 0.3%. 95% CI 0.12, 0.46 ← celecoxib
0.14, 0.49 ← NSAIDs

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Heart Failure – 2° hypercalcemic Cardiac Function

Desmond Fitzgerald – Very long duration of action after ok of Naproxen.

~~Scott Reiss~~ – ~~Pt data from Alzheimer's Release Society considering.~~

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QUESTIONS TO THE CARDIOLOGY CONSULTANTS

1. What is your interpretation of the cardiovascular data from the VIGOR study?
   a. A play of chance?
   b. A prothrombotic effect of rofecoxib?
   c. An aspirin-like vascular protective effect of naproxen?
2. How do you interpret the data in the literature that RA patients have an increased risk for cardiovascular events?
   a. Is RA a risk factor for atherosclerosis?
   b. Is RA a risk factor for thrombotic events separate from any atherosclerotic risk?
3. What was the cardiovascular impact of enrolling exclusively rheumatoid arthritis patients in the VIGOR study?
4. The two other large databases (Phase III OA and Alzheimer disease) have failed to demonstrate a difference in cardiovascular outcomes between rofecoxib and either non-NSAID comparators or placebo.
   a. How would you interpret these findings?
   b. How do these findings impact the results of the VIGOR study?
5. How did the following analyses/issues influence your decision?
   a. The subanalyses of the VIGOR study:
      i) The more substantial reduction in cardiovascular event rates in the "aspirin-indicated" group
      ii) The analysis of thrombotic event rates in patients who did or did not have hypertension-related adverse experiences
      iii) The difference in minor bleeding event rates between treatment groups
      iv) The Antiplatelet Trialists' Collaboration Endpoint analysis
   b. Statistical issues regarding the cardiovascular analysis of the VIGOR Study:
      i) The fact that the VIGOR study was not designed as a cardiovascular endpoint trial
      ii) The absence of a prespecified hypothesis regarding cardiovascular findings
   c. The clinical pharmacology studies of naproxen and rofecoxib demonstrating their differential effects on prostaglandin metabolism and platelet function
   d. The results of the Cardiovascular Meta-analysis
6. How does the fact that there was no difference in the incidence of ischemic CVAs influence your interpretation of the data?
7. Are there any other analysis of the VIGOR study or of the rofecoxib program as a whole that would be helpful in understanding the results of the study?
8. What is your overall assessment of the cardiovascular tolerability of rofecoxib?

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November 18, 2004

Exhibit 25

12/12/00 TUE 16:35 [TX/RX NO 7464]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC 12 2000

TRANSMITTED VIA FACSIMILE

Ellen R. Westrick
Executive Director
Office of Medical/Legal
Merck & Co., Inc.
P.O. Box, WP37C-116
West Point, PA 15486

RE: NDA 21-042
Vioxx (rofecoxib) Tablets
MACMIS ID #9456

Dear Ms. Westrick:

As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of audio conferences presented by Dr. Peter Holt on behalf of Merck & Co., Inc (Merck) that may be promoting Vioxx (rofecoxib) in violation of the Federal Food, Drug and Cosmetic Act and its implementing regulations.

We request that you provide the following information regarding Dr. Peter Holt's presentations:

1. Please describe your involvement with and influence on the initiation, preparation, development and publication of the audio conferences given by Dr. Peter Holt. This would include any background information provided by you, or points for emphasis suggested by you, for the preparation of the audio conferences. Please describe any contact you had with the parties responsible for producing the audio conferences, the nature of the contact, and the substance of the discussions.

2. Please describe the nature of the relationship between you and Dr. Peter Holt, including any financial, consultancy, or research relationships. This would include any prior agreements, compensations, gratuities provided, or any prior similar contacts between you and Dr. Peter Holt.

3. Please describe whether there was disclosure to the audience at the time of the audio conferences regarding your funding of the program, Dr. Holt's relationship to you, and whether any unapproved uses of Vioxx were to be discussed.

12/12/00 TUE 16:35 [TX/RX NO.7464]
TOTAL P.03

4. Please describe whether Dr. Holt has had any involvement in assisting you with respect to your sales or marketing of Vioxx. Please provide copies of all correspondence and communications between Merck and Dr. Holt relating to, or concerning, any audio conferences on Vioxx.

5. Please describe the number and location of presentations and the number of attendees who attended, or listened to, Dr. Peter Holt's audio conferences and how the audiences were selected. State whether Merck provided any payment, expenses, honoraria gifts, or other compensation to attendees.

6. Please submit copies of all documents (e.g., handouts, announcements, agendas, questionnaires, etc.) given or shown to healthcare professionals, during or for the purposes of the audio conferences presented by Dr. Peter Holt. Please describe if Merck further disseminated the information discussed in the audio conferences after the initial program and the mechanisms by which it was disseminated.

7. Please submit copies of all audiotapes, videotapes, and transcripts pertaining to the audio conferences presented by Dr. Peter Holt.

We request that you respond to this letter in writing by December 27, 2000, to me by facsimile at (301) 594-6771, or by writing at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to the MACMIS ID #9456 in addition to the NDA number.

Sincerely,

Spencer Salis

Spencer Salis, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 26

Confidential Document

STANFORD UNIVERSITY MEDICAL CENTER
STANFORD, CALIFORNIA 94305

STANFORD UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF MEDICINE
Division of Immunology and Rheumatology
1000 Welch Road, Suite 203
Palo Alto, CA 94304
(650) 723-6003
(650) 723-9656 (Fax)

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DATE
MARY G. VAN DINA, C.S.R.

January 9, 2001

Mr. Raymond Gilmartin
Chief Executive Officer
Merck and Co.
One Merck Drive
Whitehouse Station, New Jersey 08889

Dear Dr. Gilmartin,

A series of serious events involving certain employees of, and possibly a policy of, Merck & Co. has come to my attention rather accidentally and I wanted to relay these events which might have substantial implications and complications. The result is harmful to the traditionally very fine Merck public image and is counter-productive to the Vioxx sales effort. My perspective is that of the Principal Investigator of ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System). This NIH-funded national data bank first identified and quantitated the stealth epidemic of NSAID gastropathy, quantitated differences in toxicity among NSAIDs, and ARAMIS investigators have worked hard for a long time to find and implement ways of reducing the frequency of serious GI adverse events with NSAIDs. I believe that the Cox-1 sparing agents are our best approach toward better drug safety in this area.

My accidental involvement: On Saturday October 28th I received a call at home from Dr. Louis Sherwood of Merck Pharmaceuticals. Dr. Sherwood complained that Dr. Gurkirpal Singh of our group had an anti-Merck bias and was giving lectures that were irresponsibly anti-Merck and specifically anti-Vioxx. Dr. Singh was held to have used a slide which depicted a person hiding data under the covers, had called Merck the "Firestone of the drug industry", and had requested data from Merck which was not appropriate for him to have. Dr. Sherwood suggested that if this continued Dr. Singh would "flame out" and there would be consequences for myself and for Stanford. Dr. Sherwood had previously called Dr. Judith Swain, Chair of our Department, and subsequently called Dr. Edward Harris, Chair of our Division, with similar complaints. I agreed to look into the matter and to take appropriate action and indicated that it is not our policy to bias any presentation in any direction. I asked him to provide me with full details of any such transgression that occurred after this date.

I spoke with Dr. Singh and reviewed the slides of his presentation. The talk was mainly about the frequency and severity of NSAID Gastropathy and secondly about the advantages of the new Cox-1 sparing agents, of which Vioxx is one. Equal numbers of slides were devoted to Celebrex and to Vioxx. The talk was strongly in favor of broad use of the new Cox-1 sparing agents. Data were mainly from the standard studies, although three slides were from a presented but not yet published randomized renal toxicity study of Celebrex and Vioxx by Andrew Whelton comparing side-by-side renal and cardiovascular toxicity which was not in favor of Vioxx. The little man under the covers was not in the sequence, having been removed when Dr. Singh succeeded in getting the requested data (again not favorable to Vioxx), from Merck. Dr. Singh clearly did not understand the "Firestone" reference and indicated that he had not made the statement. I asked Dr. Singh to be certain to be rigorously balanced in future presentations and he agreed, although stressing that he had also been balanced in the past. I talked with three people who had been in Dr. Singh's audience; one thought the presentation contained humor directed at Merck but that the data were balanced and the other two found the presentations completely unremarkable.

The much broader issues, which surfaced at the American College of Rheumatology meetings, were most disturbing and involve suppression of data by Merck and a consistent pattern of intimidation of investigators by Merck staff, principally Dr. Sherwood but also others on his staff.

A number of physicians have concerns that Vioxx may have some serious and under-emphasized drug toxicity problems, particularly at the 50 mg dose approved for pain control—these concerns are shared by the FDA renal reviewer. Vioxx has been reported to have more frequent peripheral edema problems, more aggravated hypertension, more congestive heart failure, and more heart attacks than other NSAIDs, especially Celebrex. Some 0.4 % of Vioxx subjects had heart attacks compared with 0.1 % in the naproxen arm in the Merck-sponsored VIGOR study and this was statistically significant. Some of these data have been described in the Wall Street Journal and may have affected stock prices but there has been little information presented to date in the medical literature. Merck presented two posters on the VIGOR trial at the recent ACR meetings which did not contain data on the side effects of interest; the posters were very well attended, with everyone wanting to know about the data on these points, but it was not available. I tried unsuccessfully to get the data myself; it is hard to judge these areas without the numerical details. Yet, one could not avoid the conclusion that because of the interest in these issues the data would have been presented had they been favorable. There was a lot of muttering and a lot of people with concerns. The publication of the VIGOR trial recently in the NEJM did not contain the data on edema and fluid retention at all, and dismissed the heart attack data with weak arguments.

Even worse were the allegations of Merck damage control by intimidation, often with a pattern of going to the Dean or Department Head with complaints of anti-Merck bias and always alleging unbalanced anti-Vioxx presentations. This has happened to at least eight investigators: Dr. Singh; Dr. Peter Lipsky, now research chief at the Arthritis Institute;

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Dr. Andrew Whelton of Hopkins; Dr. Michelle Petri of Hopkins; Dr. David Yocum of Tucson, currently head of the FDA advisory panel; Dr. Lee Simon of Harvard; Dr. James McMillen; and Dr. Thomas Stillman. I suppose I was mildly threatened myself, although I have never spoken or written on these issues.

I documented the intimidation of the individuals listed above by personally speaking with each of them. Dr. Simon believes that one of his two academic appointments has been jeopardized. Dr. McMillen believes that his VCF appointment at Hershey was revoked because of these accusations. Dr. Petri had a speaking engagement unprofessionally cancelled by Merck and an unrenowned speaker substituted; he was also bothered by phone calls from Merck persons alleging unbalanced presentations. Dr. Singh had a speaking engagement cancelled and the audience was told that he had been fired. Dr. David Yocum had similar experiences. Dr. Lipsky, while at Southwestern, was forced to do a slide by slide justification of a CME program felt to be critical of Vioxx. These are respected investigators with long experience and high integrity. I also spoke with several past Merck employees who asked to remain anonymous but who confirmed the existence of a pattern of intimidation through the Department Chairs or the equivalent, often with the hint of loss of Merck funding to the institution.

An ironic result of all this is that Vioxx is getting more scrutiny of its salt and water toxicity than if the data had been clearly presented, and Merck is taking a big public relations hit among rheumatologists. The investigators whose balance was criticized are prominent and several advise the FDA—a role not often given to unbalanced presenters. In the view of most rheumatologists including myself, Vioxx (and Celebrex) represent a major medical advance in terms of improving GI safety, which is the dominant toxicity of NSAIDs and is the most common serious adverse event of NSAIDs. These drugs should on balance, save a substantial number of lives. The fluid retention and related problem data are actually not all that bad, and the cover-up is a worse problem than the side effects of fluid retention and hypertension and CHF, which could be handled by stronger labeling for at risk patients, or by other means. Else, there is a risk of case reports of seriously complicated congestive heart failure or other serious adverse reactions, which could threaten the drug approval. The heart attack data, of course, need to be confirmed or refuted by further study, as do the data on comparative renal toxicity between Cox-1 sparing agents.

I spoke with Dr. Sherwood at length on November 22 and aired the above concerns directly. He defended by saying that Merck was a great company and, therefore, could not be doing anything inappropriate. He said that he had been with Merck for 13 years and had never noticed anything that was not appropriate. He noted that he had previously been a Department Chair and that he knew what was appropriate and what was not, and that he knew how to get things done through the network. He said that if he heard about something that was alleged to be anti-Vioxx that it was his right to call anyone he wanted to about it. When told that each of the investigators maintained that presentations had been balanced he said he didn't want to get into "he said, she said" kinds of discussions. He said that there weren't any problems with the drug and that anyway they only occurred at high dose. When told that an ex-Merck employee had quoted him as saying

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"we only have three problems, Whelton, Simon, and McMillen, and Simon has been taken care of" there was a long pause and then he said that he "did not remember" saying that. When told that while both I and the people I had talked with had often had differences in viewpoint with one or another drug firm, none of us had ever heard of harassment of investigators through their institutions he did not have a response but said that he "heard me."

From the discussions above I make three conclusions. First, some investigators at some times probably do make statements that may seem seriously unbalanced to those vested or instructed in opposite opinions and that close attention to strict impartiality is essential for any person making presentations on any such subject. Second, Merck has been attempting to systematically downplay some unusual side effect patterns of Vioxx. I would hesitate to use the term "hiding data" but Merck has certainly not been forthcoming with data and has made access to the data difficult. Finally, and most importantly, Merck employees have systematically attacked those investigators or speakers who expressed what Merck staff felt were critical opinions in a manner which seriously impinges on academic freedom.

I believe that these are serious matters and that Merck should take care of them internally, in its own interest, and in the interest of patients. I will appreciate your response to the issues raised here and to learning about actions which have been taken.

Sincerely,

James F. Fries, MD/jr

James F. Fries, M. D.
Professor of Medicine

cc: Mr. David Anstice, President Merck U. S. Human Health
Dr. Ed Skolnick, President Merck Research Labs

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 27

To: Greene, Douglas Dr.; Nies, Alan S.; Reicin, Alise S.; Goldmann, Bonnie J; Gertz, Barry J.
From: Scolnick, Edward M.
Cc Slater, Eve; Blois, David W.; McGlynn, Margie G; Anstice, David W.
Bcc:
Date: 2001-01-21 13:59:47
Subject: Vigor Adv meeting

To ALL; I have been stewing about the FDA review of Vigor since reading the document Friday. Doug and I spoke briefly Sat. Morning about it. The more I think about it the more I think we need to change slightly the emphasis of the talks. Not the slides , obviously not the data but what we say.

Let me take you through the logic. (My office is undergoing asbestos repair and I am at home Monday morning before going to a MMD annual meeting in Arizona)
If you want to talk about what i am going to say please call me at home before 10 30 AM.

I think it must be stated clearly that we know the dose for RA. 25mg. That at the time we did Vigor we did not know., That it is unfortunate that Vigor came to conclusion before the RA program but that they MUST know-explicitly and not waiting for a question- that the dose for RA is 25mg.Clearly have data ready to show and acknowledge that the fDA has not seen it although I think we should send them the essence of it. A couple of tables and graphs.

Then i think as you go through the prior ulcer data which compares to ibuprofen you emphasize the DOSE RESPONSE curve. WE NOW KNOW THE ANSWER THAT WAS NOT CLEAR WHEN VIGOR WAS DESIGNED. We know that 50mg og Vioxx in 2 ulcer studies is higher than placebo. We know Mk663 at 120 mg is higher than placebo.
Heads in the sand, or hoping for a miracle which will not happen in the fianl endoscopy study will not help.. Thus we point out that it is expected that 50mg will be lower than the SECOND NSAID we tested against in Vigor ie Naproxen since it was lower than ibuprofen for ulcers even at 50mg but it will not be placebo at 50mg. The need now that we have data is to tie the ulcer data to the outcome data. We NOW can do that. By doing that we can introduce the dose response concept. THIS IS ABSOLUTELT VITAL in presenting Vigor to the committee and in a public affairs way.

We gain the following : We emphasize the safety of 12.5mg and 25mg. The benefit risk is clear. we have no appreciable hypertension or edema at 25mg, we have ulcers comparable to placebo, and we have no CV events in the placebo controlled trials including the Alzheimer's trial.We isolate the 50mg data and say THAT WE HAVE PROVEN IF THERE IS DOSAGE CREEP THAT EVEN AT 50MG WE ARE LOWER FOR GI EVENTS THAN NAPROXEN . We point out that since the ulcer data is vs Ibuprofen , and the outcomes data is vs naproxen that we have in fact tested Vioxx vs TWO NOT ONE NSAID.

This will allow us to argue that the label should reflect a different statement using the lower doses for Gi safety. for example. Assuming the warning is retained we could get to lump the ulcer data in an inteligent way to the outcomes which now should be doable. The logic is very tight that we should be able to say: the outcomes were less than naproxen at 50mg Vioxx, the ulcers which are a marker for the outcomes although not one for one, were much lower than another nsaid at 12.5 and 25 mg, Thus across the dosage range this class has lower risk of GI safety problems than the priror class. getting that bland a statement even retaining the warning would be a big win. BIG. For managed care and the class of drugs, this would be an enormous help. The logic for this approach is sound. we can stand behind it scientifically with integrity. The agency can moan and groan as usual but we can win the argument for this type of statement. But we will not win by couching our statements and not ebing explicit with the words that describe the data. The MK663 data and the table that shows ll the ulcer endo data is unambiguous.By looking at the data and not relying on our preconceived notions we can now formulate a correct strategy to the meeting and the upcoming round two battle with this group, and win the public affairs war.

As I have said if you want to talk i am at home Monday morning while an asbestos abatement is being finished in my office. I ahve asked Bob Bissett to set up a telecon wed or thur to discuss the Public Affairs handling of Vigor andwe can also talk then. But I plead and urge you to take this approach. I deeply believe we will end up in a horribel situation otherwise/ Ed

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 28

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▼ ▼ ▼ ▼ ▼ ▼

VIGOR and CLASS FDA Advisory Committee Meetings

Communications Plan

Updated to reflect FDA review package

REVISED 01/24/2001

[redacted] ▼ ▼ ▼ ▼ ▼

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Situation Overview

- FDA has scheduled back-to-back meetings: Celebrex on February 7 and Vioxx on February 8
- Merck received FDA's review package Jan. 18; extent of Celebrex sNDA, FDA review of Celebrex package unknown
- FDA, Merck, Pharmacia background packages will be posted to the web February 6 (still confirming)
- Questions to Advisory Committee questions not yet known
  - Committee may not vote on specific label changes
  - Possible that the Committee will not make a clear recommendation
- **FDA review package raises significant concerns about the likelihood of a GI label change and about potential cardiovascular safety language and creates very difficult communications challenges**

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Action Items

- Discuss scenarios and expectations for communications
- Gain agreement on objectives
- Gain agreement on preliminary messages
- Gain agreement on approach
  - Meetings with reporters in advance of Advisory Committee meeting
  - Providing our background package prior to availability on the FDA website

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FDA review package

- **Recommendations from FDA medical review of Vioxx**
  - The NSAID-class GI warning should not be removed
  - Information regarding CV thrombotic events should be added
  - Additional studies may be needed to clarify outstanding questions
- **Summary from the post-marketing AE review**

GI: Deaths from GI events have been seen in post-marketing experience; the current labeling for Vioxx and Celebrex reflect risk of fatal GI AEs

Renal: The labels for Vioxx and Celebrex are generally consistent with post-marketing AE reports

CV: "Although certain thrombotic events are mentioned in the product labeling, the continued existence of the thrombotic events particularly in high-risk population is an important finding since the actual number of cases may in fact be higher"

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Vulnerabilities from FDA review

Cardiovascular: FDA concern about higher rates of CV thrombotic events with Vioxx in VIGOR, post-marketing reports

Merck response: In VIGOR, naproxen conveyed an anti-platelet, cardioprotective effect. Analyses of all other Merck studies (Phase IIb - V) showed no difference in CV events between Vioxx and other comparator NSAIDs that are less potent blockers of platelet aggregation than naproxen. In an on-going Alzheimer's study, the rate of CV events is similar between Vioxx and placebo. Post-marketing reports of CV events in patients taking Vioxx are from a base of ~13 million patients and do not reflect a causal relationship.

GI: FDA recommends against removal of GI warning, says VIGOR and post-marketing reports are consistent with label

Merck response: In both the VIGOR trial and the IIb/III OA studies, Vioxx demonstrated a highly significant 54 to 62% lower risk of serious GI side effects. The 37 GI deaths reported post-marketing are from a base of ~13 million patients.

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Vulnerabilities, cont.

Renal/Cardiorenal: FDA concern about trend toward higher rates of renal AEs (HTN, CHF, edema) in VIGOR

Merck response: Renal effects of selective and non-selective NSAIDs are mechanism-based and dose-dependent. Vioxx is similar to non-selective NSAIDs in renal effects when dosed at similar points on their efficacy dose-response curves. Differences between Vioxx and naproxen in VIGOR are consistent with use of Vioxx at 2 times the highest chronic dose versus a common dose of naproxen.

Use of aspirin: FDA says it's unclear whether CV effects "potentially associated with" Vioxx will be prevented by ASA, and whether ASA will diminish GI benefit of Vioxx

Merck response: The CV benefit of ASA has been established. Although the definitive studies have not been done, the risk of a GI event would be lower with Vioxx + ASA versus a non-selective NSAID with or without aspirin. For appropriate patients who also need aspirin for CV benefit, the balance of risks and benefits favors Vioxx + ASA over a non-selective NSAID +/- ASA.

[redacted]

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Timeline/Vulnerabilities

- **Before the meeting:** Speculative stories about label changes, CV concerns possible, especially from Reuters
- **Tuesday, Feb. 6:** FDA posts Merck and Pharmacia's background packages (largely positive), FDA's negative review of Vioxx sNDA and FDA's negative review of Vioxx and Celebrex post-marketing AEs
  - ***Vulnerability:*** High, and increases the longer the materials are available
- **Wednesday, Feb. 7:** Advisory Committee Celebrex meeting
  - ***Vulnerability:*** High, depending on Feb. 6 coverage and outcome of Celebrex meeting
- **Thursday, Feb. 8:** Advisory Committee meeting on Vioxx
  - ***Vulnerability:*** High, depending on Feb. 7 outcome and Feb. 8 discussions/outcome

[redacted]

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Communications implications of FDA review package

- Public availability of FDA review, combined with both studies' results, create communication challenges
  - Public availability of FDA review prior to meeting (Feb. 6) enables analysts, reporters to speculate prior to Committee discussion
  - The Advisory Committee may not share same perspective of FDA reviewers, but the background package may set the tone for coverage until Committee recommendations are made, if any
  - Discussions of heart attack in VIGOR likely to be of significant interest to analysts and reporters, very likely to put CV issue into business, consumer media
  - FDA review of VIGOR GI results and ambiguous GI results for CLASS likely to be of interest to business media
  - Back-to-back comparisons of studies, results, companies are likely, as are "both companies face a battle with the FDA as..." stories

[redacted]

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Media Issues

- Some wire, print stories may appear even before Feb. 6
- Because packages are posted on the FDA website Feb. 6, reporters will be able to review recommendations and file stories -- before the meeting opens -- with spillover into analyst reports, business TV
- FDA background packages, outcome of day 1 Celebrex meeting will influence media coverage and set expectations of meeting for Vioxx
- Wire reporters very likely to file stories throughout all three days, without waiting for resolution from the Committee re: Vioxx
- Because the media will not wait until Committee discussions are done to file stories, Merck has to provide background, perspective to reporters about the study without interfering with Advisory Committee and post-meeting Merck/FDA discussions

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Objectives

- **Strengthen positioning of Vioxx**
  - Vioxx is the once-daily COX-2 selective inhibitor shown to have strength comparable to non-selective NSAIDs with a significantly reduced risk of GI side effects
- **Achieve positive, balanced coverage of safety profile of Vioxx**
  - Achieve positive coverage of GI safety findings
  - Neutralize coverage of CV, renal issues raised by FDA and limit speculative stories about CV safety
  - Limit speculation about GI label changes

Ideal outcome:

- **If meeting outcome is positive:** Generate broad media coverage of superior safety profile of Vioxx and broaden perception of GI risk from use of non-selective NSAIDs to pave the way for label change
- **If neutral or negative outcome:** Achieve balanced coverage of VIGOR results and limit concern in business, consumer media

[redacted]

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Merck Key Messages

- VIGOR confirms the superior GI safety of Vioxx over non-selective NSAIDs and confirms the excellent overall safety of Vioxx.
- Once-daily Vioxx, at a dose 2 times higher than the most commonly used dose for osteoarthritis, reduced the risk of serious GI side effects compared to non-selective NSAIDs. Non-selective NSAIDs cause serious GI complications – without warning – that are responsible for 107,000 hospitalizations and 16,500 deaths in the U.S. each year.
- Vioxx has demonstrated efficacy comparable to non-selective NSAIDs with a superior GI safety profile and an excellent non-GI safety profile.
  - The decrease in MI in VIGOR is consistent with naproxen's ability to block platelet aggregation by inhibiting COX-1like aspirin. In other studies, there was no difference between Vioxx, placebo and other NSAIDs that have different effects on COX-1 and are less potent inhibitors of blocking platelet aggregation than naproxen.
  - Hypertension and edema are dose-related, mechanism-based class effects of NSAIDs. At the doses of Vioxx used for chronic treatment, there is no difference in the incidence of hypertension and edema between Vioxx and comparator NSAIDs, and what was seen in VIGOR is consistent with the current labeling for Vioxx.

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Strategic Approach

- Initiate pre-meeting communications to targeted business and health reporters based on key messages, Qs and As
- Develop core materials for different outcome scenarios, including news releases and supplementary materials
- Prepare range of spokespeople to address key issues, e.g., GI/general safety of Vioxx, distinctions between VIGOR/CLASS
- Prior to the meeting and on site, work with media in attendance -- the drivers of coverage -- closely and extensively, particularly at the end of the day(s)
- **Prepare for crisis:** Be prepared to respond to questions, modify materials/messages during meetings and issue statements if necessary -- immediately
- Coordinate all activities with Investor Relations, USHH, WHHM for appropriate external and internal audiences

[redacted]

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Tactical Approach

- Jan. 24: Gain agreement on plan, key messages
- Jan. 25, 26: Circulate news releases, Q&A for approval
- Jan. 29, Feb. 5, 6: Media training (TBD)
- Jan. 31 - Feb. 5: Outreach to key media
- Feb. 2: Finalize draft news releases and new Q&A
- *Feb. 6: FDA posts all backgrounders on website*
  - Conduct interviews, monitor coverage, issue news release if necessary
- *Feb. 7: Celebrex meeting*
  - Conduct interviews, monitor coverage, issue news release if necessary
- *Feb. 8: Meeting on Vioxx*
  - Conduct interviews, monitor coverage, issue news release at end of day

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Tactical approach:
Before the meetings/Feb. 6

- Initiate media outreach prior to Feb. 6
- Hold face-to-face meetings with MRL and key reporters to review VIGOR and other supporting data; provide our background package to those who will keep data confidential
- Reach out to FDA Press Office to determine attendance, whether there will be a media room; if not, set up a press room on site for Feb. 8
- Prepare all materials, including news releases for different scenarios, and arrange for work room to finalize, issue statements as necessary
- **On Feb. 6:** Respond to media calls, watch coverage closely and issue statement if needed to emphasize strength of VIGOR data and clarify role of Advisory Committee. Review Celebrex data and amend statements/messages/Q&A as necessary

[redacted]

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Tactical Approach:
Feb 7th

- Attend Celebrex meeting; answer questions about VIGOR meeting to the extent possible, manage expectations, provide commentary if necessary, but maintain relatively low profile prior to review of data for Vioxx
  - Prepare, consider use of reactive materials, e.g., renal and CV safety backgrounders
  - If positive pre-meeting tone and positive outcome, talk to key reporters to ensure that Vioxx is mentioned in stories
- Monitor outcome of Celebrex meeting
- Adapt, modify materials for Vioxx as necessary after review of data for Celebrex

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Tactical Approach:
Feb 8th and after

- Maintain contact with key reporters **throughout the day** to provide perspective on meeting, answer questions
- Hand out hard copies of key slides for media, analysts; provide other slides upon request
- At the end of the day:
  - Finalize key messages in post-meeting Merck meeting; use IMMEDIATELY with reporters on deadline; offer experts
  - Finalize news release to announce committee's action at day's end; issue as soon as feasible and provide to WHHM, IR, USHH for their use
  - If meeting result is strongly positive, have video footage of Vioxx available for broadcast media; issue broadly
- Next day (TBD): Post-meeting conference call for analysts

[redacted]

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Anticipated Competitor Approach

- Pharmacia/Pfizer may capitalize on Celebrex meeting taking place first to plant questions/concerns about VIGOR, position any CV concerns as specific to Vioxx
- Pharmacia/Pfizer will use CLASS data to deliver safety messages specific to Celebrex
  - Use of aspirin in CLASS reflects "real world" use of COX-2s
  - Celebrex has comparable CV/superior renal profile vs. NSAIDs
  - Efficacy messaging unclear
- Should Pharmacia/Pfizer end the day on a negative vote, they may raise VIGOR CV, renal findings more aggressively OR
- Could try to use VIGOR to support Celebrex sNDA and establish foundation for valdecoxib, parecoxib

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Spokespeople

EXTERNAL -- for use prior to the meeting

- Dr. Loren Laine
- Dr. Claire Bombardier
- Dr. Garrett FitzGerald
- Nephrologist

INTERNAL -- for use prior to and during the meeting

- Dr. Eve Slater
- Dr. Barry Gertz

[redacted]

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Core Materials

- Key messages
- News release
  - Positive outcome
  - Neutral outcome
  - Negative outcome(s) -- GI, CV
- Video package
  - With study soundbites, manufacturing and pharmacy footage

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Core materials, cont.

- Q&A
- Background statements for use as background or in response, as necessary:
  - Heart attack rates in VIGOR, other studies of Vioxx
  - Renal effects of NSAIDs, rates of HTN and edema in other studies of Vioxx
  - Comparison of the study design of CLASS, VIGOR (6 months v. full analysis; intent to treat)
  - Statements for outcome of Pharmacia meeting

[redacted]

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Approaches -- Key Outlets

- Schedule pre-Advisory Committee meeting to go through data, provide Merck's background package: Wall Street Journal (Gardiner Harris), Associated Press (Lauran Neergaard), Star-Ledger (Silverman)
- Pre-meeting outreach with discussions limited to publicly available data: Dow Jones (Beth Mantz), Bloomberg (Brian Reid)
- Schedule pre-Advisory Committee meeting to review publicly available data, general safety with Eve Slater: Reuters (Rans Pierson)
- Contact prior to Committee meeting to assess interest in covering, then determine approach: New York Times (Melody Peterson), USA Today (Rita Rubin), Washington Post (Susan Oakey), Financial Times (Adrian Michaels), NewsHour (Susan Dentzer)

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United States Senate
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"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 29

Shari L. Targum, M.D.
Division of Cardio-Renal Drug Products, HFD-110
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20816
Tel (301) 594-5384, FAX (301) 594-5494

Memorandum

DATE: February 1, 2001

FROM: Shari L. Targum, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110
THROUGH: Norman Stockbridge, M.D., Ph.D., Team Leader
Division of Cardio-Renal Drug Products, HFD-110
Raymond J. Lipicky, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110
TO: Sandra Cook, Project Manager, Division of Anti-Inflammatory Drug Products, HFD-550
Maria L. Villalba, MD, Medical Officer, Division of Anti-Inflammatory Drug Products, HFD-550

SUBJECT: Consultation NDA 21-042, S-007
Review of cardiovascular safety database

NAME OF DRUG: Rofecoxib (MK-0966)
TRADE NAME: VIOXX™
FORMULATION: tablets

RELATED APPLICATIONS: A submission for efficacy in rheumatoid arthritis is planned for the end of 2000.
APPROVED INDICATIONS: Acute pain (50 mg/day for up to 5 days) and osteoarthritis (12.5 and 25 mg/day)
SPONSOR: MERCK Research Laboratories

DOCUMENTS AVAILABLE FOR REVIEW:
1. NDA 21-042, S-007 (electronic document room); 2. Prior Consultation from HFD-110 (Dr. Pelayo), 4/30/99;
3. Primary Medical Review (Dr. Villalba), NDA 21-042; 4. Rodriguez LA et. al: Differential Effects of Aspirin and Non-Aspirin Nonsteroidal Antiinflammatory Drugs in the Primary Prevention of Myocardial Infarction in Postmenopausal Women. *Epidemiology* 2000; 11 (4):382-387.

DATE CONSULT RECEIVED: August 16, 2000
DATE CONSULT COMPLETED: December 8, 2000

The purpose of this consultation is to address a concern regarding risk of cardiovascular events with the use of rofecoxib, a selective COX-2 inhibitor. The Medical Reviewer, HFD-550, had five specific questions (see Attached Consultation) for the Cardio-Renal Division; these questions will be addressed under Issues and Comments, page 30.

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BACKGROUND:

Prostaglandins have a role in a wide variety of processes, including inflammation and pain; inhibition of prostaglandin production by cyclooxygenase (COX) inhibitors such as aspirin and nonsteroidal anti-inflammatory has been an important means of providing analgesic and anti-inflammatory benefits.

Cyclooxygenases, enzymes that metabolize arachidonic acid to produce prostaglandins, are subdivided into two isoforms:

1. COX-1, constitutively expressed in most cells, which results in the production of homeostatic prostaglandins that maintain GI mucosal integrity as well as renal blood flow ; in addition, COX-1, found in platelets, mediates production of thromboxane A2, a prostaglandin that promotes vasoconstriction and well as platelet activation and aggregation.

2. COX-2, purportedly inducible[1] in selected tissues, which results in the production of prostaglandins at inflammatory sites as well as prostacyclin (PGI_2), a vasodilator and inhibitor of platelet aggregation. Platelets do not express COX-2; COX-2 inhibition, therefore, would not be expected to directly affect platelet function. However, COX-2 inhibition might, by suppressing prostacyclin production, "inhibit the inhibitor" of platelet aggregation.

Selective COX-2 inhibition would thus have the theoretical benefit of analgesia and decreased inflammation with fewer GI-related side effects (decreased bleeding, ulcers); however, there would also exist a theoretical concern about PGI inhibition and unopposed thromboxane production, leading to an increase in cardiovascular thrombotic events.

Evidence for inhibition of prostacyclin but not thromboxane can be found in this sNDA (CV Events Analysis, pages 79-84; see also Appendix A), where the lack of COX-2 effects on bleeding time and ex vivo platelet aggregation are noted.

It should be noted that there may be aspirin effects, other than thromboxane A2 and/or prostacyclin effects, that might alter the atherosclerotic process. While prostaglandin (thromboxane A2) inhibition has been the major mechanism of aspirin's cardiovascular benefit, it has been proposed that aspirin may also act as an antioxidant, protecting LDL from oxidative modification and improving endothelial dysfunction in atherosclerotic vessels[2]. There are currently two marketed COX-2 inhibitors: celecoxib and rofecoxib. As mentioned above, rofecoxib is approved for osteoarthritis (12.5-25 mg per day) and acute pain (50 mg/day for up to 5 days). Doses of rofecoxib up to 500 mg have been studied in man[3]. However, most of the exposure for $\geq$ 6 months has been to 12.5 and 25 mg daily; according to a prior NDA review, 272 patients have received rofecoxib 50 mg daily for $\geq$ 6 months[3]; at doses of 25-50 mg per day, hypertension, edema, and increased serum creatinine have been noted[4] in a dose-dependent manner.

The Sponsor has submitted sNDA-007 with the apparent goal of establishing a GI safety claim, i.e., reduction in GI bleeding and ulcers, for rofecoxib. An sNDA for an efficacy claim in the treatment of rheumatoid arthritis is planned for the end of 2000.

Methology:

The focus of this review was on the cardiovascular safety of rofecoxib (MK-0966) 50 mg daily in patients with rheumatoid arthritis. To accomplish this review, the Medical Reviewer used the electronic version of the sNDA submission as well as prior reviews (see footnotes) for a reference database. Unless otherwise indicated, all analyses utilized will be taken from the Sponsor's analyses and have not been corroborated by statisticians from HFD-110.

On October 13, 2000, the sponsor submitted a safety update which included 11 additional patients referred for adjudication of cardiovascular serious adverse experiences after February 10, 2000, the prespecified cut-off date in the original safety report. Where possible, the Medical Reviewer will present data from the safety update rather than the original report.

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[1] According to a prior consult from HFD-110 (Dr. Pelayo), there may be constitutive expression of COX-2 in the kidney.

[2] Awtry EH and Loscalzo J. Aspirin. *Circulation*. 2000; 101: 1206-1218.

[3] Prior Medical Officer (Dr. Villalba) review; NDA 21-042/21-052 (5/17/99): Safety Review: page 74.

[3] vide supra.

[4] Prior consult from HFD-110 (Dr. Pelayo) to HFD-550, completed April 30, 1999.

Protocol 088-04 VIGOR (VIOXX GI Outcomes Research)

Title: A Double-Blind, Randomized, Stratified, Parallel-Group Study to Assess the Incidence of PUBs[5] During Chronic Treatment With MK-0966 or Naproxen in Patients With Rheumatoid Arthritis: U.S. Cohort. (VIGOR)

Study dates: January 6, 1999 (first patient in) - March 17, 2000 (last patient out)
Number of sites: 301 (multinational)

Primary Objectives:

1. To determine the relative risk of confirmed PUB (Perforation, Ulcers, Bleeding) in patients taking MK-0966 50 mg daily compared to patients in the group taking naproxen 1000 mg/day.
2. To study the safety and tolerability of MK-0966 in patients with rheumatoid arthritis.

Study Design:

This was a Phase III parallel-group, double-blind study conducted under in-house blinding procedures. There were 2 protocols, 088 (US) and 089 (multinational); however the study was conducted as a single study with a projected total of 7000 patients, with approximately 3500 from the U.S. Treatment duration was partially event-driven, i.e. determined by the need to observe at least 120 confirmed PUBs and and at least 40 confirmed complicated PUBs, or for the minimum duration of treatment to be 6 months, whichever came last.

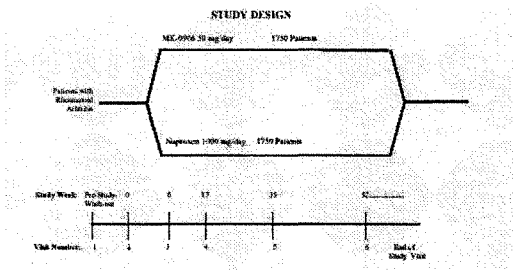
Patients were eligible if they were 50 years or older with rheumatoid arthritis and felt to require NSAID therapy for at least 1 year; patients 40 to 49 years on chronic oral steroids were also eligible. Patients were stratified by a history of a peptic ulcer, upper GI bleeding or perforation versus those without this history.

The use of low-dose aspirin was not allowed in this study; patients requiring aspirin for cardioprotection were excluded. Other "cardiac-related" exclusions: angina or congestive heart failure with symptoms at rest or minimal activity, myocardial infarction or coronary bypass grafting within 1 year, stroke or transient ischemic attack within 2 years, uncontrolled hypertension.

Those eligible were randomized to MK-0966 50 mg per day or naproxen 500 mg 2 times a day in a blinded fashion (double-dummy technique); there was no placebo arm. The primary endpoint was occurrence of PUBs. Other endpoints were related to efficacy or GI safety and included: complicated PUBs, discontinuation due to lack of efficacy, Patient Global Assessment of Disease Activity, and Investigator Global Assessment of Disease Activity.

Prespecified subgroups (for analysis) included: prior history of PUB, age, gender, race, and study region.

[5] **PUB** refers to gastrointestinal (GI) perforation, gastric outlet obstructions, complicated ulcers, severe upper GI bleeding.



Besides all serious adverse experiences and those leading to study discontinuation, prespecified adverse experiences included those related to: digestive system, hypertension, edema, renal (clinical or laboratory adverse experiences), hepatic (clinical or laboratory adverse experiences), and congestive heart failure;

Patients who discontinued were to have a discontinuation visit within 48 hours of their dropping from the study. In addition, those who discontinued were contacted 14 days after the last day of treatment for a safety follow-up. They were also contacted 45 days after the last day of treatment and at the end of study to specifically check for a GI adverse experience.

A Protocol Amendment on 9/2/99 removed the requirement for a 14 day follow up phone call for those completing the study.

Committees:

Steering Committee provided overall direction of the trial and was responsible for the trial's conduct. In the protocol, this committee was to be blinded to the results--though the DSMB (see below) had the option of "unblinding" some members of the Steering Committee to certain aspects of the data.

Executive Committee decided on practical issues during the trial and advised the Steering Committee.

Advisory Committee would meet with the DSMB, discuss recommendations to terminate the study or amend the protocol, and discuss these recommendations with the Steering Committee.

End Point Classification Committee was to define and review all PUBs (per protocol).

Case Review Committee was to have final blinded adjudication for all potential endpoints. This committee consisted of three voting clinicians, of whom at least two were gastroenterologists.

Data and Safety Monitoring Board (DSMB) monitored this trial for beneficial or adverse effects; except for a nonvoting Merck statistician, members of this committee were to be independent from the Sponsor, investigators, and patients.

A blinded, external Vascular Event Committee (VEC), containing three separate subspecialty committees (cardiac, cerebrovascular, and peripheral), existed for surveillance, monitoring, and adjudication of vascular events occurring in COX-2 inhibitor trials.

The Vascular Events Monitoring and Adjudication SOP can be found in the protocol: Category 3, Appendix 6 under 088c (sNDA, P088c: Appendix 3.2.1, pdf. Page 1681), dated August 30, 1999. Your Division, HFD-550, has been asked to clarify whether the Vascular Event Committee was prespecified, or created in response to a safety concern). The DSMB minutes begin in October, 1999.

DSMB: Minutes of the VIGOR DSMB meetings on October 4, 1999, November 18, 1999, and December 22, 1999 can be found in sNDA S-007: P088C: Appendix 3.9.1 (pdf pages 2937-2952).

The October 3, 1999 meeting was convened to discuss the first interim analysis of the VIGOR trial; at this time there was no specific mention of cardiovascular adverse events.

During the November 18, 1999 meeting, discussion focused on the "excess deaths and cardiovascular adverse experiences in Group A compared to Group B" (52 versus 29 serious cardiovascular events, respectively). In this report, there were 40 and 17 patients that discontinued the study because of cardiovascular adverse events in Groups A and B, respectively. In addition, a mean increase in systolic blood pressure (4 mm Hg) was noted in Group A and

a corresponding increase in hypertension adverse events, compared to little or no change in Group B. It was noted that this trial was unable to distinguish between a potentially harmful effect of Treatment A and a cardioprotective effect of Treatment B; in addition, the event rates were small. DSMB members expressed concern but the trial was allowed to continue. Additional analyses (Cox model, subdividing by those with underlying cardiac disease) were planned. An additional non-endpoint safety analysis was planned with a December 1 cutoff.

In a December 20, 1999 letter to the sponsor, the DSMB recommended development of a separate analysis plan for adjudicated events in the VIGOR study. This letter specifically stated that "it will be important that these events be adjudicated blinded." One concludes from this statement that the DSMB received unadjudicated adverse event data.

In the December 22, 1999 meeting the additional analysis was presented; it was noted that (as expected) a higher rate of events occurred in the higher risk patients in both treatment groups. No member felt that the trial should be stopped; members expressed belief that the effect might be "due to cardioprotective effects of Treatment B." At the time, no cardiovascular analysis plan was in place for VIGOR or VIOXX; it was again suggested that the analysis plan be developed prior to unblinding.

Results:

Patient Disposition:

The following table represents patient accounting, as noted by the sponsor. No meaningful differences in patient disposition are noted between the two treatment groups. Approximately 29% of patients did not complete this trial. The most common reason for discontinuation was the occurrence of a clinical adverse experience. There appear to be no meaningful differences between the two treatment groups in percentage discontinuing the trial and the overall reasons for discontinuation. Slightly more patients in the rofecoxib group were discontinued due to laboratory adverse experience and protocol deviations.

	Patient Accounting					
	Rofecoxib 50 mg n (%)		Naproxen 1000 mg n (%)		Total n (%)	
TOTAL PATIENTS	4047 (100.0)		4029 (100.0)		8076 (100.0)	
COMPLETED TRIAL	2862	(70.7)	2880	(71.5)	5742	(71.1)
DISCONTINUED TRIAL	1185	(29.3)	1149	(28.5)	2334	(28.9)
Clinical adverse experience	645	(15.9)	636	(15.8)	1281	(15.9)
Laboratory adverse experience	22	(0.5)	12	(0.3)	34	(0.4)
Lack efficacy	256	(6.3)	263	(6.5)	519	(6.4)
Lost to follow-up	6	(0.1)	4	(0.1)	10	(0.1)
Patient discontinued for other	27	(0.7)	30	(0.7)	57	(0.7)
Patient moved	17	(0.4)	16	(0.4)	33	(0.4)
Patient withdrew consent	138	(3.4)	130	(3.2)	268	(3.3)
Protocol deviation	74	(1.8)	58	(1.4)	132	(1.6)
Data Source: [4.7]						

(Source: Study Report 088c: pdf. page 92. Original submission: 6/29/00)

Drug Exposure:

As noted below, patients were followed for a mean of 8.0 months. There appear to be no meaningful differences in the two treatment groups in the duration of follow-up or the number of patients exposed to study drugs.
(Source: 088c Clinical study report pdf. page 93. Original submission: 6/29/00)

Time in Study†							
	Treatment			Duration of Follow-Up (Months)			
Cohort	Group	N	Mean	SD	Median	Range	Inter-Quartile Range
Overall	Rofecoxib	4047	8.0	3.1	9.0	0.5 to 13.0	7.5 to 10.1
	Naproxen	4029	8.0	3.1	9.0	0.5 to 12.7	7.6 to 10.1
	Total	8076	8.0	3.1	9.0	0.5 to 13.0	7.6 to 10.1
U.S.	Rofecoxib	1748	7.5	3.6	8.5	0.5 to 13.0	4.4 to 10.3
	Naproxen	1750	7.5	3.5	8.5	0.5 to 12.7	4.4 to 10.3
	Total	3498	7.5	3.6	8.5	0.5 to 13.0	4.4 to 10.3
Multi-national	Rofecoxib	2299	8.4	2.7	9.2	0.5 to 12.3	8.0 to 10.0
	Naproxen	2279	8.4	2.6	9.2	0.5 to 12.2	8.1 to 10.0
	Total	4578	8.4	2.7	9.2	0.5 to 12.3	8.0 to 10.0
†	Up to 14 days past discontinuation.						

Number of Patients in the Study at Different Time Points†				
		Rofecoxib	Naproxen	Total
		(N=4047)	(N=4029)	(N=8076)
Month		n (%)	n (%)	n (%)
	2	3645 (90.1)	3647 (90.5)	7292 (90.3)
	4	3407 (84.2)	3395 (84.3)	6802 (84.2)
	6	3181 (78.6)	3173 (78.8)	6354 (78.7)
	8	2806 (69.3)	2800 (69.5)	5606 (69.4)
	9	2026 (50.1)	2039 (50.6)	4065 (50.3)
	10	1072 (26.5)	1074 (26.7)	2146 (26.6)
	11	440 (10.9)	432 (10.7)	872 (10.8)
	12	57 (1.4)	60 (1.5)	117 (1.4)
†The number of patients at each time point indicated represents the number of patients completing the previous time point and at risk at the beginning of the indicated time period.				
Duration of observation includes 14 days past date of discontinuation.				
(Source: 088c Study Report pdf. page 94. 6/29/00)				

Baseline characteristics:

Baseline characteristics between the two treatment groups revealed no meaningful differences in age, weight, height, ethnic group, study region, alcohol use, duration of RA, ARA status, smoking history, or history of cardiac disease.

The study population was mostly female (approx. 80%), mainly (over 70%) under 65, and mainly (approx. 68%) Caucasian. About 43% of the total population came from the U.S. Almost half of the total population had a history of "cardiac disease"(it is unclear how this parameter was defined) and about half had a history of any cardiac risk factor; however, less than 6% had a history of atherosclerotic cardiovascular disease (see below, Table C-1, Baseline Cardiovascular Demographics). About 82% had a history of prior NSAID use (for RA or other reasons) with no difference between the two treatment groups.

Baseline Patient Characteristics by Treatment Group			

Treatment Group	N	Mean (SD)	
Age (Years)			
Rofecoxib	4047	58.0	(9.5)
Naproxen	4029	58.2	(9.6)
Total	8076	58.1	(9.5)
Weight (kg)			
Rofecoxib	4045	72.2	(17.7)
Naproxen	4027	71.9	(17.0)
Total	8072	72.1	(17.3)
Height (cm)			
Rofecoxib	4026	161.8	(10.2)
Naproxen	4010	161.8	(10.0)
Total	8036	161.8	(10.1)

Source: Sponsor: 088c: pdf. page 98. Original submission 6/29/00.

	Rofecoxib		Naproxen		Total	
Baseline Demographics	(N=4047)		(N=4029)		(N=8076)	
	n	(%)	n	(%)	n	(%)
Gender						
Female	3223	(79.6)	3215	(79.8)	6438	(79.7)
Male	824	(20.4)	814	(20.2)	1638	(20.3)
Ethnic Group						
White	2761	(68.2)	2750	(68.3)	5511	(68.2)
Black	207	(5.1)	202	(5.0)	409	(5.1)
Asian	101	(2.5)	85	(2.1)	186	(2.3)
Hispanic	501	(12.4)	516	(12.8)	1017	(12.6)
Multi-racial	464	(11.5)	466	(11.6)	930	(11.5)
Other	13	(0.3)	10	(0.2)	23	(0.3)
Study Region						
U.S.	1748	(43.2)	1750	(43.4)	3498	(43.3)
Multinational	2299	(56.8)	2279	(56.6)	4578	(56.7)
Age Group						
<40	10	(0.2)	11	(0.3)	21	(0.3)
History of Cardiac Disease						
Yes	1884	(46.6)	1838	(45.6)	3722	(46.1)
No	2163	(53.4)	2191	(54.4)	4354	(53.9)
Smoking Status						
Unknown	1	(0.0)	0	(0.0)	1	(0.0)
Never Smoked	2128	(52.6)	2150	(53.4)	4278	(53.0)
Ex-Smoker	1128	(27.9)	1100	(27.3)	2228	(27.6)
Current Smoker	790	(19.5)	779	(19.3)	1569	(19.4)
Number Cigarettes/24 Hours						
<11/day	404	(51.1)	409	(52.5)	813	(51.8)
11 to 20/day	271	(34.3)	252	(32.3)	523	(33.3)
>20/day	115	(14.6)	118	(15.1)	233	(14.9)

Source: 088c: pdf. Pages 99- 100. Original submission 6/29/00.

Baseline cardiac risk factors are presented (next page):
There appear to be no meaningful differences between the two treatment groups in age, gender, past cardiovascular history, and cardiac risk factors.

Baseline Cardiovascular Demographics in Rheumatoid Arthritis Patients	

Enrolled in the VIGOR Study				
(CV events analysis: original table, 6/29/00)				
	Rofecoxib		**Naproxen**	
	(N=4047)		(N=4029)	
Demographic	n	(%)	n	(%)
Age				
Percent <65 Years Old	3050	(75.4)	2959	(73.4)
Percent 65 Years Old	997	(24.6)	1070	(26.6)
Past Cardiovascular History				
Past History of Atherosclerotic Cardiovascular Disease	238	(5.9)	216	(5.4)
Coronary Artery Disease	171	(4.2)	153	(3.8)
Myocardial Infarction	57	(1.4)	50	(1.2)
Cerebrovascular Disease	26	(0.6)	25	(0.6)
Cerebrovascular Accident	12	(0.3)	16	(0.4)
Peripheral Arterial Disease	56	(1.4)	49	(1.2)
Cardiovascular Risk Factors				
Any Cardiovascular Risk Factor	2047	(50.6)	1988	(49.3)
Hypertension	1217	(30.1)	1168	(29.0)
Diabetes Mellitus	240	(5.9)	254	(6.3)
Current Smoker	790	(19.5)	779	(19.3)
Hypercholesterolemia	343	(8.5)	293	(7.3)
Indication for Aspirin Therapy				
Aspirin Therapy Indicated[†]	170	(4.2)	151	(3.7)

[†] Patients with past medical histories that met criteria for chronic vascular-protective aspirin therapy (past history of either cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable or stable angina, coronary artery bypass graft surgery, or percutaneous coronary interventions).
[P088C]

In the October 13, 1999 Safety Update, the Baseline Cardiovascular Demographics were further subdivided by the sponsor into US and Multinational cohorts. This reviewer found no meaningful differences between the two treatment groups in the various baseline characteristics and cardiac risk factors. These tables can be found in S-007, 10-13-2000 Safety Update Report, Attachment 5, pdf. Pages 58-59.

Dropouts:

There were 1131 and 1032 patients in the rofecoxib and naproxen groups, respectively, that discontinued the study for any reason other than the primary endpoint. The rates of discontinuation were 42.6 and 38.9 per 100 patients years, respectively. The relative risk was 1.10 (95% CI: 1.01, 1.19; p=0.033). This difference appears to be due to an increase in discontinuations due to clinical adverse experiences other than PUBs.

The findings below are consistent with a previous safety review from HFD-110 which found a dose-related increase in hypertension and edema in rofecoxib.[6] There is a numerical increase in congestive heart failure adverse experiences in the rofecoxib group; this trend was not significant. It is unclear whether this trend (or this patient population) is related to, or is separate from, the edema-related adverse experiences. It is also unclear whether the congestive heart failure is related to other events, such as hypertension or ischemia. The sponsor should be asked to clarify these respective points.

Analysis of Prespecified Adverse Experience (AE) Categories

Type of Adverse Experience	Treatment Group	N	Patients With Events	PYR†	Rates‡	Estimate	Relative Risk§ 95% CI%	p-Value
Serious clinical AEs	Rofecoxib	4047	378	2611	14.48	1.21	(1.04, 1.40)	0.013
	Naproxen	4029	315	2631	11.97			
Clinical AEs leading to discontinuation	Rofecoxib	4047	643	2649	24.27	1.01	(0.91, 1.13)	0.842
	Naproxen	4029	635	2647	23.99			
Discontinues due to GI AEs + abdominal pain	Rofecoxib	4047	307	2676	11.47	0.73	(0.63, 0.85)	<0.001
	Naproxen	4029	416	2664	15.62			
Discontinues due to edema-related AEs	Rofecoxib	4047	25	2697	0.93	1.92	(0.98, 3.75)	0.057
	Naproxen	4029	13	2698	0.48			
Discontinues due to hypertension-related AEs	Rofecoxib	4047	28	2697	1.04	4.67	(1.93, 11.28)	<0.001
	Naproxen	4029	6	2699	0.22			
CHF AEs	Rofecoxib	4047	19	2696	0.70	2.11	(0.96, 4.67)	0.065
	Naproxen	4029	9	2698	0.33			

† Patient-years at risk.
‡ Per 100 PYR.
§ Relative risk of rofecoxib with respect to naproxen from Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates and
p-value is from discrete log-rank
distribution.
% Confidence interval.
Data Source: [4.3]
Adapted from 088c: Table 44. pdf. Pages 152-153. Original submission 6/29/00.

[6] See prior consult from HFD-110 (Dr. Pelayo) to HFD-550, completed April 30, 1999.

Adjudication:

Summary of Analysis of Cardiovascular Serious Adverse Experiences Referred for Adjudication							
VIGOR Study in Patients With Rheumatoid Arthritis (10/13/00 Safety Update)							
	Updated Application Data						
	Treatment		Patients With			Relative Risk	
Event Category	Group	N	Events	PYR[†]	Rates[‡]	Estimate	95% CI
All unadjudicated thrombotic cardiovascular	Rofecoxib	4047	64	2695	2.37		
serious adverse experiences	Naproxen	4029	32	2696	1.19	0.50	(0.33, 0.76)
[†] Patient-years at risk.							
[‡] Per 100 PYR.							
Data Source: [Attachment 3]							

Serious adverse events were evaluated by an Independent Adjudication Committee. The following table shows a disposition of those events: (Source: Safety Update 10/13/2000: pdf. page 8)

Table 1		
Accounting of Cardiovascular Serious Adverse Experiences That Underwent		
Adjudication in the VIGOR Trial in Rheumatoid Arthritis Patients		
Updated Application Data		
Serious Adverse Experience Categories	Rofecoxib	Naproxen
Serious adverse experiences meeting criteria for referral to	65	33
adjudication		
Events not meeting criteria for a thrombotic cardiovascular serious	19	13
adverse experience		
Events adjudicated to be nonthrombotic serious adverse	12	9
experiences		
Events adjudicated to be hemorrhagic strokes or primary	2	1
intracranial hemorrhage events		
Events with insufficient data for adjudication	5	3
Events meeting criteria for a thrombotic cardiovascular serious	46	20
adverse experience		

The events excluded from adjudication appear to have been balanced; there were still about twice as many events in the rofecoxib group than in the naproxen group, whether unadjudicated or adjudicated.

The SOP for the vascular event monitoring and adjudication can be found in 088c: Category 3: Appendix 3.2.1(pdf. Pages 1678-1691. Original submission 6/29/00). The criteria for vascular event adjudication were reviewed; coronary events referred for adjudication included myocardial infarction, unstable angina, cardiac thrombus, resuscitated cardiac arrest, and sudden or unexplained death. Cerebrovascular events included stroke (ischemic and hemorrhagic) and transient ischemic attack. Also considered for adjudication were venous thrombosis and pulmonary embolism.

Adjudication guidelines (088c: Appendix H: pdf. Pages 1714-1717) for myocardial infarction include 1. new pathologic Q waves in 2 contiguous leads; or 2. ischemic symptoms or ischemic repolarization changes with rising cardiac enzymes. In patients undergoing invasive cardiac revascularization, criteria are: 1. Rise in CPK-MB; or 2. Rise in Cardiac Troponin I or T; or 3. Rise in CPK (in the absence of CPK-MB); in patients following CABG, new pathologic Q waves in 2 contiguous leads within 48 hours of the procedure (otherwise the criteria are the same as for those not undergoing invasive procedures).

These criteria for myocardial infarction appear to be acceptable to this Medical Reviewer.

Safety:

The approach used in the cardiovascular safety evaluation for the VIGOR study included: examination of deaths, discontinuations, serious adverse events, and treatment emergent adverse events.

Discontinuations due to serious cardiovascular adverse experiences:

The following table lists discontinuations due to serious adverse experiences. Presumably (given the numbers) these events were unadjudicated.

Number (%) of Patients Discontinued Due to Specific Serious Clinical Adverse Experiences by Body System (Incidence _0.2% in One or More Treatment Groups)				
	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Patients with one or more adverse experience	143	(3.5)	127	(3.2)
Patients with no adverse experience	3904	(96.5)	3902	(96.8)
Cardiovascular System	61	(1.5)	21	(0.5)
Cerebrovascular Accident	10	(0.2)	3	(0.1)
Myocardial Infarction	12	(0.3)	3	(0.1)
Digestive System	27	(0.7)	61	(1.5)
Gastric Ulcer	2	(0.0)	11	(0.3)
Hemorrhagic Duodenal Ulcer	4	(0.1)	7	(0.2)
Hemorrhagic Gastric Ulcer	2	(0.0)	13	(0.3)
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.				
Data Source: [4.3; 4.17]				

Source: Adapted from 088: Table 58: pdf. page 196. Original submission 6/29/00.

Dizziness (0.5 versus 0.2%), congestive heart failure (0.1 versus 0.0%), hypertension (0.6 versus 0.1%), myocardial infarction (0.3 versus 0.1%), unstable angina (0.1 versus 0.0%), all led to study discontinuation more frequently with rofecoxib compared with naproxen.

The following is the sponsor's analysis using standard composite endpoints seen in antiplatelet trials. The sponsor has further subdivided patients into "aspirin indicated," those with conditions where low-dose aspirin for cardioprotection was indicated, and "aspirin not indicated" categories.

It can be seen that, in the "All Patients" category, there is an increased rate of MI and stroke in the rofecoxib group compared with naproxen; in the MI group, the 95% confidence interval is significant. In the two subgroups, the composite endpoint and MI events are still favorable for naproxen and unfavorable for rofecoxib.

This analysis could lead one to conclude that naproxen, with a 51% risk reduction compared to rofecoxib, would be the preferred drug.

Analyses of Cardiovascular Events in the VIGOR Study Using Endpoint Definitions Standard in Large Antiplatelet Trials

Updated Application Report (Safety Update: Table C-11: pdf. Pages 30-31) 10/13/00.

	Treatment		Number of Patients			Relative Risk[§]		
Event Category	Group	N	With Events	PYR[†]	Rates[‡]	Estimate	95% CI	
All Patients								
Cardiovascular deaths[%], MI, CVA	Rofecoxib	4047	35	2698	1.30			
	Naproxen	4029	18	2698	0.67	0.51	(0.29,	0.91)
Cardiovascular deaths[%]	Rofecoxib	4047	7	2700	0.26			
	Naproxen	4029	7	2699	0.26	1.00	(0.35,	2.85)
MI	Rofecoxib	4047	20	2699	0.74			
	Naproxen	4029	4	2699	0.15	0.20	(0.07,	0.58)
Stroke[¶]	Rofecoxib	4047	11	2699	0.41			
	Naproxen	4029	9	2699	0.33	0.82	(0.34,	1.97)
Aspirin Indicated								
Cardiovascular deaths[%], MI, CVA	Rofecoxib	170	12	105	11.42			
	Naproxen	151	3	102	2.94	0.26	(0.07,	0.91)
Cardiovascular deaths[%]	Rofecoxib	170	1	106	0.95			
	Naproxen	151	2	102	1.96	2.07	(0.11, 122.10)	
MI	Rofecoxib	170	8	105	7.60			
	Naproxen	151	0	102	0.00	0.00	(0.00,	0.60)
Stroke[¶]	Rofecoxib	170	3	106	2.84			
	Naproxen	151	2	102	1.96	0.69	(0.06,	6.02)

Event Category	Treatment Group	N	Number of Patients	PYR	Rates	Relative Risk Estimate	95% CI	
Aspirin Not Indicated								
Cardiovascular deaths[%], MI, CVA	Rofecoxib	3877	23	2593	0.89			
	Naproxen	3878	15	2596	0.58	0.65	(0.34,	1.25)
Cardiovascular deaths[%]	Rofecoxib	3877	6	2594	0.23			
	Naproxen	3878	5	2597	0.19	0.83	(0.25,	2.73)
MI	Rofecoxib	3877	12	2593	0.46			
	Naproxen	3878	4	2597	0.15	0.33	(0.11,	1.03)
Stroke¶	Rofecoxib	3877	8	2593	0.31			
	Naproxen	3878	7	2597	0.27	0.87	(.32,	2.40)

† Patient-years at risk.
‡ Per 100 PYR.
§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.
% Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal gastrointestinal bleeding episode.
¶ Includes fatal and nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes.
§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.
% Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal GI bleeding episode.
¶ Includes fatal or nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes.
# "Aspirin Indicated" patients are patients with past medical histories of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions). [84] "Aspirin Not Indicated" patients are patients without a past medical history of these conditions.
[Attachment 3]

Serious Cardiovascular Adverse Experiences

The following table was sent in a 10/13/00 safety update and represents confirmed adjudicated cardiovascular serious adverse experiences, as presented by the sponsor.
Of the breakdown of thrombotic events, it is the cardiac events which are significantly different (i.e., the Confidence Interval does not cross 1.0). It should be noted that the other categories have a smaller number of events but show consistently higher numbers of events, rates, and relative risk estimates in the rofecoxib group.

Summary of Analysis of Confirmed Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences VIGOR Study in Patients With Rheumatoid Arthritis †
Updated Application
Data (10/13/00)

		Treatment		Patients With			Relative Risk§	
	Event Category	Group	N	Events	PYR‡	Rates‡	Estimate	95% CI
All thrombotic events		Rofecoxib	4047	45	2697	1.67		
		Naproxen	4029	19	2698	0.70	0.42	(0.25, 0.72)
All cardiac events		Rofecoxib	4047	28	2698	1.04		
		Naproxen	4029	10	2698	0.37	0.36	(0.17, 0.74)
All cerebrovascular events		Rofecoxib	4047	11	2699	0.41		
		Naproxen	4029	8	2699	0.30	0.73	(0.29, 1.80)
All peripheral vascular events		Rofecoxib	4047	6	2699	0.22		
		Naproxen	4029	1	2699	0.04	0.17	(0.00, 1.37)

† In keeping with the data analysis section of the Adjudication SOP, this table does not include events determined by adjudication to be hemorrhagic cerebrovascular accidents.

‡ Per 100 patient-years at risk (PYR).

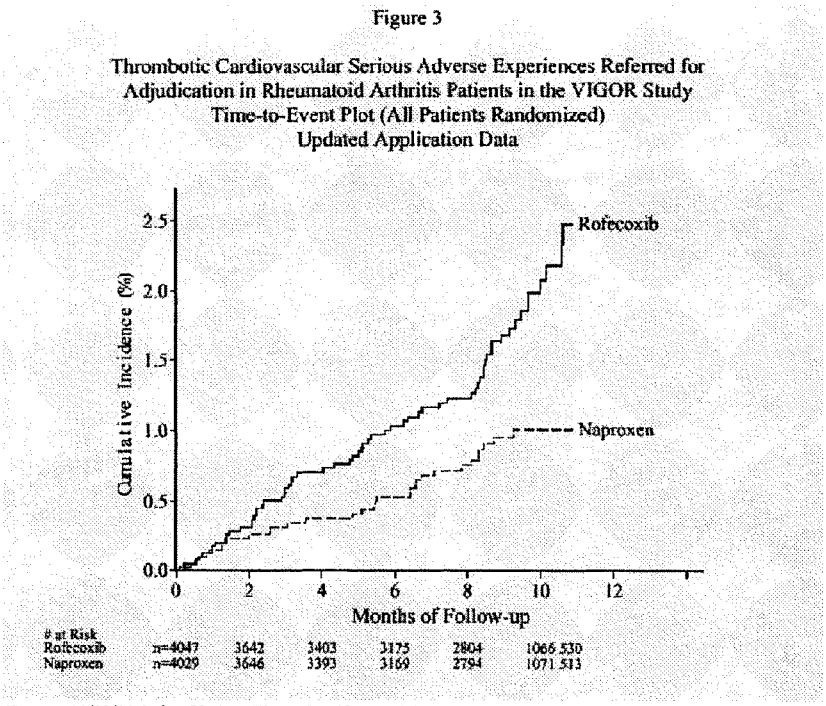
§ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
Data Source: [Attachment 3]

Time to Event: The Time-to-Event Curves for Unconfirmed and Confirmed Thrombotic Events are shown.; the curves are similar in that they begin to diverge after about 6-8 weeks. It would be helpful to further analyze these curves for differences in these two groups. In addition, what event rates would be needed to show a significant difference between rofecoxib and naproxen? Both of these graphs are taken from the 10/13/00 safety update.

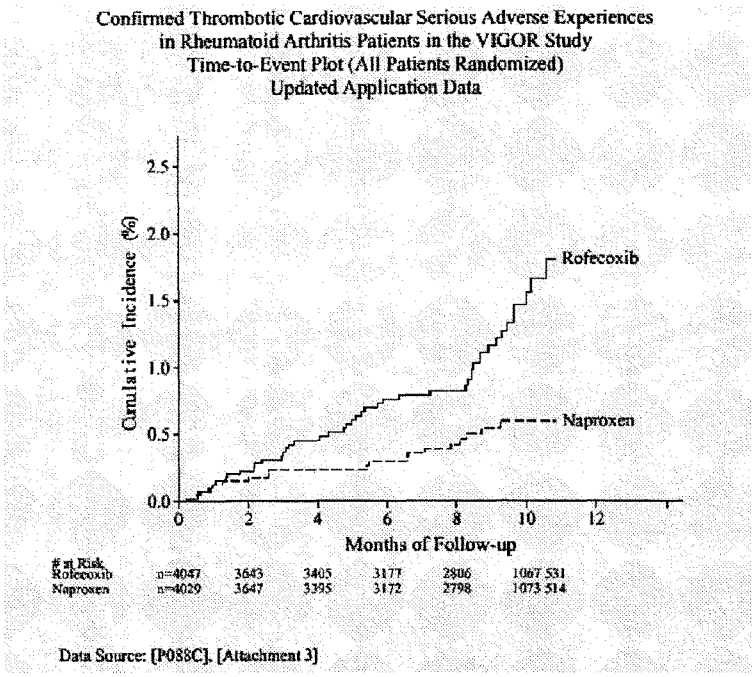
Figure 3

Thrombotic Cardiovascular Serious Adverse Experiences Referred for Adjudication in Rheumatoid Arthritis Patients in the VIGOR Study
Time-to-Event Plot (All Patients Randomized)
Updated Application Data



(Source: 10/13/00 Safety Update: Figure 3: pdf. page 41)

On the next page, the time-to-event for Confirmed Cardiovascular Thrombotic Events is shown. (Source: Safety Update Figure 1: pdf. Page 15)



Adjudicated Thrombotic Serious Cardiovascular Adverse Experiences--Specific Events

The following table lists adjudicated cardiovascular serious adverse experiences in the VIGOR Study. From this table it appears that the most striking difference between the two groups is under Myocardial Infarction (safety update 10/13/00) Please note that these are the sponsor's data. This Medical Reviewer counted at least 8 potential cardiac deaths in the rofecoxib group (see Deaths, next page). Also, hemorrhagic stroke, which may not be thrombotic, is included.

Summary of Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences VIGOR Study in Patients With Rheumatoid Arthritis Updated Application Data				
	Rofecoxib (N=4047)		Naproxen (N=4029)	
Event	n	(%)	n	(%)
Any Event†	**47**	**(1.2)**	**20**	**(0.5)**
Arterial Event†	**42**	**(1.0)**	**19**	**(0.5)**
Venous Event	5	(0.1)	1	(0.0)
Cardiovascular Death†	6	(0.1)	6	(0.1)
Fatal Acute Myocardial Infarction	2	(0.0)	0	(0.0)
Fatal Hemorrhagic Stroke	1	(0.0)	1	(0.0)
Fatal Ischemic Cerebrovascular Stroke	0	(0.0)	1	(0.0)
Sudden Cardiac Death	3	(0.1)	4	(0.1)
Cardiac Events (Fatal/Nonfatal)	28	(0.7)	10	(0.2)
Acute Myocardial Infarction	**20**	**(0.5)**	**4**	**(0.1)**
Sudden Cardiac Death	3	(0.1)	4	(0.1)
Unstable Angina Pectoris	5	(0.1)	3	(0.1)
Cerebrovascular Events (Fatal/Nonfatal)†	**13**	**(0.3)**	**9**	**(0.2)**
Hemorrhagic Stroke	2	(0.0)	1	(0.0)
Ischemic Cerebrovascular Stroke	9	(0.2)	8	(0.2)
Transient Ischemic Attack	2	(0.0)	0	(0.0)
Peripheral Vascular Events (Fatal/Nonfatal)	**6**	**(0.1)**	**1**	**(0.0)**
Peripheral Arterial Thrombosis	1	(0.0)	0	(0.0)
Peripheral Venous Thrombosis	5	(0.1)	1	(0.0)
† Includes hemorrhagic stroke.				
Note: Patients may be counted in more than 1 row, but are only counted once within a row.				

Deaths:

There were 37 deaths (all-causes) in this trial: 22 in the Rofecoxib and 15 in the Naproxen groups, respectively. In analyzing causes of death, the Medical Reviewer examined (original submission, 6/29/00) Table 55(Study Report Section 9.3; pdf. Page 169), Patient Narratives (Appendix 4.20.1: beginning pdf. Page 3255), and the Case Report Forms. It should be noted that the death analyses (above tables) in this review were performed with the sponsor's analyses and were not reanalyzed using the data from this Medical Reviewer; it is unclear if the cardiovascular deaths in the sponsor's analyses are the same as those presented below.

In the Rofecoxib group, the following deaths were possible or probable cardiovascular/cerebrovascular events (see Appendix , Table 55 for full table). Items in bold (9 cases) are possibly/probably related to thrombosis/atherosclerosis:

Deaths: Rofecoxib group: Medical Reviewer's analysis

AN	Study number	Gender	Race	Age	Relative Day of Onset	Adverse experience
324	088022	M	White	69	174	**Ventricular fibrillation/Sudden death**
1224	088140	F	White	68	46	**Myocardial infarction†**
920	088148	F	White	68	205	**Cerebrovascular accident**
2759	088149	M	White	69	94	**Myocardial infarction**

†This patient was classified in Table 55 as "multiple organ failure." However, a review of the patient narrative showed that this patient had a non Q-wave myocardial infarction (with associated symptoms, ECG changes, and cardiac enzyme elevation). The Medical Reviewer, therefore, reclassified this event as myocardial infarction. See sNDA S-007: CSR 088c: pdf page 1286 for further details.

Deaths: Rofecoxib group (cont.)

AN	Study number	Gender	Race	Age	Relative Day of Onset	Adverse experience
5305	089013	F	Multi	75	309	**Cardiac arrest/Sudden death**
7620	089021	F	Multi	55	31	Dissecting aortic aneurysm
5591	089022	F	White	51	206	**Cerebrovascular accident**
7973	089100	M	White	71	147	**Myocardial infarction**
7553	089107	F	Multi	51	28	**Dyspnea/cyanosis, unknown etiology***
7689	089127	F	White	60	107	**Sudden death‡**

*This patient, coded as "congestive heart failure" in Table 55, presented to the ER with dyspnea and cyanosis, was given aminophylline and subsequently died; the cause of death was registered as "cardiac insufficiency" and no other details (EKG, labs) are given in the narrative. There is no history of asthma in the case report form; screening cardiac/pulmonary exam was normal. See sNDA S-007: CSR 088c: pdf page 1292.
‡This patient was coded in Table 55 as "aortic stenosis." According to the narrative, this patient with hypertension and diabetes died suddenly at home. Autopsy showed cardiac hypertrophy and pulmonary congestion; no finding of aortic valve abnormalities or asymmetric septal hypertrophy were reported. In the case report form, there is notation of "idiopathic hypertrophic subaortic stenosis;" the screening cardiac exam was noted as normal and the patient was on enalapril. No autopsy or echocardiographic findings are reported. Therefore, the Medical Reviewer reclassified this event as sudden death. See sNDA S-007: CSR 088c: pdf page 1293 for further details.

In the Naproxen group, the following five deaths were possible or probable cardiovascular/cerebrovascular events:

Deaths: Naproxen Group: Medical Reviewer's Analysis

AN	Study number	Gender	Race	Age	Relative Day of Onset	Adverse experience
2923	088003	M	White	60	164	**Cerebrovascular accident**
2632	088163	F	White	70	17	**Sudden death***
7732	089016	M	White	62	61	**Sudden death ****
2229	088175	F	White	79	247	Intracranial hemorrhage
6703	089076	F	White	53	205	Intracranial hemorrhage
7769	089021	M	White	58	266	**Myocardial infarction/Sudden death°**
6057	089054	M	White	70	200	**Myocardial infarction/Sudden death°**

The Reviewer has marked in bold those events possibly related to thrombosis/ischemia.
*Coded in Table 55 as myocardial infarction; however, this was sudden death according to the narrative.
** Coded in Table 55 as Unknown cause of death; according to the narrative, this patient was found dead in his home. The only additional information is a complaint of cough and chest pain the day before his demise.
°Coded as myocardial infarction; however, there is no documentation for myocardial infarction in the case report form. These patients were not hospitalized and are listed as deaths.

Subgroup analyses of cardiovascular serious adverse experiences:

The sponsor has provided a subgroup analysis in the 10/13/00 safety update. The relative risk estimate is not significant only in the hypertensive subgroup.

Summary of Adjudicated Thromboembolic Serious AEs in Selected Subgroups
of Patients With Rheumatoid Arthritis in VIGOR
Safety Update Report

Subgroup	Treatment	N	Patients With Events	PYR[†]	Rates[‡]	Relative Risk[§] Estimate	95% CI
Males	Rofecoxib	824	20	548	3.65		
	Naproxen	814	7	556	1.26	0.34	(0.15, 0.81)
Females	Rofecoxib	3223	25	2149	1.16		
	Naproxen	3215	12	2142	0.56	0.48	(0.24, 0.96)
65+ years old	Rofecoxib	997	28	621	4.51		
	Naproxen	1070	13	662	1.97	0.43	(0.22, 0.84)
<65 years old	Rofecoxib	3050	17	2076	0.82		
	Naproxen	2959	6	2037	0.29	0.36	(0.14, 0.91)
Current smoker	Rofecoxib	790	17	516	3.29		
	Naproxen	779	5	533	0.94	0.28	(0.10, 0.76)
Ex/never smoker	Rofecoxib	3256	28	2180	1.28		
	Naproxen	3250	14	2165	0.65	0.50	(0.26, 0.96)
Cardiovascular history	Rofecoxib	238	16	147	10.92		
	Naproxen	216	5	139	3.60	0.33	(0.12, 0.90)
No cardiovascular history	Rofecoxib	3809	29	2550	1.14		
	Naproxen	3813	14	2559	0.55	0.48	(0.25, 0.91)
Hypertensive	Rofecoxib	1217	20	790	2.53		
	Naproxen	1168	12	762	1.58	0.62	(0.30, 1.27)

Aspirin indicated /Aspirin not indicated subgroup:
The sponsor has provided an analysis based on the subgroup of patients meeting criteria for aspirin use for cardioprotection (i.e. those who might have benefitted from low-dose aspirin use) . It can be seen that there are higher rates of events in the rofecoxib group (with significant confidence intervals) in both subgroups.

Incidence of Adjudicated Thrombotic Cardiovascular Serious Adverse Experiences in Patient Subgroups									
Based on a Past Medical History Meeting Criteria for Vascular-Protective Aspirin Therapy									
VIGOR Study in Rheumatoid Arthritis Patients									
Updated Application Data									
		Treatment		Patients With			Relative Risk[§]		
	Subgroup	Group	N	Events	PYR[†]	Rates[‡]	Estimate	95% CI	
All patients		Rofecoxib	4047	45	2697	1.67			
		Naproxen	4029	19	2698	0.70	0.42	(0.25, 0.72)	
Aspirin indicated[%, ¶]		Rofecoxib	170	15	105	14.29			
		Naproxen	151	3	102	2.94	0.20	(0.06, 0.71)	
Aspirin not indicated[%]		Rofecoxib	3877	30	2592	1.16			
		Naproxen	3878	16	2596	0.62	0.53	(0.29, 0.97)	
†	Patient-years at risk.								
‡	Per 100 PYR.								
§	Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.								
%	The "Aspirin Indicated" cohort represents those patients with a past medical history of cerebrovascular accident, transient ischemic attack,								
	myocardial infarction, unstable angina, stable angina, coronary artery bypass graft surgery, or percutaneous coronary intervention [3].								
	"Aspirin Not Indicated" cohort represents those patients who did not have a past medical history of any of these diseases.								
¶	Treatment-by-aspirin indicated subgroup interaction test, p=0.177.								

(Source: Safety Update: Table 9: pdf. Page 21. 10/13/00)

To assess the role of edema and hypertension in those patients with confirmed thrombotic events, the sponsor performed the following analyses:

Only 1 patient in each treatment group had both a confirmed thrombotic cardiovascular experience and edema. It appears that there is no relationship between the incidence of edema and confirmed thrombotic cardiovascular experiences.

Incidence of Edema-Related Adverse Experiences in Patients With and Without				
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences				
VIGOR Study in Rheumatoid Arthritis Patients				
Updated Application Data				
			Patients With an	
			Edema-Related	
			Adverse	
	Treatment		Experience	
Subgroup	Group	N	n	(%)
Incidence of an Edema-Related Adverse Experience				
Patients with a confirmed thrombotic cardiovascular	Rofecoxib	45	1	(2.2)
serious adverse experience				
Patients without a confirmed thrombotic cardiovascular	Rofecoxib	4002	219	(5.5)
serious adverse experience				
Patients with a confirmed thrombotic cardiovascular	Naproxen	19	1	(5.3)
serious adverse experience				
Patients without a confirmed thrombotic cardiovascular	Naproxen	4010	144	(3.6)
serious adverse experience				
Data Source: [P088C], [Attachment 3]				

(Source: 10/13/00 Safety Update: Table 17: pdf. Page 27)

Incidence of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences				
in Patients With and Without Edema-Related Adverse Experiences				
VIGOR Study in Rheumatoid Arthritis Patients				
Updated Application Data				
			Patients With a	
			Confirmed	
			Cardiovascular	
			Serious Adverse	
	Treatment		Experience	
Subgroup	Group	N	n	(%)
Incidence of Confirmed Thrombotic Cardiovascular Serious Adverse Experience				
Patients with an edema-related adverse experience	Rofecoxib	220	1	(0.5)
Patients without an edema-related adverse experience	Rofecoxib	3827	44	(1.1)
Patients with an edema-related adverse experience	Naproxen	145	1	(0.7)
Patients without an edema-related adverse experience	Naproxen	3884	18	(0.5)
Data Source: [P088C], [Attachment 3]				

(Source:10/13/00 Safety Update: Table 15: pdf. Page 26)

A similar analysis was done for hypertension and confirmed thrombotic cardiovascular experiences. Of the patients with confirmed events, a higher percent in the rofecoxib group also developed a hypertension-related adverse experience; however, most of the patients with a hypertension-related adverse experience did not have a confirmed cardiovascular thrombotic event.

Incidence of Hypertension-Related Adverse Experiences in Patients With and Without Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
VIGOR Study in Rheumatoid Arthritis Patients
Updated Application Data

Subgroup	Treatment Group	N	Patients With a Hypertension-Related Adverse Experience n	(%)
Incidence of a Hypertension-Related Adverse Experience				
Patients with a confirmed thrombotic cardiovascular serious adverse experience	Rofecoxib	45	7	(15.6)
Patients without a confirmed thrombotic cardiovascular serious adverse experience	Rofecoxib	4002	387	(9.7)
Patients with a confirmed thrombotic cardiovascular serious adverse experience	Naproxen	19	1	(5.3)
Patients without a confirmed thrombotic cardiovascular serious adverse experience	Naproxen	4010	220	(5.5)

(Source: 10/13/00 Safety Update: Table 13: pdf. page 25)

Incidence of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients With and Without Hypertension-Related Adverse Experiences
VIGOR Study in Rheumatoid Arthritis Patients
Updated Application Data

Subgroup	Treatment Group	N	Patients With a Confirmed Cardiovascular Serious Adverse Experience n	(%)
Incidence of a Confirmed Thrombotic Cardiovascular Serious Adverse Experience				
Patients with a hypertension-related adverse experience	Rofecoxib	394	7	(1.8)
Patients without a hypertension-related adverse experience	Rofecoxib	3653	38	(1.0)
Patients with a hypertension-related adverse experience	Naproxen	221	1	(0.5)
Patients without a hypertension-related adverse experience	Naproxen	3808	18	(0.5)

(Source: 10/13/00 Safety Update: Table 11: pdf. Page 24)

Comments:

This is a large comparative study using rofecoxib 50 mg daily and naproxen 1000 mg daily in patients with rheumatoid arthritis. A significant difference is seen in the composite of stroke, myocardial infarction, and cardiac death which is unfavorable for rofecoxib; consistent with this result are the time-to-event tables, and myocardial infarction, and (by the reviewer's analysis) cardiovascular death events.

Study 085:

Title: A Randomized, Placebo-Controlled, Parallel Group, Double Blind Study to Evaluate the Efficacy and Safety of MK-0966 12.5 mg vs. Nabumetone 1000 mg in Patients with Osteoarthritis of the Knee.

Primary Objective: To demonstrate superiority of MK-0966 12.5 mg to nabumetone 1000 mg in the percent of patients with good or excellent response to therapy as assessed by Patient Global Assessment of Response to Therapy in the treatment of osteoarthritis of the knee during a 6 week treatment period.

Secondary Objectives: There were 5 secondary objectives, related to efficacy of each drug versus placebo and superiority claims of rofecoxib over nabumetone using various instruments (Patient and/or Investigator Assessments of Response to Therapy) over 6 weeks.

Study design: This was a randomized, double-blind, parallel-group , placebo-controlled study of efficacy and safety or rofecoxib versus nabumetone after 6 weeks of treatment for osteoarthritis of the knee. Eligible patients were males or females over 40 years old with osteoarthritis of the knee for at least 6 months.

The rationale for dose selection was that in another study (Protocol 010), both 25 mg and 125 mg of rofecoxib were efficacious and indistinguishable in the treatment of osteoarthritis in a 6 week study; it was felt by the sponsor that there was a plateau for rofecoxib in the range of 12.5 to 25 mg. The starting dose of nabumetone (1000 mg) was chosen as the comparator. A placebo arm was included in this study with acetaminophen as the rescue medication.

Of note, patients in this study <u>were</u> allowed to take low-dose aspirin for cardioprotection. Full-dose aspirin or NSAIDs were not allowed during the treatment period. However, patients were not randomized to low-dose aspirin versus non-aspirin use.

Safety measurements included spontaneously reported adverse events, percent of patients that discontinue prematurely due to drug related adverse events, physical examination, vital signs, body weight and laboratory data.

Results:

1495 patients were screened at 113 study sites; of these, 1042 patients were randomized in a 2:2:1 ratio to rofecoxib 12.5 mg (N=424), nabumetone 1000 mg (N= 410) or placebo (N=208).

The 3 treatment groups were similar in regard to baseline characteristics. The mean age was 63.1 years (range 35-92 years); this was a majority (68.3%) female, mostly (87.9%) white population. Of the concurrent conditions, 42.1% had hypertension, , 16.9% had hypercholesterolemia, 8.3% had hyperlipidemia, and 12.4% were obese; most patients (91.0%) reported no current tobacco use and 89.1% consumed $\leq$ 4 drinks/week alcohol consumption. Throughout the trial, 11.9% of patients took low-dose aspirin (81 mg or less, once daily) for cardioprotection.
Rates of noncompliance were slightly higher in the placebo group (10.1%) but were similar between rofecoxib and nabumetone (both were 6.6%, respectively).

Of 1042 randomized, 816 (78.3%) completed the study; the percentage of those completing the study was significantly higher in the rofecoxib (82.5%) and nabumetone (79.3%) arms than placebo (67.8%, $p \leq .002$). The most frequent reason for discontinuation was lack of efficacy, which was highest in the placebo group (23%, $p < .001$ compared to rofecoxib or nabumetone). The second most frequent reason for discontinuation was clinical adverse experience, which was higher than placebo but not significantly different between treatment groups.

	MK-0966 12.5 mg		Nabumetone 1000 mg		Placebo		Total Patients	
	N=(424)		N=(410)		N=(208)		N=(1042)	
	n	(%)	n	(%)	n	(%)	n	(%)
NUMBER OF PATIENTS SCREENED							1495	
NUMBER OF PATIENTS NOT RANDOMIZED							453	
NUMBER OF PATIENTS RANDOMIZED	424		410		208		1042	
COMPLETED STUDY	350	(82.5)	325	(79.3)	141	(67.8)	816	(78.3)
DISCONTINUED STUDY	74	(17.5)	85	(20.7)	67	(32.2)	226	(21.7)
CLINICAL AE	24	(5.7)	25	(6.1)	6	(2.9)	55	(5.3)
LABORATORY AE	0	(0.0)	1	(0.2)	1	(0.5)	2	(0.2)
DEVIATION FROM PROTOCOL	4	(0.9)	4	(1.0)	6	(2.9)	14	(1.3)
PATIENT LOST TO FOLLOW-UP	5	(1.2)	1	(0.2)	0	(0.0)	6	(0.6)
PATIENT WITHDREW CONSENT	8	(1.9)	4	(1.0)	5	(2.4)	17	(1.6)
PATIENT WAS DISCONTINUED DUE TO LACK OF TEST DRUG EFFICACY	31	(7.3)	47	(11.5)	49	(23.6)	127	(12.2)
OTHER	2	(0.5)	3	(0.7)	0	(0.0)	5	(0.5)

Adapted from: 085: pdf. page 817

Safety:

There were no deaths in this study.

The following table is taken from the sponsor). About half of the patients in each treatment arm had at least one adverse experience.

Of the clinical adverse experiences reported (≥ 1%) by Body System, none are reported as cardiovascular adverse experiences. Of the serious adverse experiences, 3 are cardiovascular (1 in rofecoxib, 2 in nabumetone, 0 in placebo) in nature.

Clinical Adverse Experience Summary

	Rofecoxib 12.5 mg (N=424) n (%)	Nabumetone 1000 mg (N=410) n (%)	Placebo (N=208) n (%)
Number (%) of patients:			
with one or more adverse experiences	212 (50.0)	197 (48.0)	104 (50.0)
with no adverse experience	212 (50.0)	213 (52.0)	104 (50.0)
with serious adverse experiences	4 (0.9)	8 (2.0)	1 (0.5)
who died	0 (0.0)	0 (0.0)	0 (0.0)
discontinued due to an adverse experience	24 (5.7)	24 (5.9)‡	8 (3.8)§
discontinued due to a serious adverse experience	2 (0.5)	3 (0.7)	0 (0.0)

‡ AN 1446 in the nabumetone group was counted as discontinuing due to a clinical adverse experience of diverticulosis which began prior to randomization.

§ AN 0052 in the placebo group was counted as discontinuing due to phimosis and balanitis, even though he was counted in the Patient Status Summary as discontinuing due to a protocol violation. AN 0664 in the placebo group was counted as discontinuing due to unbearable osteoarthritis pain, even though he was counted in the Patient Status Summary as discontinuing due to lack of test drug efficacy.

Note: This table presents counts of patients. Patients are counted only once per category but may be counted in more than 1 category.

Data Source: [4.1.41; 4.12]

(sNDA: 085 clinical study report: Table 34, pdf. page 102)

Of the serious cardiovascular clinical adverse experiences, 2 can be found in the rofecoxib group and 2 in the nabumetone group, respectively. No serious cardiovascular clinical adverse experiences are noted in the placebo group.

Rofecoxib

AN	Study number	Gender	Race	Age	Adverse Experience	Rel. Day of Onset	Action Taken with Drug	Outcome
1067	021	M	White	70	Cardiac trauma	12	None	Recovered
1353	072	F	White	75	Myocardial infarction	40	Discontinued	Recovered

Nabumetone

An	Study number	Gender	Race	Age	Adverse Experience	Rel. Day of Onset	Action Taken with Drug	Outcome
1273	081	F	White	77	Urinary tract infection	3	None	Recovered
					Congestive heart failure	**4**	**None**	**Recovered**
1211	**082**	**F**	**White**	**67**	**Coronary artery disease**	**18**	**Discontinued**	**Not recovered**

(Source: 085: Table38: pdf. Page 109.)

The following table lists adverse experiences related to edema, fluid retention, hypertension, and congestive heart failure. More edema is seen in the rofecoxib group; no significant differences are seen in regard to hypertension.

Summary of Renal/Vascular Effects[†]

	Treatment Group							
	Rofecoxib 12.5 mg (N=424)		Nabumetone 1000 mg (N=410)		Placebo (N=208)		Total (N=1042)	
	n	(%)	n	(%)	n	(%)	n	(%)
Specific Edema-Related Adverse Experiences	**15**	**(3.5)**	**8**	**(2.0)**	**3**	**(1.4)**	**26**	**(2.5)**
Edema	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.1)
Facial edema	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Lower extremity edema	10	(2.4)	7	(1.7)	2	(1.0)	19	(1.8)
Peripheral edema	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)
Upper extremity edema	3	(0.7)	2	(0.5)	1	(0.5)	6	(0.6)
Fluid retention	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.1)
Other Adverse Experiences Possibly Related to Fluid Retention	**0**	**(0.0)**	**2**	**(0.5)**	**0**	**(0.0)**	**2**	**(0.2)**
Congestive heart failure	0	(0.0)	2	(0.5)	0	(0.0)	2	(0.2)
Hypertension/Increased Blood Pressure	**5**	**(1.2)**	**7**	**(1.7)**	**3**	**(1.4)**	**15**	**(1.4)**
Blood pressure increased	2	(0.5)	2	(0.5)	0	(0.0)	4	(0.4)
Hypertension	3	(0.7)	4	(1.0)	2	(1.0)	9	(0.9)
Systolic hypertension	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.1)
Uncontrolled hypertension	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.1)

[†] Based on edema-related and hypertensive adverse experiences.

Note: This table presents counts of patients. Patients are counted only once per category (in bold-faced type) but may be counted in more than 1 category.

(Source: 085: pdf. page 117)

Another subgroup analysis (below) was done by aspirin user vs. non-aspirin user. It can be noted that most of the patients who had a serious adverse experience or who discontinued due to an adverse experience were in the non-aspirin user subgroup. However, the usefulness of this analysis is limited by the differences in sample size (low-dose aspirin user versus non-aspirin user) and by the fact that these groups were not randomized; i.e., results due to differences in baseline patient characteristics cannot be excluded.

Clinical Adverse Experience Summary by Aspirin Subgroup

	Rofecoxib 12.5 mg (N=424)				Nabumetone 1000 mg (N=410)				Placebo (N=208)			
	Low-Dose Aspirin (N=46)		Non-User (N=378)		Low-Dose Aspirin (N=57)		Non-User (N=353)		Low-Dose Aspirin (N=21)		Non-User (N=187)	
	n	%	n	%	n	%	n	%	n	%	n	%
Number (%) of patients:												
With one or more adverse experiences	23	(50.0)	189	(50.0)	22	(38.6)	175	(49.6)	8	(38.1)	96	(51.3)
With no adverse experience experiences	23	(50.0)	189	(50.0)	35	(61.4)	178	(50.4)	13	(61.9)	91	(48.7)
With serious adverse experiences	0	(0.0)	4	(1.1)	3	(5.3)	5	(1.4)	0	(0.0)	1	(0.5)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to an adverse experience	3	(6.5)	21	(5.6)	2	(3.5)	22	(6.2)	0	(0.0)	8	(4.3)
Discontinued due to a serious adverse experience	0	(0.0)	2	(0.5)	0	(0.0)	3	(0.8)	0	(0.0)	0	(0.0)

Data Source: [4.1.58; 4.1.59]

Comments:

Because of the smaller sample size and event rates, the results of this study do not convince this reviewer that there is no safety issue with rofecoxib. Furthermore, the dose of rofecoxib, 12.5 mg, is lower than that used in the rofecoxib treatment arm in the VIGOR study. An increase in cardiovascular events at higher doses of rofecoxib cannot be excluded.

Study 090:

Title: A randomized, placebo-controlled, parallel-group, double-blind study to evaluate the efficacy and safety of MK-0966 (Rofecoxib) 12.5 mg versus Nabumetone 1000 mg in patients with osteoarthritis of the knee

Primary Objective: To demonstrate superiority of rofecoxib 12.5 mg to nabumetone 1000 mg
in the percent of patients with good or excellent response to therapy, as
assessed by PGART (Patient Global Assessment of Response to Therapy), in the treatment of osteoarthritis of the knee during a 6-week treatment period.

Secondary Objectives:
As with study 085, the secondary objectives were superiority of rofecoxib to nabumetone and efficacy of both drugs to placebo, using assessment instruments of response to therapy.
in the percent of patients with good or excellent response to therapy, as
Study design:
This was a double-blind, parallel-group, placebo-controlled study comparing efficacy and safety of rofecoxib versus nabumetone after 6 weeks of treatment for osteoarthritis of the knee. Following a screening period, eligible patients were randomized to either rofecoxib 12.5 mg daily, nabumetone 1000 mg daily, or placebo for 6 weeks.

Safety measurements were to include recording of adverse experiences, vital signs, and collection of laboratory data at Weeks 2 and 6.

Of note, low-dose aspirin (81 mg or less per day) for cardioprotection was allowed in this study. Concomitant use of NSAIDS and high-dose aspirin, however, were prohibited during the treatment period.

Prespecified in this study was a subgroup analysis of safety for aspirin users and non-aspirin users.

Results:

A total of 1457 patients were screened for enrollment at 115 study sites. Of these, 978 patients with osteoarthritis of the knee were randomized in a 2:2:1 ratio to 1 of 3 treatment groups: rofecoxib 12.5 mg (N=390), nabumetone 1000 mg (N=392), or placebo (N=196).

	Patient Accounting							
	Rofecoxib		Nabumetone					
	12.5 mg		1000 mg		Placebo		Total	
ENTERED:	390		392		196		978	
Male (age range)	119 (40 to 87)		114 (40 to 86)		60 (41 to 81)		293 (40 to 87)	
Female (age range)	271 (37 to 85)		278 (37 to 90)		136 (41 to 83)		685 (37 to 90)	
	n (%)		n (%)		n (%)		n (%)	
COMPLETED:	322	(82.6)*	324	(82.7)*	143	(73.0)	789	(80.7)
DISCONTINUED:	68	(17.4)	68	(17.3)	53	(27.0)	189	(19.3)
Clinical adverse experience	29	(7.4)*,**	15	(3.8)†	7	(3.6)‡	51	(5.2)
Laboratory adverse experience	2	(0.5)	0	(0.0)	0	(0.0)	2	(0.2)
Deviation from protocol	5	(1.3)	6	(1.5)	3	(1.5)	14	(1.4)
Patient lost to follow-up	2	(0.5)	3	(0.8)	4	(2.0)	9	(0.9)
Patient withdrew consent	2	(0.5)	4	(1.0)	2	(1.0)	8	(0.8)
Lack of efficacy	27	(6.9)*	39	(9.9)*	37	(18.9)	103	(10.5)
Other	1	(0.3)	1	(0.3)	0	(0.0)	2	(0.2)
† AN 2674 and AN 2676 in the nabumetone group were counted as discontinuing due to lack of test drug efficacy, even								
though they had an adverse experience of increased osteoarthritis pain which was considered to cause discontinuation.								
‡ AN 3313 in the placebo group was counted as discontinuing due to a clinical adverse experience of neck pain, which began prior to randomization.								
AN 2778 in the placebo group was counted as discontinuing due to a clinical adverse experience of worsening headaches, which began prior to randomization.								
* p .0.05 versus placebo.								
** p .0.05 versus nabumetone.								

(Source: 090: Table 15: pdf. page 64)

The 3 treatment groups were very similar with regard to demographic characteristics. Patients ranged in age from 37 to 90 years, with a mean age of 62.7 years. Although the lower age limit for inclusion in this study was 40 years, two 37-year-old patients were inadvertently enrolled in the study (one each from rofecoxib and nabumetone). Both patients met all other selection criteria and were included in all efficacy and safety analyses. The majority (70.0%) of patients were female, and most patients (87.6%) were white.

Baseline Patient Demographic Characteristics by Treatment Group

	Rofecoxib 12.5 mg (N=390)		Nabumetone 1000 mg (N=392)		Placebo (N=196)		Total (N=978)	
Gender (n, %)								
Female	271	(69.5)	278	(70.9)	136	(69.4)	685	(70.0)
Male	119	(30.5)	114	(29.1)	60	(30.6)	293	(30.0)
Age (n, %)								
40 years	3	(0.8)	3	(0.8)	0	(0.0)	6	(0.6)
41 to 65 years	232	(59.5)	215	(54.8)	115	(58.7)	562	(57.5)
66 years	155	(39.7)	174	(44.4)	81	(41.3)	410	(41.9)
Mean (SD)	62.3 (10.2)		63.2 (10.7)		62.3 (10.1)		62.7 (10.4)	
Range	37 to 87		37 to 90		41 to 83		37 to 90	
Race (n, %)								
Asian	4	(1.0)	4	(1.0)	0	(0.0)	8	(0.8)
Black	26	(6.7)	33	(8.4)	14	(7.1)	73	(7.5)
Hispanic	15	(3.8)	12	(3.1)	7	(3.6)	34	(3.5)
Indian (India)	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.1)
Native American	2	(0.5)	2	(0.5)	0	(0.0)	4	(0.4)
White	342	(87.7)	341	(87.0)	174	(88.8)	857	(87.6)
Native American and White	1	(0.3)	0	(0.0)	0	(0.0)	1	(0.1)

Data Source: [4.1.3; 4.2]
(Source: 090: pdf. Page 56)

The 3 treatment groups were also similar with regard to baseline arthritis, body mass index, arthritis treatment history; of baseline secondary diagnoses: 41.1% had hypertension, 17.6% had hypercholesterolemia, and 8.7% had obesity. There appeared to be no clinically meaningful differences between the 3 treatment groups. Low-dose aspirin for cardioprotection was used by 12.2% of patients in this study; no meaningful differences were noted in percent of aspirin use among the 3 treatment groups.

Safety:

There were no deaths in this study. The next page shows a summary of total adverse experiences.

Clinical Adverse Experience Summary

Number (%) of patients:	n	Rofecoxib 12.5 mg (N=390) (%)	n	Nabumetone 1000 mg (N=392) (%)	n	Placebo (N=196) (%)	n	Total (N=978) (%)
With one or more adverse experiences	220	(56.4)*,**	193	(49.2)	84	(42.9)	497	(50.8)
With no adverse experience	170	(43.6)	199	(50.8)	112	(57.1)	481	(49.2)
With serious adverse experiences	9	(2.3)**	2	(0.5)	1	(0.5)	12	(1.2)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to an adverse experience	29	(7.4)*	17	(4.3)‡	5	(2.6)§	51	(5.2)
Discontinued due to a serious adverse experience	8	(2.1)**	1	(0.3)	1	(0.5)	10	(1.0)

‡ AN 2674 and AN 2676 in the nabumetone group were counted as discontinuing due to increased osteoarthritis pain, even though they were counted in the Patient Status Summary as discontinuing due to lack of test drug efficacy.

§ AN 3313 in the placebo group was counted as discontinuing due to a clinical adverse experience of neck pain which began prior to randomization. AN 2778 in the placebo group was counted as discontinuing due to a clinical adverse experience of worsening headaches, which began prior to randomization.

* p 0.05 versus placebo.

** p 0.05 versus nabumetone.

Note: This table presents counts of patients. Patients are counted only once per category but may be counted in more than 1 category

Data Source: [4.1.4; 4.12]

(Source: 090: pdf. Page 107)

Number (%) of Patients With Clinical Adverse Experiences
(Incidence 1% in One or More Treatment Groups by Body System

	n	Rofecoxib 12.5 mg (N=390) (%)	n	Nabumetone 1000 mg (N=392) (%)	n	Placebo (N=196) (%)	n	Total (N=978) (%)
Patients with one or more clinical adverse experiences	220	(56.4)	193	(49.2)	84	(42.9)	497	(50.8)
Patients with no clinical adverse experience	170	(43.6)	199	(50.8)	112	(57.1)	481	(49.2)
Body as a Whole/Site	73	(18.7)	75	(19.1)	36	(18.4)	184	(18.8)
Cardiovascular System	**17**	**(4.4)**	**8**	**(2.0)**	**6**	**(3.1)**	**31**	**(3.2)**
Hypertension	6	(1.5)	2	(0.5)	2	(1.0)	10	(1.0)

Adapted from: 090: Table 35: pdf. page 110.

Below is a listing of serious cardiovascular adverse experiences (AE). In the rofecoxib group, a total of 6 serious cardiovascular AE were reported; in the nabumetone group, there were 2 AE, and in the placebo group, 1 AE, respectively. There were more myocardial infarctions in the rofecoxib group; however, the event rates are low.

Listing of Patients With Serious Clinical Adverse Experiences

AN	Study Number	Gender	Race	Age	Adverse Experience	Relative Day of Onset	Action Taken With Drug	Outcome
Rofecoxib								
2695	015	F	White	63	Myocardial infarction	8	Discontinued	Recovered
2224	022	M	White	58	Cerebrovascular accident	27	Discontinued	Recovered
2683	049	M	White	77	Atrial fibrillation	32	Discontinued	Recovered
2256	069	M	White	77	Myocardial infarction	15	Discontinued	Recovered
3177	079	F	White	75	Cerebrovascular accident	21	Discontinued	Recovered
3286	103	F	White	67	Myocardial infarction	1	Discontinued	Recovered
Nabumetone								
3441	014	F	White	71	Congestive heart failure	26	Interrupted	Recovered
3012	112	F	White	72	Myocardial infarction	3	Discontinued	Recovered
Placebo								
2502	087	M	White	48	Coronary artery occlusion	22	Discontinued	Recovered

(Source: 090: Table 38: pdf. Page 116)

More patients in the rofecoxib group discontinued due to cardiovascular adverse experiences than in the nabumetone or placebo groups. (Of the 7 in the rofecoxib group, 3 were listed as having a myocardial infarction, 2 as stroke, 1 as atrial fibrillation, and 1 with hypertension, respectively).

Number (%) of Patients Who Discontinued Due to Clinical Adverse Experiences
(Incidence >0% in One or More Treatment Groups)
by Body System

	Rofecoxib 12.5 mg (N=390)		Nabumetone 1000 mg (N=392)		Placebo (N=196)		Total (N=978)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more clinical adverse experiences	29	(7.4)	17	(4.3)	5	(2.6)	51	(5.2)
Patients with no clinical adverse experience	361	(92.6)	375	(95.7)	191	(97.4)	927	(94.8)
Cardiovascular System	**7**	**(1.8)**	**1**	**(0.3)**	**1**	**(0.5)**	**9**	**(0.9)**

Adapted from: 090: Table 39: pdf. page 120

Summary of Renal/Vascular Adverse Experiences†

Category	Treatment Group: Rofecoxib 12.5 mg (N=390) n	(%)	Nabumetone 1000 mg (N=392) n	(%)	Placebo (N=196) n	(%)	Total (N=978) n	(%)
Specific Edema-Related Adverse Experiences	**12**	**(3.1)**	**10**	**(2.6)**	**4**	**(2.0)**	**26**	**(2.7)**
Edema	1	(0.3)	2	(0.5)	1	(0.5)	4	(0.4)
Lower extremity edema	10	(2.6)	7	(1.8)	1	(0.5)	18	(1.8)
Upper extremity edema	1	(0.3)	1	(0.3)	0	(0.0)	2	(0.2)
Fluid retention	1	(0.3)	0	(0.0)	2	(1.0)	3	(0.3)
Fluid Retention								
Congestive heart failure	0	(0.0)	1	(0.3)	0	(0.0)	1	(0.1)
Hypertension/Increased Blood Pressure	**7**	**(1.8)**	**3**	**(0.8)**	**3**	**(1.5)**	**13**	**(1.3)**
Blood pressure increased	1	(0.3)	1	(0.3)	0	(0.0)	2	(0.2)
Hypertension	6	(1.5)	2	(0.5)	2	(1.0)	10	(1.0)
Hypertensive crisis	0	(0.0)	0	(0.0)	1	(0.5)	1	(0.1)

† Based on edema-related and hypertensive adverse experiences.
Note: This table presents counts of patients. Patients are counted only once per category (in bold-faced type) but may be counted in more than 1 category.
Data Source: [4.1.56; 4.12.3]
Adapted from 090: Table 43: page 130

The following table represents an analysis of adverse events by aspirin use.

Clinical Adverse Experience Summary by Aspirin Subgroup

Clinical Adverse Experiences	Rofecoxib 12.5 mg (N=390) Low dose aspirin (N=45) n	%	Non-user (N=345) n	%	Nabumetone 1000 mg (N=392) Low dose aspirin (N=47) n	%	Non-user (N=345) n	%	Placebo (N=196) Low dose aspirin (N=27) n	%	Non-user (N=169) n	%
Number (%) of Patients												
With one or more adverse experiences	30	(66.7)	190	(55.1)	30	(63.8)	163	(47.2)	13	(48.1)	71	(42.0)
With no adverse experiences	15	(33.3)	155	(44.9)	17	(36.2)	182	(52.8)	14	(51.9)	98	(58.0)
With serious adverse experiences	2	(4.4)	7	(2.0)	1	(2.1)	1	(0.3)	0	(0.0)	1	(0.6)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to an adverse experience	5	(11.1)	24	(7.0)	3	(6.4)	14	(4.1)	1	(3.7)	4	(2.4)
Discontinued due to a serious adverse experience	1	(2.2)	7	(2.0)	1	(2.1)	0	(0.0)	0	(0.0)	1	(0.6)

Adapted from 090: Table 44: page 133

Comments:

In this particular study, there are numerically more myocardial infarctions in the rofecoxib group, compared with nabumetone and placebo. There are also more cardiovascular adverse experiences and discontinuations due to cardiovascular adverse experiences in the rofecoxib group; this can be partly accounted for the incidence of hypertension. As with 085, this study has a smaller sample size and cardiovascular event rate compared with VIGOR.

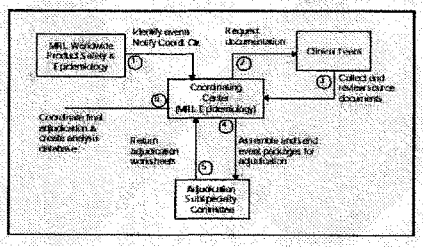
ISSUES & COMMENTS:

Specific issues requested by the Division:

1. **Adjudication Criteria and results of Adjudication in the VIGOR study (088c):**
   See Section on Adjudication (page 10). The criteria for adjudication appear to be adequate and the results appear to be balanced. In order to ascertain whether or not the adjudication was done in a blinded manner, it would be important to determine the timing of the Vascular Events Committee (i.e., when the committee was formed).

Figure C-1

Overview of Cardiovascular Event Surveillance, Monitoring, and Adjudication



2. **Evaluation of CV events in other rofecoxib studies that allowed ASA (085 and 090):**
   See Comments on 085 and 090. Despite lower dose, smaller sample size and aspirin use, the trend is against rofecoxib.

3. **Assessment of CV thrombotic risks in this database:**
   The VIGOR study was a large study with a longer drug exposure and follow-up than the two smaller studies (085 and 090). The cardiovascular thrombotic event rates, while not high, were significantly different between the two groups; most striking were the myocardial infarction event rates. Thus, to this Medical Reviewer, there are more cardiovascular thrombotic events in the rofecoxib group than in the naproxen group; the time-to-event curves are different, favoring naproxen. This Medical Reviewer is concluding that there is an increased risk of cardiovascular thrombotic events, particularly myocardial infarction, in the rofecoxib group compared with the naproxen group. More difficult is the question of a safety signal for rofecoxib. As there is no placebo group, it will be difficult to assess the CV thrombotic risk with rofecoxib use compared with no therapy at all. The sponsor provides several hypotheses to explain the data (see below);

4. **Assessment of the sponsor's claim regarding CV risks:**

The sponsor's claims:

- The sponsor claims that the difference in myocardial infarctions between the two groups is primarily due to the antiplatelet effects of naproxen. This hypothesis is not supported by any prospective placebo-controlled trials

with naproxen. One can further argue that, no matter what the attribution, the results (from a cardiovascular standpoint) are favorable for naproxen.

The sponsor stated, "Overall, the risk of the combined endpoint of cardiovascular or unknown death, myocardial infarction, and cerebrovascular accident was reduced by 47% in the naproxen group relative to the rofecoxib group in the VIGOR study." The sponsor then performed an analysis of events using standard endpoint definitions from large antiplatelet trials (see page 16). In viewing this analysis, one can argue that naproxen would be the preferred drug compared to rofecoxib.

- The sponsor claims that the majority of cardiovascular events in the VIGOR study occurred in those patients who should have been on aspirin for cardioprotection. This claim has not convinced this Medical Reviewer. The VIGOR data are consistent (i.e., increased events in the rofecoxib group) even in patients who did not fall into the "aspirin-indicated" subgroup.
- The sponsor claims that patients with rheumatoid arthritis are at increased risk for cardiovascular events, either due to chronic inflammation, vasculitis, or procoagulant antibodies. There is some literature regarding the role of inflammation in atherosclerosis, and increased CRP levels have been correlated with increased cardiovascular risk--there was no analysis in this sNDA of CRP levels, vasculitis or presence of procoagulant antibodies in the VIGOR population. If one accepts that patients with rheumatoid arthritis are at increased risk for events, one is still faced with the difference in cardiovascular events between rofecoxib and naproxen. And given the premise that rheumatoid arthritis patients are at increased risk, could one not extend this argument to any patient at increased risk of cardiovascular events?
- The sponsor claims that patients with osteoarthritis and Alzheimers disease are at lower risk for cardiovascular events; rates of cardiovascular events are similar between rofecoxib and the nonselective NSAIDS. The sponsor presents safety data for rofecoxib from the osteoarthritis and Alzheimer's disease trials. However, the dose of rofecoxib and length of exposure are not explicitly stated. Also, as the sponsor notes, these events are unadjudicated.

Incidence of Unadjudicated Thrombotic Cardiovascular Serious Adverse Experiences
Comparison of Rofecoxib With Nonselective NSAIDs
Phase IIb/III Clinical Program for Rofecoxib in Osteoarthritis Patients

	Treatment Group	N	Patients With Events	PYR†	Rate‡	Relative Risk§ Estimate	95% CI
Unadjudicated thrombotic cardiovascular serious adverse experiences	Rofecoxib	3357	34	1657	2.05	1.09	(0.60, 1.99)
	Nonselective NSAIDs	1564	16	706	2.27		

† Patient-years at risk.
‡ Per 100 PYR.
§ Relative risk of nonselective NSAIDs with respect to rofecoxib from Cox model stratified by protocol where the number of cases is at least 11, otherwise relative risk is ratio of rates and p-value is from discrete logrank distribution.
[120]

Incidence of Unadjudicated Thrombotic Cardiovascular Serious Adverse Experiences
Comparison of Rofecoxib to Placebo
Phase IIb/III Clinical Program for Rofecoxib in Osteoarthritis Patients

	Treatment Group	N	Patients With Events	PYR†	Rate‡	Relative Risk§ Estimate	95% CI
Unadjudicated thrombotic cardiovascular serious adverse experiences	Rofecoxib	1701	9	363	2.48	1.05	(0.27, 4.02)
	Placebo	514	3	127	2.36		

†Patient-years at risk.
‡Per 100 PYR.
§Relative risk of placebo with respect to rofecoxib from Cox model stratified by protocol where the number of cases is at least 11, otherwise relative risk is ratio of rates and p-value is from discrete log-rank distribution.
[120]

- The sponsor recommends use of low-dose aspirin in conjunction with rofecoxib, in those at risk for cardiovascular events. However, the "trade-off" with low-dose aspirin use might be a rise in GI toxicity, and a loss of the GI safety benefit offered by selective COX-2 inhibition[7]. The benefit of a rofecoxib-aspirin combination over naproxen is unclear and would at least require further study.
  - It is also conceivable that low-dose aspirin combined with rofecoxib might require further study in terms of dose-response and additivity; the question of drug development as a combination would need to be discussed within your Division.

5. **Suggest labeling that would properly address CV risks:** It is difficult to write labeling at this point.

[7] In one 2849 patient double-blind, controlled trial where patients were randomly assigned to 81 mg, 325 mg, 650 mg, or 1300 mg aspirin daily for 3 months, gastrointestinal bleeding appeared to be unrelated to dose. Taylor DW et. al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy; a randomised controlled trial. *Lancet* 1999; 353: 2179-2184.

As discussed with Dr. Villalba, we will be glad to discuss labeling with your Division. It would be difficult to imagine inclusion of VIGOR results in the rofecoxib labeling without mentioning cardiovascular safety results in the study description as well as the Warnings sections.

RECOMMENDATIONS:

- Your Division will need to consider the risks vs. benefits of rofecoxib and naproxen. We will be glad to discuss this issue further with you.
- We would like to see further analysis of the updated Time-to Event table to answer the following questions: 1. How significant is this table; 2. What event rate is needed to detect a significant difference between rofecoxib and naproxen.
- You should look at the VIGOR congestive heart failure results to clarify whether these events are related to edema, hypertension, or thrombotic events. You might ask the sponsor for further clarification.
- You might consider looking at celecoxib data to evaluate whether there is evidence of a class effect.
- It would be helpful if the sponsor could provide further cardiovascular safety data regarding long-term (>2 month) exposure of rofecoxib 50 mg and above, both in rheumatoid arthritis and non-rheumatoid arthritis populations.
- As we have discussed, OPDRA should be asked to look at cardiovascular safety data for the COX-2 inhibitors.

cc:
Original to NDA 21-042
HFD-550/Villalba
HFD-550/Cook
HFD-110
HFD-110/Targum
HFD-110/Stockbridge
HFD-110/Lipicky

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 30

VIOXX™ Gastrointestinal Outcome Research (VIGOR)

Arthritis Advisory Committee Meeting
February 8, 2001

Lourdes Villalba, M.D.
DAAODP, CDER, FDA

Rofecoxib Overall Safety

- VIGOR - General safety
- CV safety in other databases
- Risk/benefit assessment - Co-use of ASA
- Post-marketing safety
- Conclusions

VIGOR General Safety Summary

- GI safety favored rofecoxib
- Overall, general safety parameters trended in favor of naproxen, particularly due to the excess in serious cardiovascular events in the rofecoxib group

Rofecoxib Overall Safety

- VIGOR - General Safety
- CV safety in other databases
- Risk/benefit assessment - Co-use of ASA
- Post-marketing safety
- Conclusions

MVX for Vioxx®
Jo Jerman – Pt. RBG VP for VIOXX®
Audience – All Field Personnel Responsible for Vioxx®
February 8, 2001
Topic: FDA Advisory Committee Meetings

Hey everybody, this is Jo Jerman with an MVX to all Field Personnel responsible for VIOXX. As you know, the FDA Advisory Committee met yesterday to review the VIGOR Trial that we submitted for a Supplemental New Drug Application seeking label changes for Vioxx.

Now, let me back up and fill you in on what exactly happens during the entire FDA review process.

Last June, we took the first step and submitted a supplemental new drug application for label changes for VIOXX, based upon on the VIGOR study, our 8,000-patient gastrointestinal outcomes research study. The next step was the advisory committee meeting yesterday, to discuss our application packet. Last, negotiations about the possible label changes take place between the FDA and Merck until a final decision is made. We expect the decision on the final label recommendations to take place in the next couple of months.

So, where does that leave us?

The Advisory Committee agreed with Merck and the FDA that results from the study should be included in the labeling for VIOXX. Now the FDA is not obligated to follow the advice of the Advisory Committee, but usually does. We look forward to further discussions with the FDA to complete the review of our application.

Additionally, although the VIGOR study was a GI outcomes study and was not designed to show differences in cardiovascular effects, significantly fewer heart attacks were observed in patients taking naproxen (0.1%) compared to the group taking VIOXX 50 mg (0.5%) in this study. We have discussed this before. There was no difference in cardiovascular mortality between the groups treated with VIOXX or naproxen. Patients taking aspirin did not participate in VIGOR.

Merck scientists said the VIGOR finding is consistent with naproxen's ability to block platelet aggregation by inhibiting COX-1 like aspirin, which is used to prevent second cardiac events inpatients with a history of heart attack, stroke or other cardiac events. This is the first time this effect of naproxen in cardiovascular events has been observed in a clinical study. Other explanations were advanced by the FDA reviewer and were discussed with the Advisory Committee. The Advisory Committee recommended that the data on cardiovascular events in VIGOR be included in the labeling for VIOXX.

In addition the committee agreed that the prescribing information for both VIOXX and Celebrex should reflect the fact that neither of these selective NSAIDs confer cardioprotective benefits and are not a substitute for low-dose aspirin. The Advisory

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Committee also recommended that other studies be conducted to further explore the safety of concomitant use of selective NSAIDs and low-dose aspirin.

In the meantime, continue to stay focused on the efficacy messages for VIOXX, supported by safety and balancing information as instructed at your 1S meetings.

If you're questioned by customers about the Advisory Committee Meeting or about the VIGOR study, request a PIR.

You will receive a bulletin today that will provide direction on how to get the most current summary PIR faxed directly to your customers within 24 hours upon their unsolicited request. If a customer asks for more comprehensive information on VIGOR, you can request that a comprehensive packet be Fed Ex'ed to your customer within 2 days. Other background information will also be included in the bulletin.

Remember you do not initiate or respond to questions on the FDA Advisory Committee Review or the VIGOR study.

That's all for now guys--stay tuned for future updates...this is surely not the final word. We're at 50.5% and breaking away from the competition! Keep up the great work!

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 31

VIOXX®

HHPAC STAGE IV REVIEW MEETING

Tuesday, March 20, 2001

WHS3A-32 Conference Room

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MEMO - CONFIDENTIAL -

Date: March 13, 2001

TO: Human Health PAC
Mr. D. Anstice
Mr. R. Ghanem
Dr. D. Greene
Mr. R. Henshall
Mr. B. Kelley
Dr. P. Kim
Dr. D. Margolskee
Ms. M. McGlynn
Dr. A. Nies
Dr. E. Scolnick
Dr. B. Sheares
Dr. E. Slater
Dr. T. Verhoeven
Mr. P. Wold-Olsen
Mr. T. Woodward

VIOXX® CST Invitees:
Ms. L. Beauchard
Dr. G. Block
Dr. W. Dixon
Mr. R. El-dada
Dr. G. Geba
Dr. B. Gertz
Dr. K. Grosser
Dr. S. Harper
Ms. P. Johnson
Ms. S. Kornowski
Dr. A. Reicin
Mr. T. Ruef
Dr. R. Silverman
Ms. S. Simpson
Mr. D. Tolani
Dr. K. Truitt
Dr. E. Vadas
Dr. D. Watson

cc: Mr. B. Bissett

From: VIOXX® Commercialization Team

Attached please find the background material for the HH PAC Meeting on March 20, 2001 related to the VIOXX® Program Review.

VIOXX® STAGE IV BACKGROUND PACKAGE - March 20, 2001

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VIOXX® STAGE IV BACKGROUND PACKAGE - March 20, 2001

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Executive Summary

VIOXX® HHPAC STAGE IV REVIEW – March 20, 2001

I. Executive Summary

A. Overview

On February 15, 2001 the PAC was updated on several topics:
1) the outcomes of the CLASS and VIGOR Advisory Committee Meetings
2) the Rheumatoid Arthritis Label
3) the VIOXX® Rapidisc Formulation program

The purpose of this VIOXX®Stage IV Program Review is to update the PAC on the current competitive environment, and to review the critical issues for VIOXX® in the marketplace and the plans to address them. The discussion will include prioritization, strategy, and budget for ongoing and new 2001 VIOXX® clinical studies. These studies address some of the issues raised by the VIGOR ACM and the current competitive environment. An update on the VIOXX® Outcomes Research Activities is scheduled for the April PAC meeting. An update on the VIOXX® migraine program will be the subject of a PAC in April or May. Of note, since the last PAC, the RA sNDA was filed on time on February 28th. The sIMA is on track for a 2Q release.

Key issues and objectives for the VIOXX® franchise, which are discussed in this package, are shown on Table 1. The prioritized list of 2001 VIOXX® clinical studies and budget is shown in Table 2. The descriptions of the 2001 clinical studies are found in the Clinical Development Section IV, and the supporting information for their priorities within the franchise can be found in the Marketing Section II.

The objectives of the Stage IV PAC review are to:

- Review the key objectives and issues for the VIOXX® franchise
- Review the priorities and changes to the Clinical Development Program (MRL, CDP and CDSP)
- Provide an update on the VIOXX® Rapidisc program including the planned clinical program and a revised financial analysis
- Provide an update on the VIGOR label negotiations with the FDA
- Review the worldwide filing strategy for chronic pain and juvenile rheumatoid arthritis

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Table 1. VIOXX® Key Objectives and Issues

Objective	Study/Initiative	Issues/Risks	Mitigation Strategy
Accelerate Patient Recruitment in the A&A Market			
Obtain the most favorable wording possible in the GI warnings section of the USPC & WPC to be able to aggressively promote in the US & ex-US		- The wording in the label is too weak, i.e., the improved GI safety is limited to RA patients on naproxen; combined OA GI event analysis is not included in the U.S. label	- Regulatory negotiations on label
Publicize/highlight the economic value of VIOXX® to convince payors of the benefits of using VIOXX® over NSAIDs	- Outcomes research activities to emphasize the risk of gastropathy associated with NSAIDs use - Pharmacoeconomics studies	- The economic advantage of VIOXX® over NSAIDs is only borderline and payors cannot be convinced of the economic benefits of using VIOXX®	- Widely publish the results of pharmacoeconomics and outcomes research studies demonstrating the overall economic advantage of VIOXX® vs NSAIDS - Emphasize GI safety advantage in both "low risk" and "high risk" patients
Demonstrate that the GI safety of VIOXX® is maintained in patients who use VIOXX® concomitantly with low dose aspirin and include such a statement in the Label	- VIOXX® + Low Dose Aspirin versus ibuprofen Endoscopy Study (PN 136, ongoing)	- GI safety of VIOXX® + Low Dose Aspirin may not be superior to the GI safety of Ibuprofen - Data from one study may not be sufficient to warrant a label change - Payors and physicians do not correlate results from endoscopy studies with results from outcomes studies	- Initiate a new endoscopy study to test whether the GI safety of VIOXX® + Low Dose Aspirin is superior to the GI safety of Ibuprofen + Low Dose Aspirin in patients requiring aspirin for CV prophylaxis (the combination of both studies may warrant a label change) - Continue to emphasize the correlation between endoscopy studies and GI outcomes in the rofecoxib development program

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Table 1. VIOXX® Key Objectives and Issues (Cont'd)

Objective	Study/Initiative	Issues/Risks	Mitigation Strategy
Accelerate Patient Recruitment in the A&A Market (cont'd)			
Obtain a 6-month extension of patent exclusivity based on fulfilling a written request for pediatric study. Obtain a pediatric indication. (Projected $ value: $2Bn)	- Juvenile Rheumatoid Arthritis Efficacy Study	- Not yet known if FDMA legislation, allowing patent extension based on pediatric study, will be renewed - As of 7 March-01, FDA response to prompt for written request has not been received (prompt sent on 31-Aug-00; written request should have been received by 31-Dec-00); - Study started at risk (FPI: C-Dec-00) - FDA expressed significant conceptual concerns with JRA program during a teleconference on 01 March 01. - LPO delayed while awaiting further input from FDA; therefore it will not be possible to file by 01-Oct-01, the date recommended by Legal to avoid any issues with the sunset of the legislation - FDA may require major changes to the study design and study cannot be rescued to satisfy FDA's requirements	- Actively pursue negotiations with FDA (thus far, negotiations with FDA have led to a commitment from the Agency to extend due date for filing) - Maintain the enrollment open until the written request is received - Plan to initiate a new study according to FDA's requirements if necessary

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Table 1. VIOXX® Key Objectives and Issues (Cont'd)

Objective	Study/Initiative	Issues/Risks	Mitigation Strategy
Accelerate Patient Recruitment in the A&A Market (cont'd)			
Obtain a Chronic Pain indication	- Two 12-week Placebo-Controlled Chronic Low Back Pain Studies - 6-week Placebo-controlled & 52-week Active Controlled OA studies (*already completed*)	- FDA has to formally agree to MRL's strategy for a Chronic Pain indication	- Hold a pre-phase III meeting with FDA and get the "buy in" from the Agency on the strategy/ study design proposed by MRL - [redacted]
Establish VIOXX® as Best in the Coxib Class (Primarily based on efficacy)			
Demonstrate that VIOXX® is superior to Celebrex and Acetaminophen in the treatment of OA	- VACT-2 study (*CDP*) - VIOXX®/Celebrex CDSP Switch study	- VACT-1 study results are reproduced but DDMAC does not accept PGART (primary endpoint) as sufficient endpoint to demonstrate superiority - In patients who show inadequate clinical response to celecoxib 200 mg QD, VIOXX® 25 mg will not demonstrate superior clinical efficacy based on the primary efficacy endpoint of "pain at night while in bed"	- Publish results of VACT-1 - Publish results of VACT-2 even if DDMAC does not accept claim for superiority - Focus on positive results from other comparative studies vs. Celebrex, such as VACT-1 & VACT-2. - Team is evaluating the current Data Analysis Plan and is considering changes to the analyses based on the results of C1/C2

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MRK-ABH0002867

Table 1. VIOXX® Key Objectives and Issues (Cont'd)

Objective	Study/Initiative	Issues/Risks	Mitigation Strategy
Establish VIOXX as Best in the Coxib Class (Primarily based on efficacy) (cont'd)			
Demonstrate that VIOXX® is superior to Celebrex and Acetaminophen in the treatment of OA (continued)	- VIOXX®/Celebrex Preference Study (Crossover assessment of patient preference for VIOXX® 25 mg vs. celecoxib 300 mg QD	- Patients may not be able to translate difference in efficacy to preference	- Have Patient Global Response to Therapy as primary endpoint and preference as secondary endpoint
Demonstrate that VIOXX® is superior to narcotics in order to enhance the efficacy image of VIOXX® to better compete with Valdecoxib and Celebrex	- Dental Pain Studies vs Oxycodone/ Acetaminophen (2) - Acute Musculoskeletal Pain Pilot Study vs. Hydrocodone/ Acetaminophen /(2 tabs: 1 tab) & IM Toradol followed by two Hydrocodone/ Acetaminophen Studies in Acute Musculoskeletal Pain	- Dental pain is perceived as an insufficient pain model by specific specialties - VIOXX® is not equivalent to Toradol - VIOXX® is not superior to two tablets of Hydrocodone/ Acetaminophen - Model is not an adequate pain model	- Study is a pilot study. Future comparisons to Hydrocodone/Acetaminophen could be with a lower dose (i.e. one tablet instead of two)
Augment the image of VIOXX® as a potent analgesic with studies in cancer pain	- Cancer Pain studies	- USHH will not be able to use these studies for promotion until a Chronic Pain indication has been approved by FDA - Intrinsic risk of long term studies (12 weeks) with endpoints of pain and/ or narcotic reduction	

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Table 1. VIOXX® Key Objectives and Issues (Cont'd)

Objective	Study/Initiative	Issues/Risks	Mitigation Strategy
Establish VIOXX® as Best in the Coxib Class (Primarily based on efficacy)			
Use Rapidisc to enhance the efficacy image and extend life cycle	- Chronic PK studies with 12.5 and 25 mg RPD - Ambulatory BP study with 25 mg RPD - Consideration of 6 month RPD safety study with 25 mg (depends on results of ABPM study) - Dental pain study with 50 mg RPD	- The 12.5-mg and 25-mg Rapidisc tablet do not have a similar AUC compared with the conventional tablet with chronic dosing - The 25-mg Rapidisc Tablet has greater effects on Ambulatory BP compared with the 25-mg conventional tablet - The FDA may require a long term clinical safety program for the Rapidisc 50-mg, in addition to safety studies for the 25-mg Rapidisc ("dose creep" issue)	- Discuss development plan in advance with the FDA - Continue development of Nanosystems formulation tablet
Establish uniqueness of VIOXX® in patients allergic to sulfonamides.	Marketing initiative: Leverage the fact that VIOXX® is not a sulfonamide	- Distracts from the emphasis on efficacy - Only a small number of patients are allergic to sulfonamides	- Demonstrate the difficulty in identifying patients allergic to sulfonamide - Emphasize the seriousness of sulfonamide allergies - Promote strongly on the fact that Celebrex is a sulfonamide, but VIOXX® is not.

MRK-ABH0002868

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Table 1. VIOXX® Key Objectives and Issues (Cont'd)

Objective	Study/Initiative	Issues/Risks	Mitigation Strategy
Establish VIOXX® as Best in the Coxib Class (Primarily based on efficacy)			
Differentiate the GI safety of VIOXX® from the GI safety of Celebrex	VIGOR & CLASS trials	- How can the GI safety from CLASS be differentiated from the GI safety from VIGOR without having an overall negative impact on the Coxib class? - Will the difference between VIOXX® and Celebrex labels be enough to attain an advantage with Managed Care Organizations.	- Negotiate with FDA/ worldwide regulatory agencies and emphasize need to maintain evidentiary standard - Actively communicate through scientific meetings, to highlight the weaknesses of the CLASS trial and differences between the JAMA article and the results presented at the FDA

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MRK-ABH0002870

Table 1. VIOXX® Key Objectives and Issues (Cont'd)

Objective	Study/Initiative	Issues/Risks	Mitigation Strategy
Neutralize Non-GI Safety Concerns			
1. Renal Effects (Hypertension/Edema)			
Demonstrate that Celebrex renal effects are comparable to VIOXX® renal effects at equally efficacious doses	- Completed VIOXX®/Celebrex renal sodium handling study - Celebrex Ambulatory Blood Pressure Pilot study (*CDP*)	- Criticism that 200-mg bid of Celebrex was too high - Risks: Celebrex has a lower effect on ambulatory blood pressure than anticipated - Even at equally efficacious doses small, differences between NSAIDs and COX-2 inhibitors may exist	- Publish renal handling study and emphasize need to demonstrate safety at equally efficacious doses - Pilot study will be done before any large comparative study is initiated - Continue aggressive corporate effort to defend the renal safety profile of VIOXX® through physician education
2. Cardiovascular Effects			
- Demonstrate that CV risks with VIOXX® are similar to placebo and to other NSAIDs without sustained near maximal inhibition of platelet aggregation	- Adjudication of CV events in all COX-2 inhibitor studies - Meta-analysis of Ph IIb-V studies - CV results from interim Alzheimer study and Phase IIb/III OA Study	- Rates of MI and CV events from VIGOR will be included in the VIOXX® label while Celebrex will not have similar data in their label	- Presentation at academic meetings and publication of CV meta-analysis, Phase IIb/III OA, and interim Alzheimer CV results - By 2004, over 20,000 patient-years will have been accrued, providing over 300 CV events & >80% power to determine a 40% increase in events on VIOXX® vs. pbo

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Table 1. VIOXX® Key Objectives and Issues (Cont'd)

Objective	Study/Initiative	Issues/Risks	Mitigation Strategy
Neutralize Non-GI Safety Concerns (cont'd)			
2. Cardiovascular Effects (cont'd)			
Demonstrate that naproxen acts as a cardioprotective agent	- Epidemiologic studies demonstrating Naproxen's ability to act as a cardioprotective agent (note: preliminary results from one study demonstrated a significant reduction in thrombotic events in RA patients who used naproxen vs. those who did not. Final analysis is pending.) - African Green Monkey studies demonstrating that naproxen acts similar to aspirin in delaying the time to thrombosis and thus acts as an anti-thrombotic agent (See Figure 4).	- Naproxen would need to be taken twice daily without interruption to demonstrate a cardioprotective effect. Epidemiologic studies done on the general population will include patients who use naproxen on an intermittent basis	- Conduct and publish epidemiologic studies in RA patients who are likely to chronically use naproxen, or conduct studies only if chronic use can be ascertained from the database - Highlight and actively communicate the results of the African Green Monkey Study at scientific meetings.

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Table 1. VIOXX® Key Objectives and Issues (Cont'd)

Objective	Study/Initiative	Issues/Risks	Mitigation Strategy
Prepare for Valdecoxib & Parecoxib			
Demonstrate that VIOXX® is efficacious in the peri-operative management of postoperative pain	- Peri-Operative Analgesia studies	- Studies are not positive - No peri-operative analgesia indication exists for NSAIDs - FDA does not agree to the choice of endpoints or models - Promotion will have a limited impact because Parecoxib will have a well established position in the peri-operative analgesia market	- Meet with FDA to clarify the requirements for a potential peri-operative indication. Discuss MRL's proposed clinical program and get "buy-in" before initiating a program - Do pilot study with interim analysis to help power secondary endpoints of future studies - Publish results of GYN Study prior to filing
Demonstrate that VIOXX® is equivalent to Parecoxib	- VIOXX® versus Parecoxib in acute pain	- Ability of VIOXX® to demonstrate efficacy similar to parenteral Parecoxib	- Results of Pilot study with Toradol will help to optimize study design
Develop an IM formulation	- IM Nanosystems in development (PK & Acute Pain studies)	[redacted]	

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Table 1. VIOXX® Key Objectives and Issues (Cont'd)

Objective	Study/Initiative	Issues/Risks	Mitigation Strategy
Expand to New Market via New Indications			
1. New Indications			
Cancer Market - Demonstrate prevention of prostate cancer recurrence after prostatectomy - Demonstrate efficacy in treatment of colonic adenomas - Demonstrate prevention of recurrence of colon cancer	- Prostate Cancer Study - Effect of VIOXX® on Colon Polyps Study (SAP study) - FAP Study - Prevention of recurrence of colorectal cancer (VICTOR)	- Potential claim (sWMA: T-4Q05) - Potential claim (sWMA: T-4Q05) - Publication/ Promotion - Potential claim	
Migraine - Demonstrate efficacy in the treatment of migraine - Demonstrate efficacy in the prophylaxis of migraine	- Treatment of migraine Study - Prophylaxis Proof of Concept study	- Potential claim (sWMA: T-4Q02) - Potential claim (sWMA: T-2Q04)	
Alzheimer's Disease (AD) Demonstrate efficacy in preventing conversion to AD	- AD Prevention Studies	- Potential claim (sWMA: T-4Q03)	

MRK-ABH0002873

All commercial and clinical activities are designed to address these key issues.

1. Accelerate Patient Recruitment in the A&A Market

For VIOXX® to increase share in the arthritis and analgesia market, it will need to continue to displace traditional NSAIDs worldwide. There are three main barriers to continued Coxib penetration of the A&A market. First, many physicians perceive that GI bleeds are rare and predictable and therefore only treat patients in the highest risk category, (in their minds, those with a history of a bleed). Second, Coxibs are more expensive than generic NSAIDs worldwide and in many instances access to them is restricted. Third, some physicians believe that in patients requiring low dose aspirin, the GI benefit of a Coxib is mitigated. These elements, combined with similar efficacy in clinical trials between Coxibs and traditional NSAIDs pose a challenge to class growth.

To grow VIOXX® into the A&A market, the CST is pursuing four main activities globally. First, the Team is actively pursuing improved GI labeling for VIOXX® to facilitate enhanced formulary/re-imbursement status versus branded and generic NSAIDs and to support promotion in the U.S.. Promotion in the rest of the world is already underway. The VIGOR data provides documentation to underscore that VIOXX® represents a compelling improvement over traditional NSAIDs such as naproxen, and that serious GI events can occur without warning and early in the course of therapy. This will demonstrate that physicians cannot afford to "wait and see", but must treat presumptively as all patients on NSAIDs are at risk of GI events. The VIGOR data further demonstrates that even patients at low risk show a significant reduction in GI events over those treated with naproxen. Key audiences for the promotion of VIGOR results include not only physicians, managed care organizations and reimbursement authorities, but consumers and patients who will be reached through public affairs activities worldwide and if possible, DTC activities in the U.S. market.

Second, plans are in place to use not only the VIGOR data, but epidemiological and outcomes research data, to convince payors (either Managed Care Organizations in the U.S. or reimbursement authorities internationally) that Coxib use is cost effective. A broad mix of programs have been designed worldwide to describe the burden of illness of GI-induced gastropathy and to build a case that the use of Coxibs instead of traditional NSAIDs is cost-effective despite the higher out of pocket costs. (Note: A detailed summary of the Coxib Outcomes Research Activities will be presented to the PAC in April.)

Third, to deal with the barrier that aspirin mitigates the GI benefit of Coxib therapy versus traditional NSAIDs, MRL is conducting studies to demonstrate that the GI safety of VIOXX® plus low dose aspirin is superior to the GI safety of ibuprofen or ibuprofen plus aspirin. Ideally, these studies will be included in the VIOXX® label and available for promotion in the U.S. as well as the rest of the world. These studies

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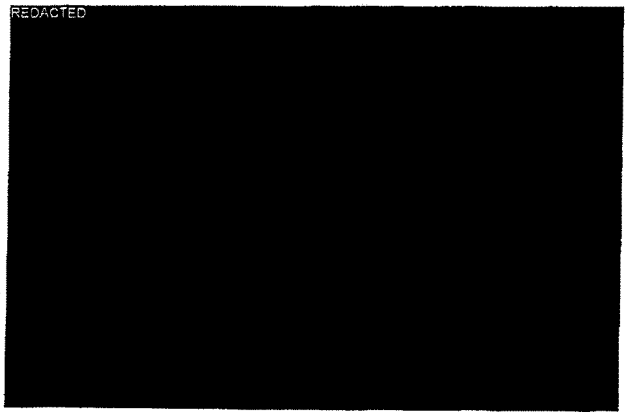
will be important to managed care organizations and reimbursement authorities in general because they remove one argument against reimbursing Coxibs.

Fourth, the Team is pursuing two new indications in the A&A market: 1) Pediatric Rheumatoid Arthritis (JRA); 2) Chronic Pain. Obviously, there are U.S. patent extension benefits from pursuing the JRA program, but the CST also believes that data in JRA will help grow VIOXX® into the A&A market in the medium term, as JRA enhances the overall safety image for the brand. In order to achieve the chronic pain indication, two 12-week studies in Chronic Low Back Pain (CLBP) will conducted. This will increase penetration in the A&A market by extending the GI safety from OA and RA to CLBP.

Interestingly, the number one reason for trying either Coxib remains dissatisfaction with the efficacy of current therapy, usually a traditional NSAID. In the U.S., this has contributed to class growth but is probably not a basis for active marketing since the entire VIOXX® clinical program demonstrates comparable efficacy between VIOXX® and comparator NSAIDs. Attribute data in the U.S. suggests that physicians do not believe they are trading better GI safety for less efficacy.



2. Establish VIOXX® as Best in Class (Primarily based on efficacy)

To maintain and grow the leadership position that VIOXX® has in the Coxib market and to capitalize fully on the growth of the class, the CST is continuing to search for ways to differentiate VIOXX® from celecoxib and the main future competitors (parecoxib/valdecoxib). The weekly Coxib market share for new prescriptions in the U.S. is 50.7% and has remained above 50% for a number of weeks. In major Ex-US

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markets, VIOXX® has demonstrated a similar strong performance vs. Celecoxib and attained a leading market position. A review of the product attributes for the brands demonstrates that although VIOXX® and celecoxib are perceived to be similar on most product attributes, there are two attributes for which VIOXX® currently has a perceptual lead: analgesic efficacy and sulfa allergies. These are the two main dimensions that the CST is currently exploiting to grow VIOXX® share of the Coxib market. Depending on the outcome of labeling negotiations in the U.S., the opportunity for exploiting differences in proven GI safety is a possible third avenue.

Regarding analgesic efficacy, a minority of physicians see VIOXX® as clearly more effective and a majority see it as being slightly more effective than celecoxib (note that 80% of the U.S. use is 25 mg of VIOXX®). In the U.S., it appears as though the acute pain indication supports this perception and dissemination of recent trial data comparing VIOXX® to Celebrex in OA, such as VACT (VIOXX®, Acetaminophen, Celebrex Trial) and protocol 116 (VIOXX® versus celecoxib), re-inforce it. To build on these trials and promote in the U.S., the VACT has been undertaken; the SWITCH trial has been initiated ex-US. VACT 2 is designed to replicate VACT and be the second supporting trial for promotion in the U.S., assuming a strong result. SWITCH is a CDSP study that is currently being conducted in Europe and evaluates the effectiveness of VIOXX® in patients who have failed on Celecoxib.

In addition to the head to head trials verus celecoxib in OA described above, several trials comparing VIOXX® to narcotics in acute pain will also heighten the perception of the efficacy of VIOXX® overall and versus celecoxib, since the latter lacks an acute pain indication and has only very limited data versus narcotics. Specifically, there is a pilot study underway comparing VIOXX® to VICODIN (hydrocodone/ acetaminophen) in acute musculoskeletal pain (a model which is more credible with orthopedic surgeons and general practioners), which will enable the team to design and power two larger trials for promotion in the U.S., beginning this year. Also, MRL is conducting two studies in dental pain versus generic PERCOCET (oxycodone/ acetaminophen). Both of these studies will also help manage valdecoxib, which we believe may be positioned similarly to VIOXX® with the added advantage of an injectable (parecoxib).

Besides the head to head trials in OA and the narcotic comparator trials in acute pain, the CST is seeking to expand the analgesic image of the brand by pursuing three additional pain models, each of which moves VIOXX® up the pain spectrum. The CST is pursuing an indication for chronic pain with low back pain studies, which is perceived as being a more severe pain than OA; an indication for migraine (see below in the new indications section), which is perceived to be more painful than OA, RA, and low back pain in general; and a study for adjunctive therapy to narcotics in cancer pain, probably the most severe chronic pain model available.

Also, the CST is pursuing a Rapidisc formulation of VIOXX®, which we think will enhance the image of the efficacy of the brand because physicians and patients believe that it will provide a faster onset of action even though PK data suggest that it is unlikely to be the case. Evidence from the migraine market and our own primary

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research suggest that this formulation will provide an advantage over celecoxib (and other NSAIDs) for some physicians in acute pain.

Regarding sulfa allergies, physicians know that VIOXX® does not have a sulfonamide allergy and clearly prefer VIOXX® in those patients.

On the issue of GI safety, the more robust result of VIGOR versus CLASS suggests an opportunity to drive a wedge between VIOXX® and celecoxib on the dimension of GI safety, perhaps based on greater selectivity. Currently, physicians perceive no difference between the two brands, however, a differentiated label for VIOXX® as a result of negotiations with the FDA would potentially allow for differentiation on this basis. Before the CST recommends pursuing this path, more clarity is needed about the eventual outcome of the label negotiations.

3. Neutralize Non-GI Safety Concerns

There are two main non-GI safety concerns that the competition has raised regarding VIOXX®. The first relates to renal effects, specifically the assertion that VIOXX® causes more hypertension and edema than celecoxib. The second relates to the cardiovascular (MI) findings from VIGOR.

Hypertension and Edema

Pharmacia/ Pfizer have aggressively attempted to portray VIOXX® as unsafe by claiming that VIOXX® has a higher incidence of edema and hypertension than traditional NSAIDs (primarily by focusing on the 50mg acute pain dose) and a higher incidence than celecoxib The latter claim is based on one study conducted by Whelton et al. It concluded that the 25 mg dose of VIOXX® causes a higher incidence of hypertension and edema than 200 mg QD of celecoxib and that VIOXX® raises systolic blood pressure more than celecoxib by several mmHg. Pharmacia/ Pfizer is also suggesting that this degree of increase in systolic BP is large enough to be of concern for MIs and other cardiovascular events. At this point, Pharmacia/Pfizer have made hypertension/edema promotion the cornerstone of their marketing campaign against VIOXX® on a worldwide basis. Because there is a high overlap of patients with OA and hypertension the message has broad appeal. The CST has received several reports of additional studies that Pharmacia/Pfizer are undertaking to build their story.

Attribute data clearly suggests that efficacy is a bigger driver of prescribing than renal effects, however, the renal issue is an important challenge for VIOXX® because it affects the ability of the brand to grow share in the chronic market (which represents about 80% of PDOT), where non-GI safety is a bigger issue for physicians. Furthermore, this initiative by Pharmacia/ Pfizer will enable them to manage their franchise by positioning valdecoxib as highly efficacious and safer than VIOXX®.

An evaluation of the data overall suggests that at supratherapeutic doses (VIOXX® 50 mg and Celebrex 400 mg bid), VIOXX® is associated with more edema and HTN compared to Celebrex. Some of this difference may be related to the fact that in the

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elderly, Celebrex is not dose proportional above 200 mg. Within the clinical dose range, when comparing equally efficacious doses the rates of edema and HTN appear to be generally similar although small differences may exist. In a recently completed sodium retention study in healthy elderly subjects on a sodium replete diet, increases in SBP were similar on VIOXX® 25 mg and Celebrex 200 mg bid. However, results from an ambulatory blood pressure monitoring study (ABPM) in hypertensive adults treated with an ACE inhibitor, demonstrated smaller increases in systolic and diastolic blood pressure with Celebrex 200 mg bid compared to a similar study conducted by Merck with VIOXX® 25 mg qd. In addition, in one of the VIOXX®/ Celebrex head to head comparison studies, mean changes in SBP in a small subgroup of hypertensive patients were slightly greater on VIOXX® 12.5mg compared to Celebrex 200 mg qd. To further understand this complex issue and minimize any risk of confirming the competitor's claims, the CST is pursuing a pilot ABPM study in hypertensive adults comparing celecoxib 200mg qd and 200mg bid versus placebo. The purpose of this study is to fully understand the behavior of celecoxib alone so that we can learn more about what effect it has on blood pressure at these doses.

Other than this study, the CST is addressing this issue with an aggressive corporate effort to defend the renal safety of VIOXX® through physician education. A joint USHH/WHHM hypertension task force was established in late 2000 with the objective of countering misleading information communicated by Pharmacia/ Pfizer, and highlighting the lack of credibility of both companies. As a result, worldwide, promotional efforts have intensified. The key messages of this effort are:

- Hypertension and edema are mechanism based class effects of all NSAIDs & Coxibs.
- Rates of hypertension and edema with VIOXX® and Celecoxib are low and consistent with NSAIDs.
- Rates of discontinuation due to hypertension and edema are very low for both Coxibs.
- In VIGOR, the same rates were observed in Phase III OA trials and there was no correlation between MI and hypertension .
- VIOXX® is more effective than celecoxib based on head to head study results and safety can only be compared at equally efficacious doses.

Numerous selling aids and resources with the above mentioned messages have been distributed to sales representatives worldwide. Examples include slide lecture kits, training programs, sales representative Q&A's, CV and Hypertension/ Edema Obstacle Handlers and the VIOXX® vs. Celebrex Comparison Cards. Opinion leader activities have been expanded to include nephrologists and abstracts supporting these messages have been submitted to various professional society meetings.

Cardiovascular Effects (MI) - VIGOR

At this point, in the minds of prescribing physicians and in the eyes of payors, the cardiovascular issue emerging from VIGOR is less a competitive issue versus celecoxib and more of an issue for VIOXX® relative to other NSAIDs. Most physicians indicate that they believe that if VIOXX® is somehow pro-thrombotic that

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it would be class effect of the coxibs and not an effect unique to VIOXX®. The proceedings at the Advisory Committee meeting seem to have re-enforced this perspective. The one circumstance that could change this would be labeling that suggested a pro-thrombotic effect unique to VIOXX®. This labeling difference would be leveraged aggressively in promotion by Pharmacia.

This issue is being addressed through ongoing clinical studies and outcomes research analyses that are being communicated to physicians as data become available. First, and most importantly, all CV events are being adjudicated in all COX-2 inhibitor studies. The objective of the adjudication is to demonstrate that CV risk with VIOXX® is similar to placebo and to other NSAIDs, with the exception of naproxen. Second, outcomes research is conducting a series of studies to demonstrate that naproxen is cardioprotective in a variety of settings and patient populations, particularly RA. Outcomes research has already published an abstract demonstrating that patients with RA are at an increased risk of a CV event.

4. Prepare for Valdecoxib and Parecoxib

The launch of Pharmacia's "next generation" COX-2 inhibitors, parecoxib and valdecoxib, represents the single greatest threat to VIOXX® since its launch in 1999. Parecoxib will be the only available injectable Coxib and is the parenteral pro-drug of the oral Coxib, valdecoxib. It will be used in the acute setting for pre- and post-surgical pain as a significant advancement to injectable Toradol based on its superior safety profile. Pharmacia poses two distinct threats. First, Pharmacia will use the parenteral formulation of parecoxib to create a halo of powerful efficacy to increase use in the acute and chronic settings. Secondly, Pharmacia will promote the use of parecoxib in the perioperative surgical and outpatient setting and provide dose transition data to increase the use of valdecoxib at discharge.

Based on the most recent competitive intelligence, we believe that Valdecoxib will be launched with a significant Phase III clinical program providing indications for acute pain, chronic pain, osteoarthritis and RA. Intelligence suggests it will be promoted as a second-generation Coxib with a superior efficacy profile to the existing marketed Coxibs. Efficacy is the number one product attribute in the A & A market and the superior efficacy positioning of valdecoxib would be a direct threat to the current analgesic positioning of VIOXX®. An efficacy position would likely be based on narcotic comparator data, narcotic sparing results in cancer pain and potential faster on-set of action due to the halo effect from parecoxib.

VIOXX® is currently used in the surgical and outpatient setting based on its distinctive value to reduce acute pain with a safety profile superior to non-selective NSAIDs. Because VIOXX® is not currently available in a parenteral formulation, Merck must execute clinical trials with the oral formulation to blunt the uptake of the new Coxibs in the acute setting and to protect its distinctive value in acute pain. The successful design and completion of a perioperative analgesia clinical program would demonstrate the efficacy of VIOXX® used prior to surgery to reduce narcotics and pain in the post-surgical setting. If successful, these data could show that there is a limited

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 32

MERCK

MEMO

TO: Wendy Dixon
Lucine Beauchard

FROM: Tracy Mills
Susan Baumgartner, PharmD

SUBJECT: Scientific Communication Plan for VIOXX® **DATE:** 03/27/01

To maintain the vigorous growth of VIOXX® in 2001 and to ensure competitive victories over Coxib competitors and non-selective NSAIDs, our team has developed the attached scientific communication plan for VIOXX®. The objectives of this plan are to:

- Expedite and expand dissemination of Merck's position on the GI safety, cardiovascular effects, and renal effects of VIOXX® to key audiences, which include RH, GI, GP/FP, IM, ORS, Pain, CD, Neph, and MCO
- Ensure understanding of and confidence in Merck's data, and
- Regain the offensive by shifting physicians' focus back to the superior pain relief and superior safety provided by VIOXX®.

In summary, the scientific communication plan for VIOXX® outlines the behavioral objectives that will drive attainment of our overall objectives, target audiences, key messages, and planned programs through which these messages will be communicated. It also highlights the demands that will be placed on the organization, and specifically on MRL, in order to fulfill the desired objectives.

A summary of the plan is provided in Attachments 1, 2, and 3, which contain the following information:

Attachment 1: Summary of message prioritization and planned programs for target audiences
Attachment 2: Support needed by MRL
Attachment 3: Internal and external speakers

The full plan provides additional details and is included as Attachment 4 for your reference.

The foundation of the plan is an evolved message platform with respect to superior pain relief, GI safety, cardiovascular effects, and renal effects of VIOXX®. The table below outlines the planned evolution of the message platform.

	STAGE 1 MESSAGES (2000 – February 2001)	*STAGE 2 MESSAGES (February – May 2001)*	*STAGE 3 MESSAGES (May 2001 +)*
Pain Relief	Superior pain relief to Celebrex, narcotics	Superior pain relief to Celebrex, narcotics	Superior pain relief to Celebrex, narcotics
GI Safety of VIOXX®	Proven GI safety	Superior study & superior GI safety	Superior study & superior GI safety
GI Data for Celebrex	Only selected data from CLASS that did not hit primary endpoint	Full CLASS data show no proof of GI safety with Celebrex	Full CLASS data show no proof of GI safety with Celebrex
Cardiovascular (MI)	CV effects similar to placebo and NSAIDs; difference in MIs in VIGOR due to cardioprotection with naproxen (based on limited data)	CV effects similar to placebo and NSAIDs without potent, sustained anti-platelet effects; difference in MIs in VIGOR due to cardioprotection with naproxen (epidemiology, primate, assay-based data); CV effects of Coxibs are comparable	Include new sub-analyses, patient subgroups, CV markers, new non-selective NSAID comparisons. As well as, potential additional data.

Renal (Hypertension/Edema)	Mechanism-based, dose-dependent renal effects of Coxibs; similar to NSAIDs; discontinuations very small	Mechanism-based, dose-dependent renal effects of Coxibs; similar to NSAIDs; discontinuations very small	Include new renal studies, renal analyses, markers, etc.

The initial message platform, designated as Stage 1 messages, includes key messages that have been delivered since the launch of the VIGOR data in the second quarter of 2000. These messages focused on superior pain relief and proven GI safety of VIOXX®. The Stage 1 messages also addressed the CLASS data as only selected data that did not achieve the primary study endpoint, renal effects of Coxibs as mechanism-based and dose-dependent, and the MI difference in VIGOR as due to a cardioprotective effect of naproxen based on limited data.

The FDA Advisory Committee Meetings on February 7 and 8, 2001, added new data and perspectives that allowed us the opportunity to further refine our message platform. These meetings exposed all of the CLASS data, which were dramatically different than the selected data that was shown in previous venues and which were not favorable for celecoxib. Furthermore, these meetings included a full discussion of the cardiovascular safety data for the Coxibs. The FDA Advisory Committee Meeting on VIGOR allowed communication of our more complete understanding of the cardioprotective potential and the cardioprotective effects of naproxen. Hence, refined messages, designated as Stage 2 messages, were developed and are currently being delivered.

The next evolution of the message platform to Stage 3 messages is required so these messages reflect all available data (across doses, patient populations, and different products) and offer a more complete understanding of current knowledge in these areas. It is also imperative that we refine the messages to ensure that they are clinically relevant to our target audiences. These messages must also answer the critical questions and frame the key issues for the medical community. Stage 3 messages represent what we need to communicate to solidify the position of VIOXX® within the Coxib class and within the A&A market.

To attain the platform for Stage 3 messages, two critical steps are needed. First, a thorough analysis of all available data on the cardiovascular and renal effects of VIOXX® and Celebrex must be conducted by the Core Franchise Team to fully understand what the data support. A meeting has been planned for March 23 to initiate this discussion. Secondly, these data and Merck's point of view on these data must be shared with our external advisors of the Cardio-renal Working Group (cardiologists and nephrologists) to allow us to attain the next level of messaging. Initial discussions with these advisors have been targeted for mid-April. Further market research will also allow us to refine the messages to ensure consistency throughout all of our communications from our scientific platform through our promotional messages.

In additional to the tremendous support needed by our MRL Team, we are also partnering with several other Franchise Business Groups. Execution of the plan will require coordination with the FOSAMAX®, ZOCOR®, and COZAAR®/HYZAAR® Teams, since their existing meetings will provide additional communication vehicles to target audiences. Coordination with these teams is already underway. Attachment 2 identifies meetings for which MRL/CDP support would be particularly helpful. A separate list of potential speakers, external and internal has also been provided. Considerable discussion has also been given to the top 6 competitive consultants, and future plans for working with them. A separate plan is under development for each of the six and will be available by the end of March.

Managed care customers are another group where there is a need for support to proactively defend the position of VIOXX® on formularies. A list of the status of the key Profit Plan accounts, the timing of their formulary reviews, and other pertinent information related to Merck's relationships with these critical accounts has been developed. A request has been made that the Managed Care Management Team review the need for MRL to conduct Personal PIRs (i.e., personal visits or teleconferences) to support these accounts so a comprehensive action plan can be finalized. It is imperative that ongoing RMD support of the targeted managed care accounts continues. However, in light of the recent activities by Pharmacia/Pfizer and the fact they will receive their label change prior to the label change for VIOXX®, a critical assessment of the need for MRL support for our managed care customers will be conducted.

Please let us know if you have any specific questions about the plan or the support requested. Thank you for your continued commitment to the success of VIOXX®.

T.L.M S.L.B.

cc: Steve Vignau

Attachments (4)

- Attachment 1: Summary of message prioritization and planned programs for target audiences
- Attachment 2: Support needed by MRL
- Attachment 3: Preferred speakers
- Attachment 4: Scientific communication plan for VIOXX*

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Attachment 1:
Summary of Message Prioritization and Planned Programs for Target Audiences

Table 1: Primary Target Audiences

Target Audience and Size	*Message Priority*				*Summary of Planned Programs*
	Pain Relief	*GI Safety*	*CV (MI)*	*Renal (HTN/ Edema)*	
Top 100 National Thought Leaders #100 (multi-specialty)	1	1	1	1	*In addition to programs offered for their respective specialties:* HSA calls ≥ 1 per month, personal PIRs as needed (visits or calls by MRL/CDP/MEDSA/RMDs), 2 advisory board meetings, individual advocate plans
Speakers #1000 (multi-specialty)	1	1	1	1	*In addition to programs offered for their respective specialties:* Slides every quarter, 1 speaker training meeting, regional speaker training meetings with launch of new data, 20 speaker training teleconferences
Targeted Rheumatologists #510	1	2	3	4	2 national and 6 regional consultants' meetings for VIOXX, 6 regional consultants' meetings for FOSAMAX, FDA Advisory Committee Meeting summary report, cardio-renal educational materials*, EULAR, other publications, ACR
Targeted Cardiologists and Nephrologists #800	4	3	1	2	2 cardio-renal advisory board meetings, presentations at 1 national and 6 regional consultants' meetings for ZOCOR/COZAAR, CV HSA calls, 1 national cardio-renal consultants' meeting for VIOXX, cardio-renal educational materials*, key CV/nephrology professional meetings (ACC, ASH, NKF, AHA), other publications
Targeted Gastroenterologists #100	3	1	2	3	CME monograph, 1 national consultants' meeting, DDW, cardio-renal educational materials*, GI advisory board meeting for FOSAMAX, ACG, other publications
IMs GPs FPs #108,000	1	4	2	3	CME audioconference series, Pri-Med symposia, publications, HEL programs, cardio-renal educational materials*, PCP consultants' meetings, other publications
Key Managed Care Customers #240	3	1	2	4	NAE calls, HSA calls for scientific support, ASR calls on managed care influencers, personal PIRs as needed (visits or calls by MRL/CDP/MEDSA/RMDs), 1 advisory board meeting, 2 national consultants' meetings, publications

Table 2: Secondary Target Audiences

Target Audience	*Message Priority*				*Summary of Planned Programs*
	Pain Relief	*GI Safety*	*CV (MI)*	*Renal (HTN/ Edema)*	
Pain Management Specialists #600 (consultants) + all targeted PMS	1	4	2	3	AAPM CME symposium and meeting report, APS CME symposium and meeting report, 2 advisory board meetings, 3 national and 6 regional consultants' meetings, cardio-renal educational materials*, other publications
Orthopedic Surgeons #385 (consultants) + all targeted ORS	1	4	2	3	AAOS CME symposium and meeting report, cardio-renal educational materials*, 1 national and 6 regional consultants' meetings, 2 advisory board meetings, other publications
Other Cardiologists and Nephrologists	4	3	1	2	Cardio-renal educational materials*, key CV/nephrology professional meetings, other publications
Other Rheums #2500	1	2	3	4	FDA Advisory Committee Meeting summary report, cardio-renal educational materials*, EULAR, other publications, ACR

*Cardio-renal educational materials to support our message platform will be determined based on input provided by the Cardio-renal Working Group and may include CME monographs, publications, slides, and other educational resources that are appropriate for each audience.

Attachment 2:
Support Needed by MRL

Italics denotes programs that are under consideration but not yet scheduled or confirmed.

PROGRAMS	*DATE*	*SUPPORT NEEDED BY MRL**
National Gastroenterology Consultants' Meeting for VIOXX	March 30-April 1, 2001	Eric Mortensen confirmed
6 Spring Regional Consultants' Meetings for ZOCOR/COZAAR	*March – May, 2001*	*Presenters needed*
One-on-one meeting with Barry Brenner in preparation for Cardio-renal Working Group Meeting	April, 2001 (not yet scheduled)	Sr. MRL Management requested
Cardio-renal Working Group Meeting	April, 2001 (not yet scheduled)	Alise Reicin requested
MRL customer visit with Aetna for information requests related to formulary review of Coxibs	April, 2001 (not yet scheduled)	Presenter needed
Top 100 national thought leader personal PIRs (phone calls or visits) as needed	April – May, 2001	Phone calls or visits by MRL as needed (based on feedback provided by HSAs and field sales) – key MRL point people assigned to Top 50 national thought leaders, additional MRL support will be requested as needed
One-on-one or small group meetings with selected thought leaders at National Kidney Foundation (NKF) Meeting or American Society of Hypertension (ASH) Meeting	April 19-22, 2001 (NKF) May 16-19, 2001 (ASH)	Participant(s) needed
National Pain Consultants' Meeting	April 26-28, 2001	Presenter needed
Managed care personal PIRs (phone calls or visits) as needed	Post-Label Change	Phone calls or visits by MRL as needed (based on feedback provided by NAEs)
National Hypertension/Heart Failure Consultants' Meeting for COZAAR	*May 3-6, 2001*	*Presenter needed*
National Orthopedic Surgery Consultants' Meeting for VIOXX	May 4-6, 2001	Briggs Morrison confirmed
National Managed Care Advisory Board Meeting for VIOXX	May 4-6, 2001	Presenter needed
National Hospital Consultants' Meeting for VIOXX – West	May 4-6, 2001	Presenter needed
National Hospital Consultants' Meeting for VIOXX – East	May 18-20, 2001	Presenter needed
VIGOR National Faculty Consultants' Meeting	May 18-20, 2001	Presenter needed
One-on-one or small group meetings with selected thought leaders at DDW	May 20-23, 2001	Participant(s) needed
Gastroenterology Advisory Board for FOSAMAX	May 23, 2001	Presenter needed
6 Regional Rheumatology Consultants' Meetings for VIOXX	*Mid-May – June, 2001*	*Presenters needed*
2 National Managed Care Consultants' Meetings (Medical and Pharmacy Directors from targeted MC accounts)	May 31-June 2, 2001 June 7-9, 2001	Presenters needed – Ed Scolnick requested for both meetings
20 VIGOR speaker training teleconferences	May – June, 2001 (to be scheduled based on presenter availability)	Presenters needed
Cardio-renal Advisory Board Meeting for VIOXX	2T01 Meeting (not yet scheduled)	Alise Reicin requested

Support Needed By MRL (continued):

PROGRAMS	*DATE*	*SUPPORT NEEDED BY MRL**
Orthopedic Surgery Advisory Board Meeting for VIOXX	June 1-3, 2001	Briggs Morrison confirmed
Pain Advisory Board Meeting for VIOXX	June 8-10, 2001	Presenter needed
One-on-one or small group meetings with selected thought leaders at EULAR	June 13-16, 2001	Participant(s) needed
6 Masters' Conferences for ZOCOR/COZAAR	*June-August, 2001*	*Presenters needed*
National Cardio-renal Consultants' Meeting for VIOXX	July-September, 2001 (not yet scheduled)	Presenter(s) needed
National Rheumatology Consultants' Meeting for VIOXX	August 2-5, 2001	Presenter needed
6 Regional Rheumatology Consultants' Meetings for VIOXX	August 10-12, August 17-19, August 24-26 (2 mtgs), September 7-9, September 14-16	Presenters needed
Multidisciplinary Advisory Board Meeting for VIOXX	September 7-9, 2001	Alise Reicin confirmed
Cardio-renal Advisory Board Meeting for VIOXX	3T01 Meeting (not yet scheduled)	Alise Reicin requested
6 Regional Pain/ORS Consultants' Meetings for VIOXX	September 14-16, September 21-23 (2 mtgs), October 5-7 (2 mtgs), October 12-14	Presenters needed
Pain Advisory Board Meeting for VIOXX	October, 2001 (not yet scheduled)	Presenter needed
Orthopedic Surgery Advisory Board Meeting for VIOXX	November, 2001 (not yet scheduled)	Presenter needed
One-on-one or small group meetings with selected thought leaders at AHA	November 11-14, 2001	Participant(s) needed
One-on-one or small group meetings with selected thought leaders at ACR	November 12-14, 2001	Participant(s) needed
Multidisciplinary Advisory Board Meeting for VIOXX	December 7-9, 2001	Alise Reicin confirmed

**** Meeting underway with Alise Reicin to determine talks, presenters***

Attachment 3:
Internal and External Speakers

Preferred Internal Speakers

MRL	*CDP*	*MEDSA*
Doug Greene	Greg Geba	Jeff Melin
Alan Nies	David Chang	
Barry Gertz		
Alise Reicin		
Eliav Barr		
Keith Gottesdiener (renal)		
Ken Truitt		
Harry Guess		

Additional Internal Speakers*

MRL	*Region Medical Directors**
Jules Schwartz (renal)	Harvey Schuck
Briggs Morrison	Bruce Freundlich
Eric Mortensen	Kerry Edwards
Peter Callegari	Fran Kaiser
Francesca Catella-Lawson	David Abramson
	Ori Ben-Yehuda

*A training session scheduled for April 10 will fully train all 30 Region Medical Directors on the available data for VIOXX^ and the Coxibs. Additional training may also be required for the identified individuals in MRL to ensure complete understanding of the data and the ability to communicate these data.

Preferred External Speakers

RHEUMS	*GASTROS*	*CARDIOLOGISTS (MI)**	*NEPHROLOGISTS (Hypertension/Edema)*
Art Weaver	Loren Laine	Marv Konstam*	Barry Brenner
Marc Hochberg	David Bjorkman	Steve Nissen	Craig Brater
Tom Schnitzer	Pete Peterson	Rob Califf	Gerald Appel
Warren Katz	Byron Cryer	Garrett Fitzgerald	Suzanne Swan
Michael Schiff	David Peura	John Oates	Matthew Weir
Claire Bombardier	Michael Wolfe	Myron Weisfeldt	Mark Perazella
Jim Williams	Jim Scheiman	Greg Fonarow*	Matthew Breyer
	Brian Fennerty	Mel Tonkon*	Ray Harris
	Richard Hunt	Jeff Anderson*	Vito Campese
			Sidney Kobrin

*All cardiologists listed have been engaged by MRL and/or their HSA and have demonstrated a clear understanding of Merck's point of view on cardiovascular and renal issues. Those cardiologists marked with an asterisk represent certified national speakers who consistently communicate Merck's point of view on these issues in presentations to their colleagues.

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 33

MERCK News Release

FOR IMMEDIATE RELEASE

Media Contacts: Jan Weiner 267/305-6462
Greg Reaves 908/423-6022
Investor Contact: Laura Jordan 908/423-5185

Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx®

UPPER GWYNEDD, Pa., May 22, 2001 -- In response to news and analyst reports of data the Company first released a year ago, Merck & Co., Inc. today reconfirmed the favorable cardiovascular safety profile of Vioxx® (rofecoxib), its medicine that selectively inhibits COX-2. Vioxx was approved by the Food and Drug Administration in May 1999 for the management of osteoarthritis and the relief of acute pain in adults based on efficacy and safety studies involving nearly 4,000 patients. More than 33 million prescriptions have been written for Vioxx in the United States since its introduction.

The results of the Vioxx Gastrointestinal Research study were first released in March 2000. Since that time, the data have been widely reported, published in *The New England Journal of Medicine* and discussed extensively by an FDA Advisory Committee.

In VIGOR, Vioxx 50 mg, a dose two-times the highest chronic dose approved for osteoarthritis, significantly reduced the risk of serious GI side effects by half compared to a commonly used dose of naproxen (1,000 mg) in rheumatoid arthritis patients. The Advisory Committee recommended that these results be included in the labeling for Vioxx. Vioxx is not indicated for rheumatoid arthritis.

Although the VIGOR study was a GI outcomes study and was not designed to show differences in cardiovascular effects, significantly fewer heart attacks were observed in patients taking naproxen (0.1 percent) compared to the group taking Vioxx 50 mg (0.5 percent) in this study. There was no difference in cardiovascular mortality

- more -

Vioxx® is the Merck registered trademark for rofecoxib.

between the groups treated with Vioxx or naproxen. Patients taking aspirin did not participate in VIGOR.

In extensive discussions, the Advisory Committee explored this finding, other studies of Vioxx and possible explanations for this result in VIGOR. In the completed osteoarthritis trials and on-going clinical trials with Vioxx 12.5 mg, 25 mg and 50 mg in 30,000 patients, there was no difference in the incidence of cardiovascular events, such as heart attacks, among patients taking Vioxx, other NSAIDs and placebo.

At the Advisory Committee meeting, Merck scientists said the VIGOR finding is consistent with naproxen's ability to block platelet aggregation by inhibiting COX-1 like aspirin, which is used to prevent second cardiac events in patients with a history of heart attack, stroke or other cardiac events. This is the first time this effect of naproxen on cardiovascular events has been observed in a clinical study. Other potential explanations were advanced by the FDA reviewer and were discussed with the Advisory Committee. The Committee recommended that the data on cardiovascular events in VIGOR be included in the labeling for Vioxx.

In addition, the Committee agreed that the prescribing information for both Vioxx and Celebrex® (celecoxib) should reflect the fact that neither of these selective NSAIDs confer cardioprotective benefits and are not a substitute for low-dose aspirin. The Committee also recommended that other studies be conducted to further explore the safety of concomitant use of selective NSAIDs and low-dose aspirin.

In a separate GI outcomes study in osteoarthritis and rheumatoid arthritis patients, celecoxib, another agent that selectively inhibits COX-2, was compared to the NSAIDs diclofenac and ibuprofen. Pharmacia, maker of celecoxib, has indicated that there were no differences among celecoxib, ibuprofen and diclofenac on these cardiovascular events. In Pharmacia's background package submitted to the FDA for the Advisory Committee meeting, the incidence of patients taking celecoxib who experienced a heart attack was cited as 0.5 percent, 0.3 percent among diclofenac patients, and 0.5 percent among patients taking ibuprofen.

Important information about Vioxx

The recommended dose of Vioxx for the treatment of osteoarthritis is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily.

Celebrex® is a registered trademark of Pharmacia Corporation.

Serious stomach problems, such as bleeding, can occur without warning symptoms. Administration of low-dose aspirin with Vioxx may result in an increased rate of GI ulcers or other complications compared to use of Vioxx alone. Physicians and patients should remain alert for signs and symptoms of gastrointestinal bleeding.

Common side effects reported in osteoarthritis clinical trials with Vioxx were upper-respiratory infection, diarrhea, nausea and high blood pressure. People who have had an allergic reaction to Vioxx, aspirin or other NSAIDs should not take Vioxx. Safety and effectiveness in children below the age of 18 have not been studied.

Merck & Co., Inc. is a global, research-driven pharmaceutical company that discovers, develops, manufactures and markets a broad range of human and animal health products, directly and through its joint ventures, and provides pharmaceutical benefit services through Merck-Medco Managed Care.

###

Full prescribing information for Vioxx® is attached and is also available by calling 1-800-753-0352, ext. 726.

If a health care provider requests to speak with a Merck health care professional, the Merck National Service Center should be called at 800-NSCMERCK (business hours of 8:00 am to 7:00 pm ET; For emergency issues, Medical Services after-hours Call Coverage is 24 hours a day/ 7 days a week.)

Remember to always provide a balanced discussion consistent with the health care provider's knowledge of the product and the product prescribing information.
Please continue to provide competitive and promotional feedback to the National Service Center (NSC). The NSC is staffed Monday through Friday, 8:00am to 7:00pm Eastern Time. Please contact the NSC at 1-800-NSC-MERCK or 1-800-672-6372.

For product and service information, call the Merck National Service Center at 1-800-NSC-Merck (1-800-672-6372).

Do not proactively discuss any of the recent press stories. Respond to questions by requesting a PIR and in accordance with the obstacle-handling guide.

This information is provided for your background information *only* and is not to be used in discussions with physicians. The following press release was issued in response to an article in Tuesday's New York Times on the cardiovascular effects of VIOXX.

Background Information:

Tuesday May 22, 1:21 pm Eastern Time

Press Release

SOURCE: Merck & Co., Inc.

Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx(R)

UPPER GWYNEDD, Pa., May 22 /PRNewswire/ -- In response to news and analyst reports of data the Company first released a year ago, Merck & Co., Inc. today reconfirmed the favorable cardiovascular safety profile of Vioxx® (rofecoxib), its medicine that selectively inhibits COX-2. Vioxx was approved by the Food and Drug Administration in May 1999 for the management of osteoarthritis and the relief of acute pain in adults based on efficacy and safety studies involving nearly 4,000 patients. More than 33 million prescriptions have been written for Vioxx in the United States since its introduction.

The results of the Vioxx Gastrointestinal Research study were first released in March 2000. Since that time, the data have been widely reported, published in The New England Journal of Medicine and discussed extensively by an FDA Advisory Committee.

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by Order of the United States District
Court of Southern District of Illinois

In VIGOR, Vioxx 50 mg, a dose two-times the highest chronic dose approved for osteoarthritis, significantly reduced the risk of serious GI side effects by half compared to a commonly used dose of naproxen (1,000 mg) in rheumatoid arthritis patients. The Advisory Committee recommended that these results be included in the labeling for Vioxx. Vioxx is not indicated for rheumatoid arthritis.

Although the VIGOR study was a GI outcomes study and was not designed to show differences in cardiovascular effects, significantly fewer heart attacks were observed in patients taking naproxen (0.1 percent) compared to the group taking Vioxx 50 mg (0.5 percent) in this study. There was no difference in cardiovascular mortality between the groups treated with Vioxx or naproxen. Patients taking aspirin did not participate in VIGOR.

In extensive discussions, the Advisory Committee explored this finding, other studies of Vioxx and possible explanations for this result in VIGOR. In the completed osteoarthritis trials and on-going clinical trials with Vioxx 12.5 mg, 25 mg and 50 mg in 30,000 patients, there was no difference in the incidence of cardiovascular events, such as heart attacks, among patients taking Vioxx, other NSAIDs and placebo.

At the Advisory Committee meeting, Merck scientists said the VIGOR finding is consistent with naproxen's ability to block platelet aggregation by inhibiting COX-1 like aspirin, which is used to prevent second cardiac events in patients with a history of heart attack, stroke or other cardiac events. This is the first time this effect of naproxen on cardiovascular events has been observed in a clinical study. Other potential explanations were advanced by the FDA reviewer and were discussed with the Advisory Committee. The Committee recommended that the data on cardiovascular events in VIGOR be included in the labeling for Vioxx.

In addition, the Committee agreed that the prescribing information for both Vioxx and Celebrex® (celecoxib) should reflect the fact that neither of these selective NSAIDs confer cardioprotective benefits and are not a substitute for low-dose aspirin. The Committee also recommended that other studies be conducted to further explore the safety of concomitant use of selective NSAIDs and low-dose aspirin.

In a separate GI outcomes study in osteoarthritis and rheumatoid arthritis patients, celecoxib, another agent that selectively inhibits COX-2, was compared to the NSAIDs diclofenac and ibuprofen. Pharmacia, maker of celecoxib, has indicated that there were no differences among celecoxib, ibuprofen and diclofenac on these cardiovascular events. In Pharmacia's background package submitted to the FDA for the Advisory Committee meeting, the incidence of patients taking celecoxib who experienced a heart attack was cited as 0.5 percent, 0.3 percent among diclofenac patients, and 0.5 percent among patients taking ibuprofen.

Focus:
Remain focused on your efficacy messages for VIOXX. Remember that the primary attribute for physicians and patients is pain relief.

For product and service information, call the Merck National Service Center at 1-800-NSC MERCK (1-800-672-6372).

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 34

E-SERVED
08/09/04
07:35 PM ET
VioxX (NJ)

To: Demopoulos, Laura A.; Greene, Douglas Dr.; Gertz, Barry J.; Dixon, Wendy L.
From: Nies, Alan S.
Cc Reicin, Alise S.; DiBattiste, Peter; Kasper, Karen A.
Bcc:
Date: 2001-06-12 16:16:59
Subject: RE: Topol manuscript

I made a few comments on the manuscript--p4, 14, 15. Also, I dont know if we are pointing out the placebo controlled and other nsaid controlled data specifically enough in the discussion.
alan

-----Original Message-----
From: Demopoulos, Laura A.
Sent: Monday, June 11, 2001 11:50 PM
To: Greene, Douglas Dr.; Nies, Alan S.; Gertz, Barry J.; Dixon, Wendy L.
Cc: Reicin, Alise S.; DiBattiste, Peter; Kasper, Karen A.
Subject: Topol manuscript

Please find attached the original and revised versions of the manuscript by Eric Topol from the Cleveland Clinic regarding the risk of CV events in patients treated with COX 2 inhibitors. As you may recall, Eric submitted the original manuscript to JAMA (and as of a week ago had not yet received a response), but he gave us the opportunity to submit comments prior to its publication.

Pete DiBattiste and I have worked with Alise to incorporate additional data which balance the perspective of the original paper, but have not challenged Eric's premise that the issue needs further study before the concern of an adverse effect can be ruled out.

If you have comments, please forward them back to me by Wednesday morning, if possible, as we have a teleconference with Eric scheduled for Wednesday afternoon to discuss the revisions.

We recognize that the revised manuscript does not completely neutralize the potential negative impact of the publication, but feel it is substantially improved from the original. We felt that revising it further to more completely present a Merck perspective might alienate the authors, and thereby jeopardize our opportunity to contribute at all.

L.

<< File: COX-2JAMA11 >>
original version

<< File: COX-2JAMA rev 6-12-01 revisions accepted.doc >>

revised version

Attachments:

COX-2JAMA rev 6-12-01 revisions accepted.doc

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 35

No. COX 01-037
Jun 28, 2001

Bulletin for VIOXX®:
Voluntary Recall of VIOXX (Rofecoxib) 50 mg Bulk Bottle (100-Count) Tablets

TO:

All Field Representations with Responsibility for VIOXX	Action Required
All Hospital Representatives	Action Required
A & A Specialty Representatives	Action Required
A & A HSAs	Action Required
Urology Representatives	Action Required
Neurology Representatives	Action Required
HIV Specialty Representatives	Action Required
Managed Care NAEs and Customer Managers (all segments)	Action Required

PURPOSE:

To provide you with important information and direction about the recent voluntary recall of VIOXX 50 mg Bulk Bottle (100 count) tablets due to an error in the package label. **The quality, safety and efficacy of VIOXX tablets are not in question.** This does not effect any of your current samples or stock bottles of 50mg, 25mg or 12.5 mg.

ACTION:

Print copies of the recall notice in the attached PDF file. Do not make any changes to the notice.


RecallVIOXX50mg.pdf

For your pharmacy and wholesale customers: As part of your regular calls, please confirm they received the recall notice from Merck in regards to the VIOXX 50 mg Bulk Bottle (100 count). If they have not received the notice, provide them with a hard copy of the letter through July 31. It is important to let your pharmacist know that all other configurations of VIOXX 50 mg, as well as other tablet strengths, are not effected. There is no need to change your regular routing.

For customer inquiries: Provide a copy of the recall notice and respond to the inquiry as outlined below:

"Merck identified an omission from the package label for certain lots of the 100-count bulk bottles of VIOXX 50-mg tablets ONLY. The label is missing 3 standard statements that indicate that the package is not intended to be given to a consumer. All other label information was complete and correct. The printing omissions limited to the 100-count bottle, 50-mg tablet strength only. The quality, safety, and efficacy of the tablets are not impacted. "

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BACKGROUND INFORMATION:

The following information is for your background information only and is not be used in discussions with healthcare professionals or anyone outside of Merck.

Merck discovered an error in the package label for VIOXX 50-mg bulk bottle (100-count) tablets. The label is missing 3 standard statements for bulk containers:

1. "This is a bulk package not intended for dispensing."
2. "Package not child resistant."
3. "Dispense in a tightly-closed container."

Merck issued a voluntary Class II Recall to the Pharmacy level of VIOXX 50-mg bulk bottle (100 count) tablets to prevent the unlikely occurrence of this product being dispensed to patients in this bulk bottle since it does not have a child resistant cap. The FDA has been notified about our voluntary recall of these packages from the market.

Merck is not anticipating any market supply problems as a result of this recall. Replacement VIOXX 50-mg bulk bottle (100-count) tablets are already being packaged and marketed in the United States with the correct package labels.

Remember: The quality, safety and efficacy of VIOXX tablets are not in question.

For product and service information, call the Merck National Service Center at 1-800-NSC MERCK (1-800-672-6372).

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"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 36

Merck & Co., Inc.
P.O. Box 4
West Point PA
19486-0004

MERCK

August 2001

Dear Healthcare Provider:

You and your patients may have seen recent reports in the media regarding the cardiovascular safety profile of agents that specifically inhibit COX-2. These reports are based on an article published in the August 22–29, 2001, *Journal of the American Medical Association* regarding VIOXX® (rofecoxib) and Pharmacia's Celebrex (celecoxib). The article reviews selected data on VIOXX that have been available to the medical and scientific communities for almost 18 months. The article is not based on any new clinical study.

Merck & Co., Inc., stands behind the overall and cardiovascular safety profile and the favorable gastrointestinal (GI) profile of VIOXX. Merck believes VIOXX is an appropriate and efficacious therapy for relief of the signs and symptoms of osteoarthritis and the management of acute pain in adults.

Patient safety is of paramount importance to Merck. We routinely review data from completed studies and clinical use of our products. Consistent with this approach, we will continue to evaluate such data on agents that specifically inhibit COX-2 to enhance our understanding of these medicines and assess the potential value of future trials.

Selected Safety Information
VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX. VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

Serious GI toxicity can occur with or without warning symptoms with NSAIDs. As with all NSAIDs, VIOXX should be used with caution in patients with fluid retention, hypertension, or heart failure. VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. Concomitant administration of low-dose aspirin with VIOXX may result in an increased risk of GI ulceration or other complications compared with use of VIOXX alone.

Common adverse events in osteoarthritis studies included upper respiratory infection (8.5%), diarrhea (6.5%), nausea (5.2%), and hypertension (3.5%).

Before prescribing VIOXX, please read the accompanying complete Prescribing Information.

Thank you for your continued confidence in VIOXX.

Sincerely,

Louis M. Sherwood

Louis M. Sherwood, MD, FACP
Senior Vice President
US Medical and Scientific Affairs

VIOXX is a registered trademark of Merck & Co., Inc. Celebrex is a registered trademark of G.D. Searle & Co. vioxx.com

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 37

8/22

Kenneth Sperber, MD
Primary Care Center of Quality Hill
174 Armistice Boulevard
Pawtucket, RI 02860
August 28, 2001

RECEIVED
AUG 31 2001
JAMA

Editor
JAMA & Archives Journals
515 N State St
Chicago, IL 60610

To the editor:

I was outraged this week by the letter I received by overnight FedEx delivery from Louis Sherwood, MD, Senior Vice President for US Medical and Scientific Affairs at Merck. He sent the "Dear Healthcare Provider" letter in response to the JAMA article "Risk of Cardiovascular Events Associated With Selective COX-2 Inhibitors" (JAMA 286;8). I have written both to Merck as well as the FDA to complain about the impropriety of the letter in which Merck directly disparages the JAMA review article as "not new" and offers to supplant its findings with Merck's "confidence" in their product. Included in the overnight delivery was a full text copy of the package insert.

What disturbs me is the aggressive effort (how much did it cost to send a 5 page mass mailing by FedEx overnight?) to "spin" the medical literature. If Merck disagrees with the findings of an article published in a peer-reviewed journal they should not hesitate to send a letter to the editor, submit an editorial, and contact the authors, just like everyone else.

We in the medical community must reserve the right to publish our findings even if they do raise questions about the safety of Merck's products. We in the medical community must reserve the right to read peer-reviewed journals and use our hard-earned expertise in interpretation of medical literature to understand such publications appropriately. Those of us who passed our first year medical school courses in the principles of medical research are quite capable of recognizing the difference between a review article and new research. It is simply inappropriate for the pharmaceutical industry to bypass those processes in an effort to "spin" what we read there in a misguided attempt to protect their products from ongoing scrutiny and evaluation. This transparent attempt at "damage control" and "spinning" of the medical literature is out of bounds.

Yours truly,

Kenneth Sperber, MD
Pawtucket, RI

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 38

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

a1951d

TRANSMITTED BY FACSIMILE

Raymond V. Gilmartin
President and CEO
Merck & Co., Inc.
P.O. Box 1000, UG3BC-10
North Wales, PA 19454-1099

SEP 17 2001

RE: NDA 21-042
Vioxx (rofecoxib) tablets
MACMIS ID # 9456

WARNING LETTER

Dear Mr. Gilmartin:

This Warning Letter concerns Merck & Co. Inc.'s (Merck) promotional activities and materials for the marketing of Vioxx (rofecoxib) tablets. Specifically, we refer to promotional audio conferences given on behalf of Merck by Peter Holt, MD, a press release, and oral representations made by Merck sales representatives to promote Vioxx. As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed your promotional activities and materials and has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (the Act) and applicable regulations. See 21 U.S.C. §§ 331(a) and (b), 352(a), (f), and (n), and 355 (a).

You have engaged in a promotional campaign for Vioxx that minimizes the potentially serious cardiovascular findings that were observed in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, and thus, misrepresents the safety profile for Vioxx. Specifically, your promotional campaign discounts the fact that in the VIGOR study, patients on Vioxx were observed to have a four to five fold increase in myocardial infarctions (MIs) compared to patients on the comparator non-steroidal anti-inflammatory drug (NSAID), Naprosyn (naproxen).

Although the exact reason for the increased rate of MIs observed in the Vioxx treatment group is unknown, your promotional campaign selectively presents the following hypothetical explanation for the observed increase in MIs. You assert that Vioxx does not increase the risk of MIs and that the VIGOR finding is consistent with naproxen's ability to block platelet aggregation like aspirin. That is a possible explanation, but you fail to disclose that your explanation is hypothetical, has not been demonstrated by substantial evidence, and that there is another reasonable explanation, that Vioxx may have pro-thrombotic properties.

You have also engaged in promotional activities that minimize the Vioxx / Coumadin (warfarin) drug interaction, omit important risk information, make unsubstantiated superiority claims against other NSAIDs, and promote Vioxx for unapproved uses and an unapproved dosing regimen. In addition, in misrepresenting the Vioxx / warfarin drug interaction you also misrepresent Vioxx's safety profile by minimizing the potentially serious risk of significant bleeding that can result from using Vioxx and warfarin concomitantly.

Your minimizing these potential risks and misrepresenting the safety profile for Vioxx raise significant public health and safety concerns. Your misrepresentation of the safety profile for Vioxx is particularly troublesome because we have previously, in an untitled letter, objected to promotional materials for Vioxx that also misrepresented Vioxx's safety profile.

Background

Vioxx is a NSAID with selective cyclooxygenase 2 (COX-2) inhibitory properties. It was approved on May 20, 1999, for the treatment of primary dysmenorrhea, for the management of acute pain in adults, and for relief of the signs and symptoms of osteoarthritis.

Prior to approval, endoscopy studies were submitted to the original NDA database demonstrating that treatment with Vioxx 25 mg or 50 mg daily was associated with a significantly lower percentage of endoscopically apparent gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. Because the correlation between findings of endoscopic studies and the relative incidence of clinically serious upper gastrointestinal (GI) events was unknown, after approval, Merck sponsored the VIGOR study to obtain information regarding clinically meaningful upper GI events and to develop a large controlled database for overall safety assessment.

The VIGOR study included approximately 4000 patients per treatment arm (Vioxx 50 mg a day or naproxen 1000 mg a day) treated for a median time of 9 months. The primary endpoint of the study was the relative risk of confirmed PUBs (perforations, symptomatic ulcers, and GI bleeds) in patients with rheumatoid arthritis taking Vioxx 50 mg daily (two to four times the approved dosing regimen for Vioxx in osteoarthritis), compared to patients taking naproxen, 1000 mg daily. The study also compared the safety and tolerability of the two treatments in patients with rheumatoid arthritis. The results of the study demonstrated that patients on Vioxx had a significantly lower cumulative incidence of PUB's compared to patients on naproxen (2.08% and 4.49% for Vioxx and naproxen, respectively).

Other important results from the VIGOR study included the unexpected findings that investigator reported serious cardiovascular events occurred in 101 patients (2.5%) in the Vioxx treatment group compared to 46 patients (1.1 %) in the naproxen treatment group, and MIs occurred in 20 patients among 4047 in the Vioxx treatment group (0.5%), compared to four patients among 4029 in the naproxen treatment group (0.1%). These unexpected findings were extensively discussed at the FDA Arthritis Advisory Committee Meeting on February 8, 2001. Although, the reason for these differences is not clear, possible explanations include both an ability of naproxen to function as a cardioprotective agent and a pro-thrombotic property of Vioxx.

Promotional Audio Conferences

We are aware of six promotional audio conferences, presented on behalf of Merck by Peter Holt, MD that are in violation of the Act and its implementing regulations. These audio conferences were held on June 8, 2000, June 13, 2000, June 16, 2000, and three on June 21, 2000, and were moderated by Merck employees.

On December 12, 2000, we sent you a written inquiry about your involvement with and influence on the initiation, preparation, development, and publication of audio conferences given by Dr. Holt. We also asked you to describe the nature of the relationship between you and Dr. Holt. In your response dated January 5, 2001, you stated that, "Dr. Holt entered into a speaker contract with Merck on June 22, 1999." You also stated that, "Merck has determined that we arranged for Dr. Holt to speak at ten audio conferences in 2000. Merck Business Managers provided him with the topic for the audio conferences and, for two of the audio conferences, asked him to address the safety profiles of Vioxx and other NSAIDs."

The promotional audio conferences identified above, arranged by, and presented on behalf of, Merck were false or misleading in that they minimized the MI results of the VIGOR study, minimized the Vioxx / Coumadin drug interaction, omitted important risk information, made unsubstantiated superiority claims, and promoted Vioxx for unapproved uses and an unapproved dosing regimen. Our specific objections follow.

Minimization of MI Results

Statements made during the promotional audio conferences identified above minimize the potentially serious MI risk that may be associated with Vioxx therapy. For example, in your June 21, 2000, audio conference you begin your discussion of the MI rates observed in the VIGOR study by stating, "When you looked at the MI rate the rate was different for the two groups. The MI rate for Vioxx was 0.4 percent and if you looked at the Naprosyn arm it was 0.1 percent, so there was a reduction in MIs in the Naprosyn group." You then present your explanation as to why the Vioxx treatment arm had an increased rate of MIs compared to the naproxen treatment arm. Specifically, you state that,

> Vioxx is a wonderful, effective, selective COX-2 inhibitor that inhibits COX-2 but at the doses used does not inhibit COX-1. So therefore without the COX-1 inhibition you don't inhibit platelets, you don't prolong bleeding time and therefore it cannot be used as a cardiovascular protective drug. Naprosyn on the other hand is a wonderful platelet inhibitor, prolongs bleeding time and inhibits platelets identically to aspirin. Obviously the binding with Naprosyn is reversible and with aspirin is irreversible, but the effect on platelets and bleeding time is identical in terms of its effect and therefore functions as a wonderful drug for cardiovascular prophylaxis. So basically the MI rates are in sync with what we know about Vioxx and what we know about Naprosyn.

In fact, the situation is not at all clear. There are no adequate and well-controlled studies of naproxen that support your assertion that naproxen's transient inhibition of platelet aggregation is pharmocodynamically comparable to aspirin or clinically effective in decreasing the risk of MIs. Therefore, your representation that naproxen prolongs bleeding time and inhibits platelets identically to aspirin is misleading, and minimizes the potential seriousness of this finding. As you know, the

reason for the difference between Vioxx and naproxen has not been determined; it is also possible that Vioxx has pro-thrombotic properties. Also, the MI rate that you report for Vioxx is inaccurate; the MI rate for Vioxx in the VIGOR study was 20 MIs among 4047 patients (0.5%), not 0.4%, as you stated.

Your minimization of the seriousness of the MI rates observed in the Vioxx treatment arm of the VIGOR trial is further reinforced in your audio conferences by your discussion of a retrospective analysis of this trial. For example, in your June 21, 2000, audio conference, you state that,

> ...Merck went and pulled out those patients that again were enrolled in VIGOR and asked the question, who were those patients that really needed secondary cardiovascular prophylaxis from the get go, and that ended up being four percent of the study group in VIGOR based on whether there was a prior MI, stroke, TIA, angina, CABG or PTCA....Now if you look at the remaining part of VIGOR, which is 96 percent of the VIGOR population, and once again looked for the MI rate between Naprosyn and Vioxx, there's no statistically significant difference in the MI rate between Naprosyn and Vioxx. In fact, Naprosyn is 0.2 percent and Vioxx is 0.1 percent.

Your claim that the MI rate for naproxen was 0.2 percent and for Vioxx was 0.1 percent is again inaccurate. Contrary to your claim that there was a higher rate of MIs in the naproxen group compared to the Vioxx group, the MI rate for Vioxx in this subpopulation was 12 MIs among 3877 patients (0.3%) as compared to 4 MIs among 3878 patients (0.1%) for naproxen.

Moreover, you again minimize the Vioxx MI rate observed in the VIGOR study by your comparison of this rate to the rate of MIs observed for Celebrex (celecoxib) in the Celebrex Long-Term Arthritis Safety Study (CLASS). For example, in your June 21, 2000, audio conference you state, "Now if you remember the crude MI rate of Vioxx in VIGOR that number was 0.4 percent which is basically the same or in fact a little bit less then the crude MI rate of Celebrex in CLASS which is 0.5 percent." Your claim that the MI rates of Vioxx compared to Celebrex were basically the same, "or in fact a little bit less" is misleading. You are comparing MI rates from two different trials with different patient populations. For example, patients who had angina or congestive heart failure with symptoms that occurred at rest or minimal activity and patients taking aspirin, including low-dose (325 mg or less, daily or every other day) or other antiplatelet agents (e.g., ticlopidine) were excluded from the VIGOR trial. The CLASS trial in contrast, did not exclude patients of this type. The CLASS trial thus may have included patients at a higher risk for MIs.

Minimization of Vioxx / Coumadin Interaction

Statements made during your promotional audio conferences also minimize the risk of Vioxx therapy in patients who are taking warfarin. For example, in your June 16, 2000, audio conference you stated that, "...if you look at the thromboembolic events it's very clear that these selective COX-2 inhibitors have the benefit of not having platelet aggregation and bleeding time, and therefore, can be used safely in terms of post-op and with Coumadin." Your statement that Vioxx can be used safely with warfarin minimizes the precaution in the PI that states that "...in post-marketing experience, bleeding events have been reported, predominately in the elderly, in association with increases in prothrombin time in patients receiving Vioxx concurrently with warfarin." Your promotion minimizing the risk of using Vioxx and warfarin concurrently is particularly troublesome because Merck was aware of this potentially dangerous drug interaction in 1999, well before these audio conferences occurred. In fact,

Merck began disseminating a revised PI in October 1999, which included new information about this risk.

The seriousness of this interaction is further minimized by your suggestion that COX-2 inhibitors, including Vioxx, can be used safely with warfarin because it "has the benefit of not having platelet aggregation and bleeding time." This claim implies that Vioxx is safer than other NSAIDS used in combination with warfarin. However, Vioxx has not been studied in head-to-head trials prospectively designed to assess this specific endpoint. Your superiority claim is therefore misleading.

We note that earlier in your June 16, 2000, promotional audio conference you state, "It can be used in people with Coumadin, although with Coumadin you've got to check their INR three and four days after you add the Cox inhibitor to the Coumadin because there may be a bump in the INR." This disclosure does not correct the overall misleading message, however, nor does it correct your suggestion that Vioxx is safer than other NSAIDs in patients taking warfarin.

Omission of Important Risk Information

Your promotional audio conferences fail to present serious and significant risks associated with Vioxx therapy. For example, your promotional audio conferences fail to state that Vioxx is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. You also fail to present the gastrointestinal (GI) warning about the possibility of serious GI toxicity such as bleeding, ulceration, or perforation in patients taking Vioxx. Moreover, you fail to present Vioxx's precautions for use in patients who have liver and kidney disease, information about patient populations in which Vioxx's use is not recommended, such as women in late pregnancy, and information about Vioxx's most common adverse events.

Unsubstantiated Superiority Claims

You make several unsubstantiated superiority claims for Vioxx throughout your promotional audio conferences. For example, in your June 16, 2000, audio conference, you claim that, "The importance of [VIGOR and CLASS] is that the data is going to really help change I believe the package inserts for [Vioxx and Celebrex] down the road because it really shows once again that they are safer than non-steroidals." Your suggestion that COX-2 inhibitors, including Vioxx, have an overall safety profile that is superior to other NSAIDs is misleading because such an advantage has not been demonstrated. In fact, in the VIGOR study the incidence of serious adverse events was **higher** in the Vioxx treatment group than in the naproxen treatment group (9.3% and 7.8% for Vioxx and naproxen, respectively). The results of safety analyses that were pre-specified in the protocol for the VIGOR trial, such as CHF-related adverse events and discontinuations due to edema-related adverse events, hepatic-related adverse events, hypertension-related adverse events, and renal-related adverse events were all numerically higher (in some cases statistically significantly higher) in the Vioxx treatment group than in the naproxen treatment group. Furthermore, your claim that the VIGOR and CLASS trials "show once again that they are safer than non-steroidals" is also misleading because it implies that the results of the VIGOR trial (i.e., patients on Vioxx had a significantly lower cumulative incidence of PUBs than patients on naproxen) can be applied to the entire class of NSAIDs.

In your June 16, 2000, audio conference you state, "...if you look at the thromboembolic events it's very clear that these selective COX-2 inhibitors have the benefit of not having platelet aggregation and

bleeding time, and therefore, can be used safely in terms of post-op and with Coumadin." This claim suggests that Vioxx is safer, or has fewer side effects, than other NSAIDs used in the post-operative setting because COX-2 inhibitors do not affect platelet aggregation and bleeding time. Vioxx has not been studied, however, in head-to-head trials prospectively designed to assess its safety compared to other NSAIDS in the post-operative setting. Your superiority claim is therefore misleading.

Further examples of your unsubstantiated superiority claims include your claim that, "In terms of half life Vioxx has a half life of 17 hours and is truly a once a day drug, whereas Celebrex has a half life of 11 hours and is a BID (twice a day) drug," stated in your June 16, 2000, audio conference. This claim is misleading because it suggests that Celebrex must be dosed twice a day for all of its approved indications. In fact, Celebrex is approved for use either twice a day, or once a day, for the treatment of osteoarthritis. Therefore, your claim that Celebrex is a "BID drug" is misleading.

Promotion of Unapproved Uses

Your audio conferences are misleading because they promote Vioxx for unapproved uses. For example, in your June 21, 2000, conference, you claim that in the VIGOR study, "...the Vioxx 50 milligrams a day and the Naprosyn, a gram a day, were absolutely equally effective in terms of treating the patients with rheumatoid arthritis." Your claim is misleading because it suggests that Vioxx is effective for the treatment of rheumatoid arthritis when this has not been demonstrated. The VIGOR study was not designed to assess the efficacy of Vioxx for the treatment of rheumatoid arthritis. Your claim that Vioxx is "absolutely equally effective" to naproxen in treating patients with rheumatoid arthritis is also misleading because this has not been demonstrated by adequate and well-controlled clinical studies, and because the VIGOR study was not capable of assessing their comparative effectiveness.

Your promotional audio conferences are also misleading because they suggest that Vioxx is safe and effective for other unapproved uses such as the prevention of cancer and invasive cancer, and for the treatment of Alzheimer's disease and gout. Examples of claims that promote Vioxx for unapproved uses, include, but are not limited to, your claims in your June 16, 2000 audio conference that, "...COX-2 seems to be able to interfere with...programmed cell death. Therefore, you get this increased cell growth which allows polps to form, cancer and then invasive cancer. And by blocking COX-2 you can actually prevent the development of colon polyps, cancer and invasive cancer." Additional examples include your claims that "So we tried it [Vioxx] after Vioxx was released and really within one or two pills acute attacks of gout were being shut down," and "Specifically, if you looked at potential uses of these drugs, the most exciting right now I guess in two areas, one is Alzheimer's disease...."

Press Release

We have identified a Merck press release entitled, "Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx," dated May 22, 2001, that is also false or misleading for similar reasons stated above. Additionally, your claim in the press release that Vioxx has a "favorable cardiovascular safety profile," is simply incomprehensible, given the rate of MI and serious cardiovascular events compared to naproxen. The implication that Vioxx's cardiovascular profile is superior to other NSAIDs is misleading; in fact, serious cardiovascular events were twice as frequent in the VIOXX treatment group (101 events, 2.5%) as in the naproxen treatment group (46 events, 1.1%) in the VIGOR study.

Oral Representations

Merck sales representatives have engaged in false or misleading promotional activities that also minimize the potentially serious MI results observed in the VIGOR trial. Specifically, Merck sales representatives made false or misleading statements to DDMAC reviewers at two different professional meetings. At your exhibit booth during the 119th Annual Meeting of the Maryland Pharmacists Association (MPhA), in Ocean City, Maryland, June 9 – June 12, 2001, your representative stated that the increased MI rate seen in patients on Vioxx in the VIGOR study is due to the fact that naproxen works just like aspirin (i.e., inhibits clotting and platelet aggregation). In addition, during the Annual Meeting of the American Society of Health-Systems Pharmacists (ASHP), in Los Angeles, California, June 3 – June 6, 2001, your representative stated that Vioxx had a greater MI rate in the VIGOR trial because naproxen is cardioprotective, having platelet effects similar to aspirin. These statements made by your sales representatives are misleading for the reasons stated above.

Conclusions and Requested Actions

The promotional activities and materials described above minimize the potentially serious cardiovascular findings that were observed in the VIGOR study, minimize the Vioxx / Coumadin drug interaction, omit crucial risk information associated with Vioxx therapy, contain unsubstantiated comparative claims, and promote unapproved uses. On December 16, 1999, we also objected to your dissemination of promotional materials for Vioxx that misrepresented Vioxx's safety profile, contained unsubstantiated comparative claims, and lacked fair balance.

Due to the seriousness of these violations, and the fact that your violative promotion of Vioxx has continued despite our prior written notification regarding similar violations, we request that you provide a detailed response to the issues raised in this Warning Letter on or before October 1, 2001. This response should contain an action plan that includes a comprehensive plan to disseminate corrective messages about the issues discussed in this letter to the audiences that received these misleading messages. This corrective action plan should also include:

1. Immediately ceasing all violative promotional activities, and the dissemination of violative promotional materials for Vioxx.

2. Issuing a "Dear Healthcare provider" letter to correct false or misleading impressions and information. This proposed letter should be submitted to us for review prior to its release. After agreement is reached on the content and audience, the letter should be disseminated by direct mail to all healthcare providers who were, or may have been exposed to the violative promotion.

3. A written statement of your intent to comply with "1" and "2" above.

Your written response should be received no later than October 1, 2001. If you have any questions or comments, please contact Lesley Frank, Ph.D., JD, by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #9456 in addition to the NDA number.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of your promotional campaign for Vioxx, and may determine that additional remedial messages will be necessary to fully correct the false or misleading messages resulting from your violative conduct.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug Marketing,
Advertising, and Communications

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 39

MERCK

Merck & Co., Inc.
PO Box 4
West Point, PA 19486-0004

IMPORTANT
CORRECTION
OF DRUG
INFORMATION

OR SAMPLE
STREET ADDRESS
CITY ST ZIP

FIRST CLASS MAIL
U S POSTAGE PAID
MERCK

VIOXX
20112247(1, 2, 3)

November 2001

Merck & Co., Inc
PO Box 4
West Point, PA 19486-0004

IMPORTANT
CORRECTION
OF DRUG
INFORMATION

MERCK

Dear Healthcare Provider:

This letter is being sent to you at the request of the U.S. Food and Drug Administration ("FDA"). The FDA's Division of Drug Marketing, Advertising, and Communications has notified Merck & Co., Inc., ("Merck") that it considered audioconferences that you attended concerning Vioxx (*rofecoxib*) tablets, given on behalf of Merck by a physician speaker, to be false or misleading in violation of the Federal Food, Drug, and Cosmetic Act.

Specifically, the FDA has objected to claims made by the speaker that FDA asserts were misleading about the significant cardiovascular findings in the Vioxx Gastrointestinal Outcomes Research ("VIGOR") study. The speaker presented as fact only one of several possible explanations for why in VIGOR 0.5% of patients on Vioxx had a myocardial infarction compared to 0.1% of patients on the comparator drug, naproxen. Additionally, the FDA has objected to other statements made by the speaker.

Therefore, the FDA has requested that we correct these promotional messages.

- **Alternative interpretations have been proposed for the difference in the rates of myocardial infarctions (MI) in the Vioxx treatment group in comparison with the naproxen treatment group. Possible explanations include that Vioxx increased the MI rate or naproxen decreased the MI rate.** The underlying reason for the difference has not been established in prospectively designed clinical studies.
- **Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing Vioxx therapy in patients receiving warfarin or similar agents,** since these patients are at an increased risk of bleeding complications. In post-marketing experience, **bleeding events have been reported predominantly in the elderly,** in association with increases in prothrombin time in patients receiving Vioxx concurrently with warfarin.
- **Serious gastrointestinal toxicity** such as bleeding, ulceration, or perforation of the stomach, small intestine, or large intestine, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, including Vioxx.

- **Vioxx (rofecoxib) is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.** Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients. Vioxx is also contraindicated in patients with known hypersensitivity to rofecoxib or any other component of Vioxx.
- **Vioxx has not been proven to be safer or have fewer side effects than other NSAIDs on measures of overall safety.**
- Vioxx is indicated ONLY for relief of the signs and symptoms of osteoarthritis, management of acute pain in adults, and treatment of primary dysmenorrhea.

If you have any questions about the use of Vioxx, please refer to the enclosed full prescribing information.

Sincerely,

Louis M. Sherwood

Louis M. Sherwood, M.D.
Senior Vice President,
U.S. Medical & Scientific Affairs

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Minimum 10% Recycled Paper

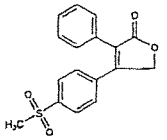
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

VIOXX®

(rofecoxib tablets and oral suspension)

DESCRIPTION

VIOXX® (rofecoxib) is described chemically as 4-[4-(methylsulfonyl)phenyl]-2-phenyl-2(5*H*)-furanone. It has the following chemical structure:



Rofecoxib is a white to off-white to light yellow powder. It is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol, and insoluble in water. The empirical formula for rofecoxib is $C_{17}H_{14}O_4S$, and the molecular weight is 314.36.

Each tablet of VIOXX for oral administration contains either 12.5 mg, 25 mg, or 50 mg of rofecoxib and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide. The 50 mg tablets also contain red ferric oxide.

Each 5 mL of the oral suspension contains either 12.5 or 25 mg of rofecoxib and the following inactive ingredients: citric acid (monohydrate), sodium citrate (dihydrate), sorbitol solution, strawberry flavor, xanthan gum, and purified water. Added as preservatives are sodium methylparaben 0.13% and sodium propylparaben 0.02%.

CLINICAL PHARMACOLOGY

Mechanism of Action

VIOXX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Pharmacokinetics

Absorption

The mean oral bioavailability of VIOXX at therapeutically recommended doses of 12.5, 25, and 50 mg is approximately 93%. The area under the curve (AUC) and peak plasma level (C_{max}) following a single 25-mg dose were 2286 (±843) ng·hr/mL and 297 (±111) ng/mL, respectively. Both C_{max} and AUC are roughly dose proportional across the clinical dose range. At doses greater than 50 mg, there is a less than proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. The plasma concentration-time profile exhibited multiple peaks. The median time to maximal concentration (T_{max}), as assessed in nine pharmacokinetic studies, is 2 to 3 hours. Individual T_{max} values in these studies ranged out to even 2 to 9 hours. This may not reflect rate of absorption as T_{max} may occur as a secondary peak in some individuals. With multiple dosing, steady-state conditions are reached by Day 4. The AUC_{0-24h} and C_{max} at steady state after multiple doses of 25 mg rofecoxib were 4018 (±1410) ng·hr/mL and 321 (±104) ng/mL, respectively. The accumulation factor based on geometric means was 1.67.

VIOXX Tablets 12.5 mg and 25 mg are bioequivalent to VIOXX Oral Suspension 12.5 mg/5 mL and 25 mg/5 mL, respectively.

Food and Antacid Effects

Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of rofecoxib when VIOXX Tablets were taken with a high fat meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1 to 2 hours. The food effect on the suspension formulation has not been studied. VIOXX tablets can be administered without regard to timing of meals.

There was a 23% and 8% decrease in AUC when VIOXX was administered with calcium carbonate antacid and magnesium/aluminum antacid to elderly subjects, respectively. There was an approximate 20% decrease in C_{max} of rofecoxib with either antacid.

Distribution

Rofecoxib is approximately 87% bound to human plasma protein over the range of concentrations of 0.05 to 25 mcg/mL.

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The apparent volume of distribution at steady state (V_{ss}) is approximately 91 L following a 12.5-mg dose and 86 L following a 25-mg dose.

Rofecoxib has been shown to cross the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Metabolism of rofecoxib is primarily mediated through reduction by cytosolic enzymes. The principal metabolic products are the *cis*-dihydro and *trans*-dihydro derivatives of rofecoxib, which account for nearly 58% of recovered radioactivity in the urine. An additional 8.8% of the dose was recovered as the glucuronide of the hydroxy derivative, a product of oxidative metabolism. The biotransformation of rofecoxib and the metabolite is reversible in humans to a limited extent (<5%). These metabolites are inactive as COX-1 or COX-2 inhibitors.

Cytochrome P450 plays a minor role in metabolism of rofecoxib. Inhibition of CYP 3A activity by administration of ketoconazole 400 mg daily does not affect rofecoxib disposition. However, induction of general hepatic metabolic activity by administration of the non-specific inducer rifampin 600 mg daily produces a 50% decrease in rofecoxib plasma concentrations. (Also see *Drug Interactions*.)

Excretion

Rofecoxib is eliminated predominantly by hepatic metabolism with little (<1%) unchanged drug recovered in the urine. Following a single radiolabeled dose of 125 mg, approximately 72% of the dose was excreted into the urine as metabolites and 14% in the feces as unchanged drug.

The plasma clearance after 12.5- and 25-mg doses was approximately 141 and 120 mL/min, respectively. Higher plasma clearance was observed at doses below the therapeutic range, suggesting the presence of a saturable route of metabolism (i.e., non-linear elimination). The effective half-life (based on steady-state levels) was approximately 17 hours.

Special Populations

Gender

The pharmacokinetics of rofecoxib are comparable in men and women.

Geriatric

After a single dose of 25 mg VIOXX in elderly subjects (over 65 years old) a 34% increase in AUC was observed as compared to the young subjects. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

Pediatric

VIOXX has not been investigated in patients below 18 years of age.

Race

Meta-analysis of pharmacokinetic studies has suggested a slightly (10-15%) higher AUC of rofecoxib in Blacks and Hispanics as compared to Caucasians. No dosage adjustment is necessary on the basis of race.

Hepatic Insufficiency

A pharmacokinetic study in mild (Child-Pugh score ≥5) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. Limited data in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency suggest a trend towards higher AUC (about 89%) of rofecoxib in these patients, but more data are needed to evaluate pharmacokinetics in these patients. Patients with severe hepatic insufficiency have not been studied.

Renal Insufficiency

In a study (N=6) of patients with end stage renal disease undergoing dialysis, peak rofecoxib plasma levels and AUC declined 16% and 3%, respectively, when dialysis occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the elimination profile of rofecoxib was unchanged. While renal insufficiency does not influence the pharmacokinetics of rofecoxib, use of VIOXX in advanced renal disease is not recommended at present because no safety information is available regarding the use of VIOXX in these patients.

Drug Interactions (Also see PRECAUTIONS, *Drug Interactions*.)

General

In human studies the potential for rofecoxib to inhibit or induce CYP 3A4 activity was investigated in studies using the intravenous erythromycin breath test and the oral midazolam test. No significant difference in erythromycin demethylation was observed with rofecoxib (75 mg daily) compared to placebo, indicating no induction of hepatic CYP 3A4. A 20% reduction of the AUC of midazolam was observed with rofecoxib (25 mg daily). This reduction is most likely due to increased first pass metabolism through induction of intestinal CYP 3A4 by rofecoxib. *In vitro* studies in rat hepatocytes also suggest that rofecoxib might be a mild inducer for CYP 3A4.

Drug interaction studies with rofecoxib have identified potentially significant interactions with rifampin, methotrexate and warfarin. Patients receiving these agents with VIOXX should be appropriately monitored. Drug interaction studies do not support the potential for clinically important interactions between antacids or cimetidine with rofecoxib. Similar to experience with other nonsteroidal anti-inflammatory drugs (NSAIDs), studies with rofecoxib suggest the potential for interaction with ACE inhibitors. The effects of rofecoxib on the pharmacokinetics and/or pharmacodynamics of ketoconazole, prednisone/prednisolone, oral contraceptives, and digoxin have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Osteoarthritis (OA)

VIOXX has demonstrated significant reduction in joint pain compared to placebo. VIOXX was evaluated for the treatment of the signs and symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of 6 to 86 weeks duration that enrolled approximately 3900 patients. In patients with OA, treatment with VIOXX 12.5 mg and 25 mg once daily resulted in improvement in patient and physician global assessments and in the WOMAC (Western Ontario and McMaster Universities) osteoarthritis questionnaire, including pain, stiffness, and functional measures of OA. In six studies of pain accompanying OA flare, VIOXX provided a significant reduction in pain at the first determination (after one week in one study, after two weeks in the remaining five studies) this continued for the duration of the studies. In all OA clinical studies, once daily treatment in the morning with VIOXX 12.5 and 25 mg was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg, the effectiveness of VIOXX was shown to be comparable to ibuprofen 800 mg TID and diclofenac 50 mg TID for treatment of the signs and symptoms of OA. The ibuprofen studies were 6-week studies; the diclofenac studies were 12-month studies in which patients could receive additional analysis medication during the last 6 months.

Analgesia, including Dysmenorrhea

In acute analgesic models of post-operative dental pain, post-orthopedic surgical pain, and primary dysmenorrhea, VIOXX relieved pain that was rated by patients as moderate to severe. The analgesic effect (including onset of action) of a single 50-mg dose of VIOXX was generally similar to 550 mg of naproxen sodium or 400 mg of ibuprofen. In single-dose post-operative dental pain studies, the onset of analgesia with a single 50-mg dose of VIOXX occurred within 45 minutes. In a multiple-dose study of post-orthopedic surgical pain in which patients received VIOXX or placebo for up to 5 days, 50 mg of VIOXX once daily was effective in reducing pain. In this study, patients on VIOXX consumed a significantly smaller amount of additional analgesic medication than patients treated with placebo (1.5 versus 2.5 doses per day of additional analgesic medication for VIOXX and placebo, respectively).

Special Studies

Upper Endoscopy in Patients with Osteoarthritis

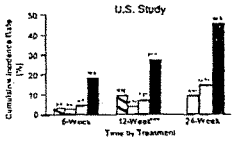
Two identical (U.S. and Multinational) endoscopy studies in a total of 1516 patients were conducted to compare the percentage of patients who developed endoscopically detectable gastroduodenal ulcers with VIOXX 25 mg daily or 50 mg daily, ibuprofen 2400 mg daily, or placebo. Entry criteria for these studies permitted enrollment of patients with active *Helicobacter pylori* infection, baseline gastroduodenal erosions, prior history of an upper gastrointestinal perforation, ulcer, or bleed (PUB), and/or age ≥65 years. However, patients receiving aspirin (including low-dose aspirin for cardiovascular prophylaxis) were not enrolled in these studies. Patients who were 50 years of age and older with osteoarthritis and who had no ulcers at baseline were evaluated by endoscopy after weeks 6, 12, and 24 of treatment. The placebo-treatment group was discontinued at week 12 by design.

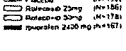
Treatment with VIOXX 25 mg daily or 50 mg daily was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. However, the studies cannot rule out at least some increase in the rate of endoscopic gastroduodenal ulcers when comparing VIOXX to placebo. See Figures 1 and 2 and the accompanying tables for the results of these studies.

Figure 1

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3mm [†] **(Intention-to-Treat)**





† p < 0.001 versus ibuprofen 2400 mg

** Results of analyses using a "3mm gastroduodenal ulcer endpoint" were consistent

*** The primary endpoint was the cumulative incidence of gastroduodenal ulcers at 12 weeks

VIOXX® (rofecoxib tablets and oral suspension)

Circular Number 9183809

VIOXX® (rofecoxib tablets and oral suspension)

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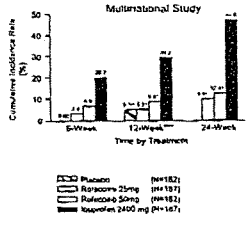
VIOXX® (rofecoxib tablets and oral suspension)

TABLE 1
Endoscopic Gastroduodenal Ulcers at 12 weeks
U.S. Study

Treatment Group	Number of Patients with Ulcer/Total Number of Patients	Cumulative Incidence Rate*	Ratio of Rates vs Placebo	95% CI for Ratio of Rates
Placebo	15/358	9.9%		
VIOXX 25 mg	7/186	4.1%	0.41	(0.16, 1.09)
VIOXX 50 mg	12/178	7.3%	0.74	(0.33, 1.64)
Ibuprofen	42/182	27.1%	2.71	(1.67, 4.39)

*By life table analysis

Figure 2
COMPARISON TO IBUPROFEN
Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3mm** (Intention-to-Treat)



* p < 0.001 versus ibuprofen 2400 mg
** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were similar.
*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

TABLE 2
Endoscopic Gastroduodenal Ulcers at 12 weeks
Multinational Study

Treatment Group	Number of Patients with Ulcer/Total Number of Patients	Cumulative Incidence Rate*	Ratio of Rates vs Placebo	95% CI for Ratio of Rates
Placebo	5/182	3.1%	-	-
VIOXX 25 mg	9/187	5.2%	1.69	(0.56, 5.08)
VIOXX 50 mg	15/182	8.8%	2.73	(0.98, 7.67)
Ibuprofen	49/167	29.5%	9.72	(3.76, 25.15)

*By life table analysis

The correlation between findings of endoscopic studies and the relative incidences of clinically serious upper GI events that may be observed with different products has not been fully established. Serious clinically significant upper GI bleeding has been observed in patients receiving VIOXX in controlled trials, albeit infrequently (see WARNINGS, *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation*). Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIOXX versus comparator NSAID products have not been performed.

Assessment of Fecal Occult Blood Loss in Healthy Subjects

Occult fecal blood loss associated with VIOXX 25 mg daily, VIOXX 50 mg daily, ibuprofen 2400 mg per day, and placebo was evaluated in a study utilizing ^{51}Cr-tagged red blood cells in 67 healthy males. After 4 weeks of treatment with VIOXX 25 mg daily or VIOXX 50 mg daily, the increase in the amount of fecal blood loss was not statistically significant compared with placebo-treated subjects. In contrast, ibuprofen 2400 mg per day produced a statistically significant increase in fecal blood loss as compared with placebo-treated subjects and VIOXX-treated subjects. The clinical relevance of this finding is unknown.

Platelets

Multiple doses of VIOXX 12.5, 25, and up to 375 mg administered daily up to 12 days had no effect on bleeding time relative to placebo. Similarly, bleeding time was not altered in a single dose study with 500 or 1000 mg of VIOXX. There was no inhibition of ex vivo arachidonic acid- or collagen-induced platelet aggregation with 12.5, 25, and 50 mg of VIOXX.

INDICATIONS AND USAGE

VIOXX is indicated:

For relief of the signs and symptoms of osteoarthritis.

For the management of acute pain in adults (see CLINICAL STUDIES).

For the treatment of primary dysmenorrhea.

CONTRAINDICATIONS

VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX.

VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, *Anaphylactoid Reactions* and PRECAUTIONS, *Preexisting Asthma*).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

It is unclear, at the present time, how the above rates apply to VIOXX (see CLINICAL STUDIES, *Special Studies, Upper Endoscopy in Patients with Osteoarthritis*). Among 3357 patients who received VIOXX in controlled clinical trials of 6-weeks to one-year duration (most were enrolled in six-month or longer studies) at a daily dose of 12.5 mg to 50 mg, a total of 4 patients experienced a serious upper GI event, using protocol-derived criteria. Two patients experienced an upper GI bleed within three months (at day 62 and 82, respectively) (0.06%). One additional patient experienced an obstruction within six months (Day 130) and the remaining patient developed an upper GI bleed within 12 months (Day 322) (0.12%). Approximately 23% of these 3357 patients were in studies that required them to be free of ulcers at study entry. It is unclear if this study population is representative of the general population. Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIOXX vs comparator NSAID products have not been performed.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to VIOXX. In post-marketing experience, rare cases of anaphylactic anaphylactoid reactions and angioedema have been reported in patients receiving VIOXX. VIOXX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, *Preexisting Asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

No safety information is available regarding the use of VIOXX in patients with advanced kidney disease. Therefore, treatment with VIOXX is not recommended in these patients. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, *Renal Effects*).

Pregnancy

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

VIOXX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may diminish the utility of these

diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure some with fatal outcome have been reported with NSAIDs, including VIOXX. In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.8% of patients taking rofecoxib (12.5 or 25 mg QD) and 0.1% of patients taking placebo had notable elevations of ALT or AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with VIOXX. Use of VIOXX is not recommended in patients with moderate or severe hepatic insufficiency (see *Pharmacokinetics, Special Populations*). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), VIOXX should be discontinued.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg have shown renal effects (e.g., hypertension, edema) similar to those observed with comparator NSAIDs; these occur with an increased frequency with chronic use of VIOXX at doses above the 12.5 to 25 mg range. (See ADVERSE REACTIONS.)

Caution should be used when initiating treatment with VIOXX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIOXX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS, *Advanced Renal Disease*).

Hematological Effects

Anemia is sometimes seen in patients receiving VIOXX. In placebo-controlled trials, there were no significant differences observed between VIOXX and placebo in clinical reports of anemia. Patients on long-term treatment with VIOXX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. VIOXX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages (see CLINICAL STUDIES, *Special Studies, Platelets*).

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking VIOXX (see ADVERSE REACTIONS). VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, VIOXX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients

VIOXX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation*).

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

Drug Interactions

ACE inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. In patients with mild to moderate hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mm Hg compared to ACE inhibitor alone. This interaction should be given consideration in patients taking VIOXX concomitantly with ACE inhibitors.

Aspirin: Concomitant administration of low-dose aspirin with VIOXX may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX alone. At steady state, VIOXX 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by ex vivo platelet aggregation and serum TXB_2 generation in clotting blood. VIOXX is not a substitute for aspirin for cardiovascular prophylaxis.

Cimetidine: Co-administration with high doses of cimetidine (800 mg twice daily) increased the $C_{ss,max}$ of rofecoxib by 21%, the $AUC_{ss,12hour}$ by 23% and the $t_{1/2}$ by 19%. These small changes are not clinically significant and no dose adjustment is necessary.

Digoxin: Rofecoxib 75 mg once daily for 11 days does not alter the plasma concentration profile or renal elimination of digoxin after a single 0.5 mg oral dose.

Furosemide: Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Ketoconazole: Ketoconazole 400 mg daily did not have any clinically important effect on the pharmacokinetics of rofecoxib.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. In post-marketing experience there have been reports of increases in plasma lithium levels. Thus, when VIOXX and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: VIOXX 75 mg administered once daily for 10 days increased plasma concentrations by 23%, as measured by AUC_{0-24hr}, in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. An equivalent magnitude of reduction in methotrexate renal clearance was observed. At 24 hours postdose, a similar proportion of patients treated with methotrexate alone (94/31) and subsequently treated with methotrexate co-administered with 75 mg of rofecoxib (88/5) had methotrexate plasma concentrations below the measurable limit (5 ng/mL). The effects of the recommended doses for osteoarthritis (12.5 and 25 mg) of VIOXX on plasma methotrexate levels are unknown. Standard monitoring of methotrexate-related toxicity should be continued if VIOXX and methotrexate are administered concomitantly.

Oral Contraceptives: Rofecoxib did not have any clinically important effect on the pharmacokinetics of ethinyl estradiol and norethindrone.

Prednisone/prednisolone: Rofecoxib did not have any clinically important effect on the pharmacokinetics of prednisolone or prednisone.

Rifampin: Co-administration of VIOXX with rifampin 600 mg daily, a potent inducer of hepatic metabolism, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, a starting daily dose of 25 mg of VIOXX should be considered for the treatment of osteoarthritis when VIOXX is co-administered with potent inducers of hepatic metabolism.

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing VIOXX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. In single and multiple dose studies in healthy subjects receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rofecoxib was not carcinogenic in mice given oral doses up to 30 mg/kg (males) and 80 mg/kg (females) (approximately 5- and 2-fold the human exposure at 25 and 50 mg daily based on AUC_{0-24}) and in male and female rats given oral doses up to 8 mg/kg (approximately 6- and 2-fold the human exposure at 25 and 50 mg daily based on AUC_{0-24}) for two years.

Rofecoxib was not mutagenic in an Ames test or in a V-79 mammalian cell mutagenesis assay, nor clastogenic in a chromosome aberration assay in Chinese hamster ovary (CHO) cells, in an in vitro and an in vivo alkaline elution assay, or in an in vivo chromosomal aberration test in mouse bone marrow.

Rofecoxib did not impair male fertility in rats at oral doses up to 100 mg/kg (approximately 20- and 7-fold human

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exposure at 25 and 50 mg daily based on the AUC_{0-24}) and rofecoxib had no effect on fertility in female rats at doses up to 30 mg/kg (approximately 19- and 7-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}).

Pregnancy

Teratogenic effects: Pregnancy Category C.

Rofecoxib was not teratogenic in rats at doses up to 50 mg/kg/day (approximately 28- and 10-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). There was a slight, non-statistically significant increase in the overall incidence of vertebral malformations only in the rabbit at doses of 50 mg/kg/day (approximately 1- or <1-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). There are no studies in pregnant women. VIOXX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects

Rofecoxib produced peri-implantation and post-implantation losses and reduced embryo/fetal survival in rats and rabbits at oral doses ≥10 and ≥75 mg/kg/day, respectively (approximately 9- and 3-fold [rats] and 2- and <1-fold [rabbits] human exposure based on the AUC_{0-24} at 25 and 50 mg daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function. There was an increase in the incidence of postnatal pup mortality in rats at ≥5 mg/kg/day (approximately 5- and 2-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). In studies in pregnant rats administered single doses of rofecoxib, there was a treatment-related decrease in the diameter of the ductus arteriosus at all doses used (3-300 mg/kg; 3 mg/kg is approximately 2- and <1-fold human exposure at 25 or 50 mg daily based on AUC_{0-24}). As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX during the third trimester of pregnancy should be avoided.

Labor and delivery

Rofecoxib produced no evidence of significantly delayed labor or parturition in females at doses 15 mg/kg in rats (approximately 10- and 3-fold human exposure as measured by the AUC_{0-24} at 25 and 50 mg). The effects of VIOXX on labor and delivery in pregnant women are unknown.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to VIOXX while pregnant. Healthcare providers are encouraged to report any prenatal exposure to VIOXX by calling the Pregnancy Registry at (800) 986-8999.

Nursing mothers

Rofecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. There was an increase in pup mortality and a decrease in pup body weight following exposure of pups to milk from dams administered VIOXX during lactation. The dose tested represents an approximate 18- and 6-fold human exposure at 25 and 50 mg based on AUC_{0-24}. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VIOXX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Of the patients who received VIOXX in osteoarthritis clinical trials, 1455 were 65 years of age or older (this included 460 who were 75 years or older). No substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

In one of these studies (a six-week, double-blind, randomized clinical trial), VIOXX 12.5 or 25 mg once daily was administered to 174 osteoarthritis patients ≥80 years of age. The safety profile in this elderly population was similar to that of younger patients treated with VIOXX.

ADVERSE REACTIONS

Osteoarthritis

Approximately 3600 patients with osteoarthritis were treated with VIOXX; approximately 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for one year or longer. The following table of adverse experiences lists all adverse events, regardless of causality, occurring in at least 2% of patients receiving VIOXX in nine controlled studies of 6-week to 6-month duration conducted in patients with OA at the therapeutically recommended doses (12.5 and 25 mg), which included a placebo and/or positive control group.

Clinical Adverse Experiences occurring in ≥ 2.0% of Patients Treated with VIOXX

	Placebo	VIOXX 12.5 or 25 mg daily	Ibuprofen 2400 mg daily	Diclofenac 150 mg daily
	(N = 783)	(N = 2829)	(N = 847)	(N = 498)
Body As A Whole/Site Unspecified				
Abdominal Pain	4.1	3.4	4.6	5.8
Asthenia/Fatigue	1.0	2.2	2.0	2.6
Dizziness	2.2	3.0	2.7	3.4
Influenza-Like Disease	3.1	2.9	1.5	3.2
Lower Extremity Edema	1.1	3.7	3.8	3.4
Upper Respiratory Infection	7.8	8.5	5.8	8.2
Cardiovascular System				
Hypertension	1.3	3.5	3.0	1.6
Digestive System				
Diarrhea	6.8	6.5	7.1	10.6
Dyspepsia	2.7	3.5	4.7	4.0
Epigastric Discomfort	2.8	3.8	9.2	5.4
Heartburn	3.6	4.2	5.2	4.6
Nausea	2.9	5.2	7.1	7.4
Eyes, Ears, Nose, And Throat				
Sinusitis	2.0	2.7	1.8	2.4
Musculoskeletal System				
Back Pain	1.9	2.5	1.4	2.8
Nervous System				
Headache	7.5	4.7	6.1	8.0
Respiratory System				
Bronchitis	0.8	2.0	1.4	3.2
Urogenital System				
Urinary Tract Infection	2.7	2.8	2.5	3.6

The general safety profile of VIOXX 50 mg QD in OA clinical trials of up to 6 months (476 patients) was similar to that of VIOXX at the recommended OA doses of 12.5 and 25 mg QD, except for a higher incidence of gastrointestinal symptoms (abdominal pain, epigastric pain, heartburn, nausea and vomiting), lower extremity edema (6.3%) and hypertension (8.2%).

In the OA studies, the following spontaneous adverse events occurred in >0.1% to 1.9% of patients treated with VIOXX regardless of causality:

Body as a Whole: abdominal distension, abdominal tenderness, abscess, chest pain, chills, contusion, cyst, diaphragmatic hernia, fever, fluid retention, flushing, fungal infection, infection, laceration, pain, pelvic pain, peripheral edema, postoperative pain, syncope, trauma, upper extremity edema, viral syndrome.

Cardiovascular System: angina pectoris, atrial fibrillation, bradycardia, hematoma, irregular heart beat, palpitation, premature ventricular contraction, tachycardia, venous insufficiency.

Digestive System: acid reflux, aphthous stomatitis, constipation, dental caries, dental pain, digestive gas symptoms, dry mouth, duodenal disorder, dysgeusia, esophagitis, flatulence, gastric disorder, gastritis, gastroenteritis, hematochezia, hemorrhoids, infectious gastroenteritis, oral infection, oral lesion, oral ulcer, vomiting.

Eyes, Ears, Nose, and Throat: allergic rhinitis, blurred vision, cerumen impaction, conjunctivitis, dry throat, epistaxis, laryngitis, nasal congestion, nasal secretion, ophthalmic injection, otic pain, otitis, otitis media, pharyngitis, tinnitus, tonsillitis.

Immune System: allergy, hypersensitivity, insect bite reaction.

Metabolism and Nutrition: appetite change, hypercholesterolemia, weight gain.

Musculoskeletal System: ankle sprain, arm pain, arthralgia, back strain, bursitis, cartilage trauma, joint swelling, muscular cramp, muscular disorder, muscular weakness, musculoskeletal pain, musculoskeletal stiffness, myalgia, osteoarthritis, tendinitis, traumatic arthropathy, wrist fracture.

Nervous System: hypesthesia, insomnia, median nerve neuropathy, migraine, muscular spasm, paresthesia, sciatica, somnolence, vertigo.

Psychiatric: anxiety, depression, mental acuity decreased.

Respiratory System: asthma, cough, dyspnea, pneumonia, pulmonary congestion, respiratory infection.

Skin and Skin Appendages: abrasion, alopecia, atopic dermatitis, basal cell carcinoma, blister, cellulitis, contact dermatitis, herpes simplex, herpes zoster, nail unit disorder, perspiration, pruritus, rash, skin erythema, urticaria, xerosis.

Urogenital System: breast mass, cystitis, dysuria, menopausal symptoms, menstrual disorder, nocturia, urinary retention, vaginitis.

The following serious adverse events have been reported rarely (estimated <0.1%) in patients taking VIOXX, regardless of causality. Cases reported only in the post-marketing experience are indicated in italics.

Cardiovascular: cerebrovascular accident, congestive heart failure, deep venous thrombosis, myocardial infarction, pulmonary embolism, transient ischemic attack, unstable angina.

Gastrointestinal: cholecystitis, colitis, colonic malignant neoplasm, *duodenal perforation*, duodenal ulcer, *esophageal ulcer*, gastric perforation, *gastric ulcer*, gastrointestinal bleeding, *hepatic failure*, *hepatitis*, intestinal obstruction, *jaundice*, *pancreatitis*.

Hemic and lymphatic: agranulocytosis, leukopenia, lymphoma, *thrombocytopenia*.

Immune System: anaphylactic/anaphylactoid reaction, angioedema, bronchospasm, hypersensitivity vasculitis.

Nervous System: aseptic meningitis.

Psychiatric: confusion, hallucinations.

Skin and Skin Appendages: severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Urogenital System: acute renal failure, breast malignant neoplasm, *hyperkalemia*, *interstitial nephritis*, prostatic malignant neoplasm, urolithiasis, *worsening chronic renal failure.*

In 1-year controlled clinical trials and in extension studies for up to 86 weeks (approximately 800 patients treated with VIOXX for one year or longer), the adverse experience profile was qualitatively similar to that observed in studies of shorter duration.

Analgesia, including primary dysmenorrhea

Approximately one thousand patients were treated with VIOXX in analgesia studies. All patients in post-dental surgery pain studies received only a single dose of study medication. Patients in primary dysmenorrhea studies may have taken up to 3 daily doses of VIOXX, and those in the post-orthopedic surgery pain study were prescribed 5 daily doses of VIOXX.

The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies. The following additional adverse experience, which occurred at an incidence of at least 2% of patients treated with VIOXX, was observed in the post-dental pain surgery studies: post-dental extraction alveolitis (dry socket).

In 110 patients treated with VIOXX (average age approximately 65 years) in the post-orthopedic surgery pain study, the most commonly reported adverse experiences were constipation, fever, and nausea.

OVERDOSAGE

No overdoses of VIOXX were reported during clinical trials. Administration of single doses of VIOXX 1000 mg to 6 healthy volunteers and multiple doses of 250 mg/day for 14 days to 75 healthy volunteers did not result in serious toxicity.

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

Rofecoxib is not removed by hemodialysis; it is not known whether rofecoxib is removed by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

VIOXX is administered orally. The lowest dose of VIOXX should be sought for each patient.

Osteoarthritis

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended initial dose of VIOXX is 50 mg once daily. Subsequent doses should be 50 mg once daily as needed. Use of VIOXX for more than 5 days in management of pain has not been studied (see CLINICAL STUDIES, *Analgesia, including Dysmenorrhea*).

VIOXX Tablets may be taken with or without food.

Oral Suspension

VIOXX Oral Suspension 12.5 mg/5 mL or 25 mg/5 mL may be substituted for VIOXX Tablets 12.5 or 25 mg, respectively, in any of the above indications. Shake before using.

HOW SUPPLIED

No. 3810 — Tablets VIOXX, 12.5 mg, are cream/off-white, round, shallow cup tablets engraved MRK 74 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0074-31 unit of use bottles of 30
NDC 0006-0074-28 unit dose packages of 100
NDC 0006-0074-68 bottles of 100
NDC 0006-0074-82 bottles of 1000
NDC 0006-0074-80 bottles of 8000.

No. 3834 — Tablets VIOXX, 25 mg, are yellow, round tablets engraved MRK 110 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0110-31 unit of use bottles of 30
NDC 0006-0110-28 unit dose packages of 100
NDC 0006-0110-68 bottles of 100
NDC 0006-0110-82 bottles of 1000
NDC 0006-0110-80 bottles of 8000.

No. 3835 — Tablets VIOXX, 50 mg, are orange, round tablets engraved MRK 114 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0114-31 unit of use bottles of 30
NDC 0006-0114-28 unit dose packages of 100
NDC 0006-0114-68 bottles of 100
NDC 0006-0114-74 bottles of 500
NDC 0006-0114-81 bottles of 4000.

No. 3784 — Oral Suspension VIOXX, 12.5 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

NDC 0006-3784-64 unit of use bottles containing 150 mL (12.5 mg/5 mL).

No. 3785 — Oral Suspension VIOXX, 25 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

NDC 0006-3785-64 unit of use bottles containing 150 mL (25 mg/5 mL).

Storage

VIOXX Tablets:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

VIOXX Oral Suspension:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

Rx only

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued July 2001
Printed in USA

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx: Putting Patient Safety First?"

November 18, 2004

Exhibit 40

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12/11/2001 - Updated 11:36 AM ET

Spotlight falls on drug ads

By Rita Rubin, USA TODAY

Turn on your television, and you could just as well see a commercial for Nexium, a heartburn remedy, as for Nikes. Flip open a magazine, and you'll find ads for Claritin — by now, just about everyone knows that's an allergy medication — next to ones for Clairol.

More than ever, drugmakers are pitching their prescription products directly to consumers instead of relying on doctors to spread the word. Five years ago, few non-medical types had ever heard of erectile dysfunction, generalized anxiety disorder or gastroesophageal reflux disease. Thanks to Bob Dole, the Heartburn Hotel's talking stomach and other pitchmen, though, such ailments are nearly as well-known as, well, Dole and Elvis.

No wonder. Spending on direct-to-consumer, or DTC, advertising of prescription drugs rose roughly 39% in 2000 from the previous year.

And spending on prescription drugs has kept pace. In the mid-1990s, as DTC marketing started to take off, total spending on drugs began rising faster than doctor and hospital costs, notes Larry Levitt, a Kaiser Family Foundation vice president. Today, prescription drugs represent 10% of the nation's annual personal health care bill.

How drug ads rank in ad spending

The 2000 consumer advertising budget, in millions of dollars, of the top 10 most heavily advertised drugs, with sales rankings:

Drug	Ad budget	Sales rank
Vioxx	$160.8	10
Prilosec	107.5	1
Claritin	99.7	6
Paxil	91.8	8
Zocor	91.2	5
Viagra	89.5	17
Celebrex	78.3	7
Flonase	73.5	22
Allegra	67.0	13
Meridia	65.0	41

Source: National Institute for Health Care Management

Coincidence? Some consumer advocates and managed-care plans think not. They claim that DTC ads spur patients to demand prescriptions for expensive, newer drugs when cheaper, older medications would do. On the other hand, the pharmaceutical industry argues that DTC ads play a vital role in educating patients, sometimes motivating them to seek needed medical attention.

The ads "are intended to provide enough information to patients so that they are able to have an informed conversation with their doctor about new treatments that may be available to them," says Alan Holmer, president of the Pharmaceutical Research and Manufacturers of America, a trade group.

Clearly, the drugs most heavily promoted to consumers, such as the painkiller Vioxx and its competitor, Celebrex, also rank among the top sellers.

In the USA last year, according to a new report by the National Institute for Health Care Management, a non-profit group in Washington, D.C., Merck spent more promoting Vioxx to consumers — $160.8 million — than PepsiCo spent advertising Pepsi.

That concerns pharmacologist Raymond Woosley, dean of the University of Arizona College of Medicine.

"The thing that's missing is the bigger-picture warning, the fact that, hey, these are new drugs," says Woosley, who has long studied drug safety.

DTC ads should alert consumers that drugs are tested in only a few thousand patients before coming on the market, he says. "I think they should move more toward a PSA (public service announcement) approach and get away from the hype," Woosley says.

Expensive as they are, DTC ads represent a relatively small chunk of drugmakers' marketing budgets. Last year, only about 16% of the $15.7 billion spent promoting prescription drugs went toward DTC ads, according to the National Institute for Health Care Management. Half of that total covered free samples distributed to doctors, a quarter went toward sending sales reps to doctors, while the rest went to medical journal ads and sales calls to hospitals.

Although DTC ads unquestionably are a windfall for television networks, magazines and newspapers, surprisingly little is known about their impact.

For example, it's not clear how much — if any — DTC ads actually contribute to sales, says Scott Neslin, a marketing professor at Dartmouth College. Apparently, Neslin says, drug companies believe that marketing products to consumers raises brand awareness. But that doesn't necessarily translate to increased sales, he says.

And, while some observers worry that ads may drive consumers to seek drugs they don't need, "there's only indirect information right now on whether patients are asking for things that are inappropriate," says Richard Kravitz, director of the Center for Health Services Research in Primary Care at the University of California-Davis.

Geriatrician Jeffrey Berger says his elderly patients frequently come in asking for drugs similar to those they're already taking.

One patient excitedly asked about a drug he'd learned about from a direct-mail advertisement, recalls Berger, director of clinical ethics in the department of medicine at Winthrop University Hospital in Mineola, N.Y.

While the man did indeed suffer from the ailment treated by the drug, "he had a heart condition that made it impossible for me to prescribe the medication," Berger says. "He was so disappointed."

Critics of the ads say they tend to hype the benefits and downplay the risks. "It's just hard to do justice to some of these issues in a 30-second television spot," says Martin Lipsky, chair of family medicine at Northwestern University Medical School in Chicago.

In 1997, the FDA decided that drug companies did not have to include detailed information about side effects in commercials as long as they directed viewers to call toll-free numbers, buy a magazine or go online for more information. "To rely on the observer to go pursue more information, I think, is unrealistic, for the most part," Berger says.

Even if consumers do go out and buy a magazine to see a drug's print ad, they might not get much out of it, says Rep. Pete Stark, D-Calif., who is pushing for more balanced ads.

"There's a page of mouse tracks that I swear to God, with my eyes, I can't read," says Stark, referring to the fine print accompanying such ads that often is simply lifted from prescribing information for doctors in the drug's package insert.

Since the FDA relaxed rules about television commercials in 1997, they've come to represent nearly two-thirds of the DTC advertising budget, according to the National Institute for Health Care Management.

A new Kaiser Family Foundation study provides an intriguing glimpse at what consumers take away from prescription drug commercials.

The study involved a nationally representative random sample of 1,872 volunteers. About 30% of them had at some time talked to a doctor about a drug they'd seen advertised, the study found. Of those, 44% said their doctor prescribed the drug they'd asked about.

As part of the Kaiser study, three-fourths of the volunteers were shown ads for Nexium for acid reflux, Lipitor for high cholesterol or Singulair for asthma. Immediately afterward, they were asked what they remembered from the drug ad. Overall, those who had just been shown a commercial were more likely to know about the drug's benefits and side effects than those who had not watched a commercial.

Still, only about 40% of the commercial viewers said they knew "a lot more" or "somewhat more" about the medication.

About 30% said they knew a lot more or somewhat more about the condition for which the drug is prescribed.

Says Linda Golodner, president of the National Consumers League: "Unfortunately, it looks like a lot of the messages aren't getting across to consumers."

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NOVEMBER 2001

Prescription Drugs and Mass Media Advertising, 2000

A research report by
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Summary of Key Findings

• A relatively small number of prescription drugs that were advertised to the public in 2000 contributed significantly to the increase in pharmaceutical spending in the U.S. from 1999 to 2000.

• Increases in the sales of the 50 drugs most heavily advertised to consumers in 2000 were responsible for almost half (47.8%) of the $20.8 billion increase in retail spending on prescription drugs from 1999 to 2000. Increases in the sales of all other prescription drugs (numbering about 9,850 in the retail market) accounted for 52.2% of the one-year rise in retail pharmaceutical spending. (See Figures 2 and 5)

• Retail sales of the 50 most heavily advertised drugs rose an aggregate 32% from 1999 to 2000, compared to 13.6% for all other drugs combined. (See Figures 1 and 5)

• The number of prescriptions for the 50 most heavily advertised drugs rose 24.6% from 1999 to 2000, compared to an increase of 4.3% for all other drugs combined. (See Figures 1 and 5)

• The top 50 most heavily advertised drugs had combined sales of $41.3 billion in 2000, 31.3% of retail prescription drug sales (of $131.9 billion) in 2000. (See Figure 5)

• Spending on mass media (also called "direct-to-consumer" or DTC) advertising of prescription drugs rose 35% from 1999 to 2000 — from $1.8 billion to $2.5 billion. DTC ad spending has more than doubled since 1997. (See Figure 8)

• TV ads accounted for the largest portion (57%) of the costs of mass media prescription drug advertising. Spending on TV ads increased to $1.4 billion in 2000 from $1.1 billion in 1999, an increase of 27.3%. (See Figure 3)

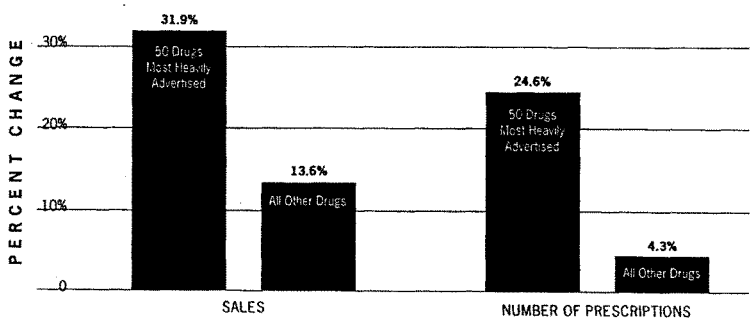
• A few leading pharmaceutical companies sharply increased their DTC ad spending in 2000. For example, Merck spent 117.7% more on DTC ads in 2000 than in 1999. Likewise, Pfizer's DTC spending almost doubled, from $126 million to $250 million. (See Figure 6)

• The anti-arthritis drug Vioxx was the most heavily advertised drug to consumers in 2000. Its maker, Merck, spent $160.8 million promoting the drug in the mass media. Retail sales of Vioxx (approved in 1999) quadrupled from $329.5 million in 1999 to $1.5 billion in 2000. (See Figure 5)

• Spending on DTC ads for prescription drugs accounted for a relatively small share (15.7%) of all promotional spending on prescription drugs in 2000. However, if the retail value of drug "samples" (which doctors get free from companies) is subtracted from total pharmaceutical promotional spending in 2000, DTC ads would account for almost 32% of drug promotional spending in that year. (See Figure 3)

FIGURE 1

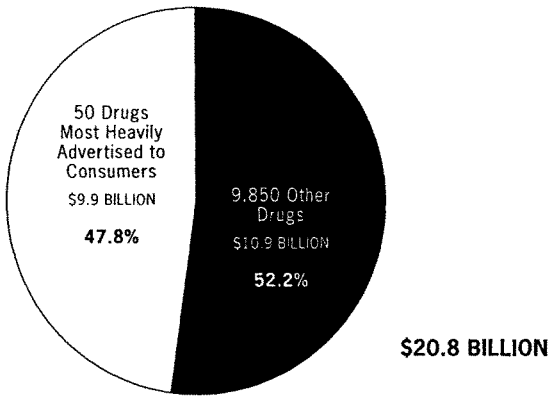
Change in Sales and Number of Prescriptions, 1999–2000



SOURCE: American Institutes for Reseach analysis of Competitive Media Reporting data cited in June 2001 Med Ad News and Scott-Levin Year 2000 Prescription Audit data.

FIGURE 2

Increase in Retail Prescription Drug Sales, 1999–2000



SOURCE: American Institutes for Research analysis of Competitive Media Reporting data cited in June 2001 Med Ad News and Scott-Levin Year 2000 Prescription Audit data.

Introduction

The Food and Drug Administration (FDA) in 1997 relaxed its rules on mass media advertising for prescription drugs. The action made it easier for pharmaceutical companies to promote their products in 30-second or 60-second TV ads without giving detailed medical information on the indications, potential side effects, or proper use.

Since then, spending on mass media advertising for prescription drugs has risen steadily and sharply — from $1.1 billion in 1997 to $2.5 billion in 2000. (See Figure 8)

The growth in mass media drug ads has coincided with a rapid rise in spending on prescription drugs in the U.S. Such spending has increased between 13% and 20% *each year* since 1995 and is now the fastest growing health care expense.[1]

A link between direct-to-consumer (DTC) advertising and escalating drug spending has been suggested. This purported link, along with concern that DTC ads don't contain adequate information on the potential side effects of prescription drugs, has generated growing public policy interest in prescription drug advertising. Among the questions being asked:

- Are DTC ads inducing consumers to press their doctors for specific drugs?
- Are doctors complying with such requests?
- Are the ads driving consumers to desire expensive new brand name drugs when less expensive drugs might be better in some cases?
- Are the ads leading to the inappropriate clinical use of some drugs?
- Do DTC ads contain sufficient information on the potential side effects of drugs?
- How much of the recent rise in drug spending can be attributed to DTC advertising?

Unfortunately, available data and research do not permit clear-cut answers to these questions at this point.[2] There are, in fact, many other forces at work affecting which drugs get prescribed and prescription drug spending. Among the most important:

- The number of drugs being approved has grown in recent years; many of these new drugs are indicated for chronic

conditions such as asthma, heart disease, depression, arthritis and diabetes, and are thus taken over extended periods. This increases drug utilization.

• The incidence and prevalence of many of these conditions has increased in recent years, in part because the population is aging but also, in some cases, because it is less healthy.

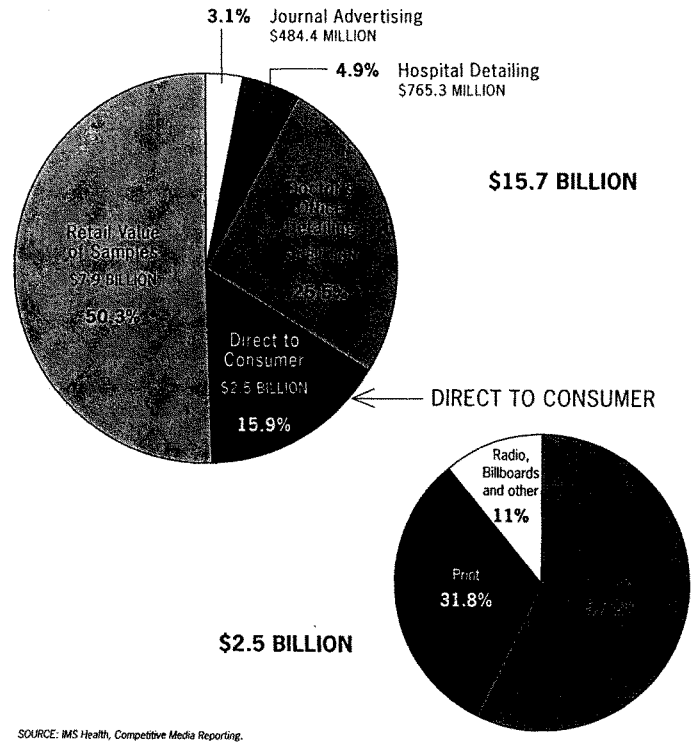
• Doctors are diagnosing — and treating — many chronic illnesses at a higher rate than in the past.

• Doctors are using a wider array of drugs more often. In 1999 doctors prescribed 146 drugs for every 100 office visits, up from 109 drugs per 100 office visits in 1985. Patients got at least one prescription and/or a free drug sample at 66% of office visits in 1999, and doctors were more likely than in the past to prescribe more than one drug per patient.[3]

• Health insurance companies cover more of the costs for prescription drugs than they did a decade ago —

FIGURE 3

Promotional Spending on Prescription Drugs, 2000



SOURCE: IMS Health, Competitive Media Reporting.

sharply lowering the financial barrier to patients for the purchase of drugs.

• Many newer drugs are significantly more expensive than the drugs they supplant — causing overall expenditures to rise as doctors prescribe more of the expensive new drugs and fewer older drugs.

• Many drug companies extend the "franchise" of their important blockbuster drugs by securing patent protection for new formulations. This strategy can add to overall pharmaceutical costs by stalling generic competition.

DTC advertising is also but one avenue of drug marketing and promotion. And DTC advertising typically occurs simultaneously with drug promotion campaigns aimed at physicians. That makes it difficult to tease out the independent effect of DTC advertising.

In 2000, pharmaceutical companies spent $15.7 billion promoting prescription drugs, up from $13.9 billion in 1999, a 13% increase. (See Figure 3) Most of that money was spent promoting drugs to doctors and giving away free drug samples. Companies in 2000 spent $4 billion on one-to-one promotion by some 83,000 drug "reps" or "detailers" making hundreds of thousands of visits to doctors' offices. That was up from a $3.6 billion expenditure on such visits in 1999 and $2.5 billion in 1996. Drug companies spent another $765 million promoting their products to doctors and staff in hospitals. In both their offices and at hospitals or clinics, doctors dispensed an estimated $7.9 billion worth of free samples to patients in 2000, up from $7.2 billion worth in 1999 and $4.9 billion in 1996. (The figure is the retail value of the drugs; that is the estimated revenue they would generate if sold at a pharmacy.)[4]

The growth in "detailing" and "sampling" has thus grown rapidly in recent years. This powerful form of promotion sets up a chain reaction. Doctors are grateful to drug companies for the thousands of dollars worth of free drugs they can then give away to patients. They are induced to use the samples and write prescriptions for the drug for several reasons. First, it's there; they have it right on hand. Second, they know patients are more likely to take a free sample of a drug and then fill a prescription for a sampled drug. Third, giving out free samples endears them to patients. Free samples are very popular with patients, who view both the doctor and the drug favorably because it was free. The patient benefits clinically if the drug is appropriate and works, making them more likely to want to continue taking it.

The pharmaceutical industry also uses other means to market their products — means not counted in the above data. Most notably, they hold thousands of "educational" meetings each year. Doctors are invited to attend such meetings to listen to lectures about specific drugs and their use. Some of these are short one to two hour sessions at which a buffet lunch or carry out dinner may be served. (These are often called "dine and dash" events). Other events are more elaborate half-day or day-long seminars at premier hotels for which doctors can qualify for continuing medical education (CME) credits. More creative venues — such as wine tastings, celebrity autograph signings, dinner theater shows and even Halloween hayrides — are also used.[5]

Drug companies hosted an estimated 314,000 such educational events in 2000 at a cost of $1.9 billion, up from 280,000 in 1999 at a cost of $1.68 billion and 70,000 events (at unknown cost) in 1993.[6]

Pharmaceutical companies have also begun to commit more resources to promoting prescription drugs to consumers via the internet. Most companies now sponsor

Drug Ad Spending in Context

Pharmaceutical companies spent $2.5 billion in 2000 on mass media ads for prescription drugs. What part of overall advertising spending is that? A small portion. U.S. companies spent $101.6 billion advertising consumer products in the "mainstream" U.S. mass media in 2000. That includes internet ad spending of $2.9 billion. Thus, DTC prescription drugs ads represent 2.5% of overall mass media ad spending.[8]

Even so, the most heavily advertised prescription drugs — those with ad spending of around $60 million and up each — were in 2000 among the consumer products with the largest ad spending budgets.[9] For example:

• PepsiCo spent $125 million advertising its premier product, Pepsi — less than the top promoted drug Vioxx with DTC ad spending of $160 million.

• Vioxx also beat out Budweiser beer, with an ad spending of $146 million in 2000, and was close to the most heavily advertised car — GM's Saturn — with ad spending of $169 million in 2000.

• Ad spending for Vioxx exactly matched Dell Computer Company's ad expenditure of $160 million for its top brands of computer-s.

• Each of the top seven most heavily advertised drugs (See Figure 4) beat out Nike's ad budget of $78.2 million for its top shoes.

• Each of the top 15 individual drugs had ad spending that exceeded Campbell's $58 million expenditure for its soups.

dedicated web sites for their largest selling drugs. For example, information about the new heartburn drug Nexium, successor to Prilosec, can be found at both www.acidcontrol.com and www.purplepill.com. Both are sponsored by AstraZeneca, which makes both Nexium and Prilosec. And Pfizer sponsors the popular Lipitor.com site.

No one yet tracks how much the industry is spending on such sites, many of which have been created as a direct result of the FDA's regulations on DTC ads. The regulations require companies airing broadcast ads to give consumers an 800 number or web site where they can get further detailed information on the drug. The sites can end up being promotional because DTC ads spawn traffic to them. That in turn makes the site among the most visited — if not *the* most visited — on a particular disease or drug. Search engines then list the sites as among the most visited when people type in a drug's brand name. Importantly, the FDA does regulate the information on these sites but they do not have the means to police the sites on a regular basis.

Putting DTC ads in context then, they accounted for just 16% of total prescription drug promotion in 2000 — $2.5 billion of $15.7 billion (again, not counting educational meetings). (See Figure 3) It is worth noting that DTC ads would have accounted for 31.8% of total drug promotion if the retail value of free samples were subtracted out. In 1998 and 1999, DTC ad spending accounted for 22% and 27%, respectively, of total promotional spending without the retail value of samples included.[7]

Consumers are highly aware of prescription drugs ads. Recent surveys by the FDA and *Prevention* magazine show that and also reveal that consumers are potently influenced by the ads. A 1999 FDA telephone survey of 1,081 consumers found, for example, that three-quarters remembered seeing a prescription drug ad in the previous three months, most on TV. About 25% who had seen an ad said they had asked a doctor about a condition or illness referred to in an ad; 13% asked for a specific drug and about half got it.[10]

A similar telephone survey of 1,222 people in June 2000, commissioned by *Prevention* magazine, found that 91% had seen or heard a prescription drug ad. Thirty-two percent of consumers who saw an ad talked with their doctor about an advertised medicine and 26% of that group (in other words, 8.3% of all 1,222 respondents) asked for a specific medicine. Of those who asked for a prescription for a drug they had seen advertised, 71% got it. Ten percent got a prescription for another drug and 19% did not get a prescription.[11]

That means of the 1,222 consumers surveyed, 72 (6%) ended up with a prescription drug at least in part because they saw an advertisement for it.

Such telephone surveys suggest that DTC ads are having an impact. But telephone surveys are limited. They rely on consumer recall. And in this case, involving detailed questions about prescription drugs, it is possible that some respondents were confused about which drugs they were actually prescribed. Most experts agree that no scientifically rigorous studies have yet quantified the magnitude of the impact of DTC advertising on consumer behavior, physician prescribing patterns, or public health. Likewise, no detailed studies have yet proven a direct cause and effect link between DTC ads and rising pharmaceutical costs.[12]

Several recent analyses strongly suggest such a link, however. One, from the National Center for Health Statistics and Centers for Disease Control and Prevention, looked in detail at data on physician office visits through 1999. The study found that the drugs most heavily prescribed by doctors between 1997 and 1999 were those most heavily advertised. Specifically, the analysis found that 80% of drugs approved over the last several years that were heavily marketed to consumers were in the top 20% of drugs physicians prescribed. In contrast, only 10% of new drugs that were not heavily advertised were in the top 20% of medicines prescribed.[13] The analysis we present below is similar.

Methodology

This study uses data on DTC ad spending and prescription drug retail sales in 1999 and 2000 to address the following two questions: Are sales of the drugs being most heavily advertised to the public contributing disproportionately to the rise in pharmaceutical spending? And are the drugs being most heavily advertised experiencing a faster rate of increase in their use and sales than other drugs?

Data on DTC advertising comes from two sources: (1) Competitive Media Reporting (CMR), a New York-based company that collects information on mass media advertising expenditures for numerous consumer goods and services, and (2) IMS Health, a pharmaceutical market research company based in Westport, CT. IMS Health includes in its compilation of DTC ad spending the amount spent on all forms of such ads — including those that may not mention a drug by name. In contrast, the CMR data we use only includes spending for ads that mention a drug by name. (See sidebar — "What Are the Rules? — on page 14) These data were reported in the June 2001 issue of the trade publication *Med Ad News*.[14]

We cite both data sets and note the difference where appropriate. Importantly, the data we present on DTC ad spending in Figures 4 and 5 are from CMR as presented in *Med Ad News*. As such, these data exclude spending on ads that do not mention drugs by name. In addition, Figures 4 and 5 list only the top 50 most heavily advertised drugs,

which accounted for 95% of all DTC spending in 2000. We focus on these drugs. Both CMR and *Med Ad News* present a total list of 103 drugs that were advertised to consumers in 2000. Below the top 50, DTC ad spending drops off sharply.

Our data on prescription drug spending come from Scott Levin, a pharmaceutical market research firm based in Newtown, PA. Its annual Source Prescription Audit projects, through a sampling methodology involving close to 40,000 stores, all outpatient prescriptions dispensed by retail pharmacy outlets in the U.S. Such outlets include chain and independent drug stores, food and discount stores, and mass merchandisers. Importantly, these data do not include sales of prescription drugs by mail order or through nursing homes, hospitals or other health facilities.

Findings

Prescription drugs that were heavily advertised to the public in 2000 accounted for a significant portion of the one-year increase in pharmaceutical spending from 1999 to 2000.

Increases in the sales of the 50 drugs most heavily advertised to consumers in 2000 were responsible for 47.8% ($9.9 billion) of the $20.8 billion increase in retail spending on prescription drugs from 1999 to 2000. Increases in the sales of all other drugs (numbering about 9,850 in the retail market) accounted for 52% of the one-year rise in retail pharmaceutical spending. (See Figure 5)

The 50 most heavily advertised drugs had total retail sales in 2000 of $41.3 billion, 31.3% of the $131.9 billion in total retail sales that year. The aggregate increase in sales of these 50 drugs from 1999 to 2000 was 31.9%. By comparison, the increase in the sales of all other drugs combined was 13.6%. Retail sales of all drugs combined increased 18.8% from 1999 to 2000.[15] (See Figure 5)

Thus, sales of the most heavily advertised drugs increased at 2.3 times the rate of all other drugs.

Much of the sales increase for heavily advertised drugs came from a jump in the number of prescriptions. For the 50 most heavily advertised drugs, the number of prescriptions increased 24.6%. The number of prescriptions for all other drugs rose just 4.3%. Prescriptions for all drugs combined were up 7.5% in 2000, to 2.9 billion from 2.7 billion. (See Figure 5)

Thus, the number of prescriptions for the 50 most heavily advertised drugs grew at a rate six times that for other drugs.

These findings are consistent with those from a previous NIHCM Foundation study, released in May 2001. That study found that the number of prescriptions for the top 50 best selling drugs in 2000 rose 18.6% from 1999 to 2000. The number of prescriptions for all other drugs rose just 3.4%.[16]

Predictably, there is substantial overlap between the two lists — the top 50 most heavily advertised drugs and the top 50 best selling drugs for 2000. Twenty-two of the top 50 most heavily advertised drugs in 2000 were also on the list of the 50 best selling drugs that year. Among the most notable drugs on both lists are Prilosec, Lipitor, Prevacid, Vioxx, Paxil, Prozac, Claritin, Zocor, Pravachol, Celebrex, and Viagra.

Prilosec was the best selling drug in 2000, with retail sales in the US market of $4.1 billion, up 13% from $3.6 billion in sales in 1999. Prilosec was the second most widely promoted drug to consumers. Its maker AstraZeneca spent $107.5 million advertising Prilosec, which is used to treat ulcers and heartburn. (See Figure 4)

The cholesterol-lowering drug Lipitor was the second best selling drug in 2000. Lipitor sales reached $3.7 billion, up 39% from 1999. Lipitor was the 15th most heavily advertised drug to consumers. Its maker, Pfizer, spent $58.2 million on DTC ads. Lipitor was also the second largest contributor to the one-year rise in retail pharmaceutical spending, accounting for 5% of the $20.8 billion growth in sales from 1999 to 2000.

Zocor, Lipitor's rival in the cholesterol-lowering market, also experienced a sales jump in 2000 — of 22.2%. It was the 10th largest contributor to the one-year growth in sales and the 5th largest selling drug. It was also the 5th most heavily promoted to consumers, with a DTC expenditure of $91.2 million. Likewise, Pravachol was the 15th largest selling drug and ranked 35th on the list of drugs contributing most to the one-year increase in spending. Bristol-Myers Squibb spent $62 million promoting the drug to consumers in 2000.

The increase in the sales of Vioxx from 1999 to 2000 accounted for 5.7% of the one-year increase in drug spending, more than any other single prescription drug. It was the 13th best selling drug in 2000, with retail sales of $1.5 billion, up 360%. Vioxx, used to treat arthritis, was also the most heavily DTC advertised drug in 2000. Its maker, Merck, spent $160.8 million promoting the drug to consumers.

Celebrex, Vioxx's main competitor among arthritis drugs, was the fourth largest contributor to prescription drug sales growth in 2000 and the sixth largest selling drug that year. It was the 7th most widely promoted drug to consumers. Its maker, Pfizer, spent $78.3 million on DTC ads.

Paxil and Prozac compete against each other in the antidepressant market. Paxil was the 8th largest selling drug in 2000. Its sales were up 25%. That made it the 13th largest contributor to the overall spending growth in 2000. Prozac was the 4th largest selling drug in the retail market but its sales were up only 5%. That relegated it to 49th place as a contributor to spending growth. The difference in the two drugs sales growth was perhaps related to their DTC promotion. Paxil's maker, GlaxoSmithKline, spent $91.8

FIGURE 4

2000 Direct-to-Consumer Spending

(Drugs Ranked in Terms of Year 2000 DTC Spending)

Rank	Name	Type of Drug	DTC Spending in 2000 ($millions)	DTC Share of Spending	Cumulative Share of DTC Spending
1	Vioxx	Antiarthritic	$160.8	7.1%	7.1%
2	Prilosec	Antiulcerant	$107.5	4.8%	11.9%
3	Claritin	Oral Antihistamine	$99.7	4.4%	16.3%
4	Paxil	Antidepressant	$91.8	4.1%	20.4%
5	Zocor	Cholesterol Reducer	$91.2	4.0%	24.4%
6	Viagra	Sex Function Disorder	$89.5	4.0%	28.4%
7	Celebrex	Antiarthritic	$78.3	3.5%	31.8%
8	Flonase	Respiratory Steroids (Inhaled)	$73.5	3.3%	35.1%
9	Allegra	Oral Antihistamine	$67.0	3.0%	38.0%
10	Meridia	Antiobesity	$65.0	2.9%	40.9%
11	Flovent	Respiratory Steroids	$62.9	2.8%	43.7%
12	Pravachol	Cholesterol Reducer	$62.0	2.7%	46.5%
13	Zyrtec	Oral Antihistamine	$60.2	2.7%	49.1%
14	Singulair	Asthma Treatment	$59.3	2.6%	51.7%
15	Lipitor	Cholesterol Reducer	$58.2	2.6%	54.3%
16	Nasonex	Respiratory Steroids (Inhaled)	$53.2	2.4%	56.7%
17	Ortho Tri-Cyclen	Oral Contraceptive	$47.0	2.1%	58.8%
18	Valtrex	Antiviral	$39.7	1.8%	60.5%
19	Lamisil	Antifungal	$39.3	1.7%	62.2%
20	Prempro	Sex Hormones	$37.9	1.7%	63.9%
21	Sonata	Non-Barbiturate Sedative	$37.5	1.7%	65.6%
22	Imitrex	Non-narcotic Painkiller	$37.1	1.6%	67.2%
23	Xenical	Antiobesity	$35.5	1.6%	68.8%
24	Prevacid	Antiulcerant	$34.4	1.5%	70.3%
25	Avandia	Oral Diabetes	$33.9	1.5%	71.8%
26	Detrol	Bladder Control	$33.8	1.5%	73.3%
27	Zyban	Smoking Cessation	$30.9	1.4%	74.7%
28	Diflucan	Antifungal	$29.9	1.3%	76.0%
29	Remicade	Crohn Disease	$29.0	1.3%	77.3%
30	Buspar	Antianxiety	$28.7	1.3%	78.6%
31	Tamiflu	Influenza	$28.4	1.3%	79.8%
32	Synvisc	Antiarthritic	$25.9	1.1%	81.0%
33	Glucophage	Oral Diabetes	$25.8	1.1%	82.1%
34	Procrit	Anemia	$25.5	1.1%	83.2%
35	Patanol	Allergic Conjunctivitis	$25.1	1.1%	84.4%
36	Prozac	Antidepressant	$23.3	1.0%	85.4%
37	Relenza	Influenza	$22.5	1.0%	86.4%
38	Aricept	Alzheimers Disease	$20.6	0.9%	87.3%
39	Denavir	Herpes Treatment	$19.9	0.9%	88.2%
40	Rhinocort Aqua	Respiratory Steroids (Inhaled)	$19.3	0.9%	89.0%
41	Propecia	Hair Treatment	$18.0	0.8%	89.8%
42	Glucovance	Oral Diabetes	$16.4	0.7%	90.6%
43	Sarafem	Premenstrual Syndrome	$14.4	0.6%	91.2%
44	Claritin D	Oral Cold Preparation	$14.2	0.6%	91.8%
45	Flomax	Benign Prostate Disease	$12.5	0.6%	92.4%
46	Differin	Acne Treatment	$12.1	0.5%	92.9%
47	Prevnar	Pneumococcal vaccine	$11.2	0.5%	93.4%
48	Ambien	Non-Barbiturate Sedative	$11.1	0.5%	93.9%
49	Ditropan XI	Bladder Control	$11.0	0.5%	94.4%
50	Zithromax	Broad Antibiotic	$9.8	0.4%	94.8%
	Rest of Market		$117.1	5.2%	5.2%
	Total market		**$2,258.4**	**100.0%**	**100.0%**

SOURCE: American Institutes for Reseach Analysis of Competitive Media Reporting data cited in June 2001 Med Ad News.

FIGURE 5

Sales and Utilization Change of 50 Most Heavily Promoted Drugs (DTC Only), 1999–2000

(Drugs Ranked in Terms of Year 2000 DTC Spending)

	Name	Type of Drug	2000 Sales ($million)	2000 DTC Spending ($million)	Change in Sales, 1999–2000 ($million)	Percent Change in Sales, 1999–2000	Percent Change in Utilization, 1999–2000
1	Vioxx	Antiarthritic	1,518.0	160.8	1,188.5	360.7%	331.2%
2	Prilosec	Antiulcerant	4,102.2	107.5	452.8	12.4%	5.6%
3	Claritin	Oral Antihistamine	2,035.4	99.7	264.2	14.9%	8.3%
4	Paxil	Antidepressant	1,808.0	91.8	355.6	24.5%	17.2%
5	Zocor	Cholesterol Reducer	2,207.0	91.2	400.2	22.2%	14.6%
6	Viagra	Sex Function Disorder	809.4	89.5	192.4	31.2%	30.2%
7	Celebrex	Antiarthritic	2,015.5	78.3	739.5	58.0%	42.4%
8	Flonase	Respiratory Steroids (Inhaled)	618.7	73.5	129.2	26.4%	18.9%
9	Allegra	Oral Antihistamine	1,120.4	67.0	382.2	51.8%	38.8%
10	Meridia	Antiobesity	113.2	65.0	–10.0	–8.1%	–11.3%
11	Flovent	Respiratory Steroids	652.7	62.9	260.9	66.6%	61.4%
12	Pravachol	Cholesterol Reducer	1,203.5	62.0	166.3	16.0%	6.7%
13	Zyrtec	Oral Antihistamine	848.9	60.2	230.5	37.3%	32.3%
14	Singulair	Asthma Treatment	676.5	59.3	316.5	87.9%	74.3%
15	Lipitor	Cholesterol Reducer	3,692.7	58.2	1,032.8	38.8%	32.3%
16	Nasonex	Respiratory Steroids (Inhaled)	392.0	53.2	128.0	48.5%	42.2%
17	Ortho Tri-Cyclen	Oral Contraceptive	617.0	47.0	185.5	43.0%	36.8%
18	Valtrex	Antiviral	311.1	39.7	77.7	33.3%	22.0%
19	Lamisil	Antifungal	498.3	39.3	32.0	6.9%	–20.9%
20	Prempro	Sex Hormones	711.8	37.9	106.3	17.6%	3.8%
21	Sonata	Non-Barbiturate Sedative	97.8	37.5	85.5	694.3%	597.3%
22	Imitrex	Non-narcotic Painkiller	1,026.1	37.1	51.6	5.3%	–1.7%
23	Xenical	Antiobesity	237.0	35.5	92.3	63.8%	65.1%
24	Prevacid	Antiulcerant	2,832.6	34.4	773.6	37.6%	31.0%
25	Avandia	Oral Diabetes	617.6	33.9	514.9	501.5%	457.4%
26	Detrol	Bladder Control	319.2	33.8	82.0	34.6%	24.9%
27	Zyban	Smoking Cessation	126.1	30.9	–9.1	–6.7%	–14.7%
28	Diflucan	Antifungal	386.9	29.9	56.6	17.1%	24.8%
29	Remicade	Crohn Disease	2.7	29.0	1.5	132.6%	0.0%
30	Buspar	Antianxiety	702.3	28.7	170.8	32.1%	16.8%
31	Tamiflu	Influenza	43.5	28.4	34.8	403.0%	393.8%
32	Synvisc	Antiarthritic	23.0	25.9	2.4	11.6%	6.1%
33	Glucophage	Oral Diabetes	1,630.3	25.8	472.5	40.8%	23.6%
34	Procrit	Anemia	298.8	25.5	74.8	33.4%	19.2%
35	Patanol	Allergic Conjunctivitis	152.2	25.1	43.8	40.5%	27.5%
36	Prozac	Antidepressant	2,567.1	23.3	120.5	4.9%	–1.0%
37	Relenza	Influenza	16.6	22.5	6.4	61.8%	61.9%
38	Aricept	Alzheimers Disease	384.1	20.6	66.5	20.9%	17.5%
39	Denavir	Herpes Treatment	36.2	19.9	18.0	98.4%	91.2%
40	Rhinocort Aqua	Respiratory Steroids (Inhaled)	73.4	19.3	73.4	N/A	N/A
41	Propecia	Hair Treatment	122.6	18.0	8.9	7.8%	0.1%
42	Glucovance	Oral Diabetes	21.0	16.4	21.0	N/A	N/A
43	Sarafem	Premenstrual Syndrome	8.1	14.4	8.1	N/A	N/A
44	Claritin D	Oral Cold Preparation	896.5	14.2	76.6	9.3%	0.4%
45	Flomax	Benign Prostate Disease	226.8	12.5	88.8	64.3%	53.2%
46	Differin	Acne Treatment	136.0	12.1	26.6	24.3%	12.2%
47	Prevnar	Pneumococcal vaccine	0.6	11.2	0.6	N/A	N/A
48	Ambien	Non-Barbiturate Sedative	798.9	11.1	159.6	25.0%	18.1%
49	Ditropan XI	Bladder Control	174.1	11.0	113.7	188.2%	153.8%
50	Zithromax	Broad Antibiotic	1,364.4	9.8	107.8	8.6%	5.1%
	SUMMARY						
	Top 50 Drugs		$41,274.8 *31.3% of total*	$2,141 *94.8% of total*	$9,976 *47.8% of total*	31.9%	24.6% *18.0% of all prescriptions*
	Rest of Market		$90,697.0 *68.7% of total*	$117 *5.2% of total*	$10,891 *52.2% of total*	13.6%	4.3%
	Total Market		**$131,971.8**	**$2,258**	**$20,866**	**18.8%**	**7.5%**

SOURCE: American Institutes for Research analysis of Competitive Media Reporting data cited in June 2001 Med Ad News and Scott-Levin Year 2000 Prescription Audit data.

million promoting the drug to consumers. In contrast, Eli Lilly spent only $23.3 million promoting Prozac to consumers in the last full year the drug had patent protection.

The allergy drug Claritin continues to be one of the most heavily advertised drugs, along with its rivals Allegra and Zyrtec. Claritin's maker, Schering-Plough, spent $99.7 million promoting all forms of the drug to consumers in 2000. It was the third most heavily advertised drug. That comes on top of expenditures on DTC ads for Claritin of $137 million in 1999 and $185 in 1998 — a total of $421.7 million over three years. Retail sales of Claritin rose 15% in 2000 and 21% in 1999. The main form of Claritin (a 10 mg tablet) was the 9th best selling drug in 2000 and the 34th largest contributor to the one-year rise in sales in 2000.

Allegra was the 26th best selling drug in 2000. Its retail sales grew 52% from 1999 to 2000 — to $1.1 billion. Aventis spent $67 million advertising the drug to consumers in 2000, up from $42.8 million in 1999. Likewise, Zyrtec ranked 32nd on the list of best selling drugs in 2000, with sales up 34% to $849 million. Pfizer spent $60.2 million promoting the drug to consumers, up from $57 million in 1999.

No discussion of DTC ads is complete without mention of Viagra. The first drug approved to treat erectile dysfunction, Viagra and its ads have been highly visible in the media. That was in part because some ads featured former senator and presidential candidate Bob Dole. Retail sales of Viagra rose 32% in 2000, to $809 million. It was the 27th largest selling drug. Pfizer spent $89.5 million advertising the drug to consumers in 2000, up from $53 million in 1999.

While aggregate sales of the top 50 drugs advertised to consumers rose 32%, many individual drugs on this list had much sharper sales and utilization increases. (See Figure 5) Drugs to treat asthma are most notable here. For example, sales of Flovent, a respiratory steroid, rose 66.6% in 2000. Flovent was the 11th most heavily advertised drug to consumers in 2000 with a DTC ad spend of

FIGURE 6

Direct-to-Consumer Spending by Company, 2000

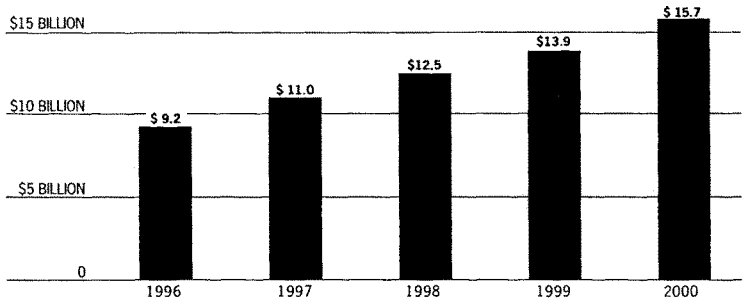
(Ranked in Terms of Year 2000 DTC Spending)

Rank	Pharmaceutical Company	DTC expenditure, 2000 ($millions)	DTC expenditure, 1999 ($millions)	Percent Change, 1999-2000
1	GlaxoSmithKline	417.2	296.9	40.5%
2	Merck & Co.	331.8	152.4	117.7%
3	Pfizer	249.9	125.9	98.5%
4	Schering-Plough	167.1	189.2	-11.7%
5	Bristol-Myers Squibb	140.6	44.4	216.7%
6	AstraZeneca	137.1	163.3	-16.0%
7	Pharmacia	128.1	73.7	73.8%
8	American Home Products	120.4	62.3	93.3%
9	Johnson & Johnson	118.5	100.9	17.4%
10	Hoffman-La Roche	70.7	77.9	-9.2%
11	Aventis Pharmaceuticals	67.2	72.5	-7.3%
12	Abbot Laboratories	64.9	43.5	49.2%
13	Novartis	51.6	13.3	287.9%
14	Eli Lilly	46.5	7.1	554.9%
15	Nestle	37.9	36.6	3.6%

SOURCE: Competitive Media Reporting.

FIGURE 7

Promotional Spending on Prescription Drugs, 1996–2000



SOURCE: IMS Health.

$63 million. Likewise, sales of Singular rose 88%. It was the 14th most heavily advertised drug. Sales of Flonase climbed 26.4%. GlaxoSmithKline spent $73.5 million promoting Flonase to consumers.

Several new drugs appeared to get a boost from DTC ads. Among them was Sonata, a non-barbiturate sedative from American Home Products, approved in August 1999. Sonata sales leaped to almost $100 million from less than $10 million in its first year. The company spent $37.5 million promoting the drug to consumers in 2000. The new diabetes drug Avandia from GlaxoSmithKline and Bristol-Myers Squibb (approved in May 1999) had a sales surge of $515 million. The companies spent $34 million advertising the drug to consumers.

Importantly, not all drugs that were promoted to consumers saw use and sales rise. The weight control/anti-obesity drug Meridia experienced an 8% decline in sales despite DTC ad spending of $65 million by Abbott Labs. Knoll Pharmaceuticals first marketed the drug in December 1997. Abbott acquired Knoll in early 2001. Not suprisingly, an Abbott official said in June that the company would "reconfigure its (Meridia) marketing efforts...to focus on physicians, not the patients."[17]

Likewise, Lamisil, an anti-fungal drug marketed to treat toenail fungus, saw sales rise only 7% as the number of prescriptions for the drug fell 21%. Novartis spent $39.3 million on DTC advertising for Lamisil. Similarly, the migraine drug Imitrex had an anemic sales increase of 5.3% as prescriptions declined about 2%. Imitrex maker GlaxoSmithKline spent $37 million on DTC ads. Zyban, used to help people quit smoking, had a decline is sales of almost 7% despite $31 million in DTC advertising.

Pharmaceutical companies spent a total of $2.5 billion on DTC advertising in 2000, up from $1.8 billion in 1999. Of this $2.5 billion, $2.26 billion was spent on ads that mentioned the name of a drug. About $240 million was spend on ads that didn't mention the name of a drug; instead such ads talk about a disease or condition that the company sponsoring the ads makes a drug to treat.

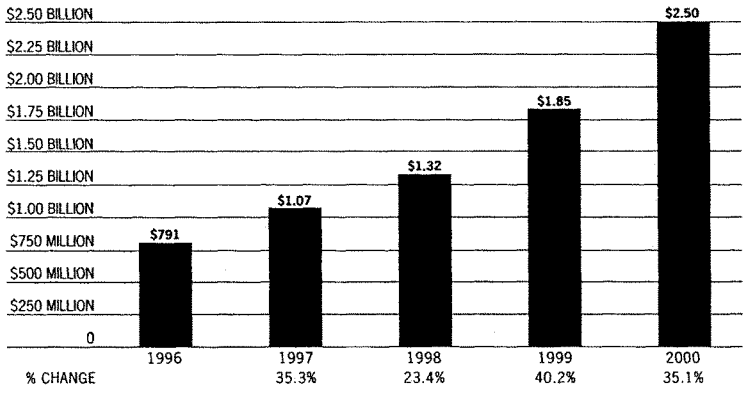
In 2000, companies sponsored DTC ads for 103 drugs.[18] Spending per drug ran from a low of $12,000 to a high of $160.8 million. The top 50 advertised drugs accounted for around 95% of all DTC ad spending in 2000. (See Figure 1) And the top 25 most heavily advertised drugs accounted for 72% of total DTC ad spending. In 1999, the pharmaceutical industry spent a total $1.8 billion on DTC ads. $1.6 billion of that was spend on ads for 92 prescription drugs; companies spend about $200 million in 1999 on "see your doctor" ads that mentioned only a medical condition but not a specific drug.

In 2000, TV ads accounted for the largest portion (57.2%) of the costs of mass media prescription drug advertising. Spending on TV ads increased to $1.4 billion in 2000 from $1.1 billion in 1999, an increase of 27.3%.

Several leading pharmaceutical companies sharply increased their DTC ad spending in 2000. (See Figure 6) For example, Merck spent 117.7% more on DTC ads in 2000

FIGURE 8

Direct to Consumer Advertising Spending, 1996–2000



SOURCE: IMS Health.

than in 1999. Likewise, Pfizer's DTC spending almost doubled, from $126 million to $250 million. Bristol-Myers Squibb spent more than three times as much on DTC ads in 2000 as the company did in 1999 — $140.6 million compared to $44.4 million. Novartis and Eli Lilly also committed more resources to DTC ads. Eli Lilly's DTC spending rose from $7 million in 1999 to $46.5 million in 2000. Most of that was for Prozac.

The bulk of spending on mass media ads in 2000 was for drugs to treat chronic illnesses or common conditions and symptoms that afflict millions of Americans. This is not surprising since these drugs have the largest potential markets. Among the 50 most heavily advertised were:

- Five drugs to treat asthma
- Three drugs to treat arthritis
- Three drugs to treat diabetes
- Three drugs to treat allergies
- Three cholesterol lowering drugs
- Two antidepressants
- Two sedatives
- Two drugs to treat the symptoms of the flu
- Two drugs to treat incontinence
- Two drugs to treat fungal infections

A significant number of the 50 most heavily advertised drugs were promoted to consumers for the first time in 2000. Many but not all were new, having been approved in 1998 or 1999. Of the total 103 drugs with any DTC spending in the 2000, 34 were not promoted to consumers in 1999.

Recent Developments Related to DTC Drug Advertising

The following is a chronological list of key political, legal, regulatory, and research developments over the past year (September 2000 to September 2001) related to DTC prescription drug advertising. We would note that while many of the developments presented below involve FDA actions, the majority of DTC ads have not been challenged by that agency.

◆ The U.S. Drug Enforcement Administration in September 2001 sent a "cease and desist" letter to Celltech, asking the company to halt its DTC ads for the drug Metadate CD.

The drug is used to treat Attention Deficit Hyperactivity Disorder (ADHD). The ads in question appeared in *Ladies' Home Journal*, *Parade*, and several other women's magazines. The DEA classifies drugs to treat ADHD as Schedule II drugs — potentially addictive and open to abuse. By long standing agreement between the pharmaceutical industry and drug regulatory agencies in some 30 counties, including the U.S, such drugs are not advertised by name to consumers. The FDA said it was also reviewing the ads. Celltech is headquartered in England.

◆ A Boston-based consumer group (Prescription Access Litigation) filed a class action law suit in New Jersey in August 2001 alleging that DTC ads for the allergy drug Claritin (Schering-Plough) were "false and misleading." The complaint alleges that the ads overstate the allergy relief consumers who take the drug get. The suit is pending.

◆ The FDA warned GlaxoSmithKline in August 2001 to stop airing what it termed a "misleading" TV ad for the diabetes drug Avandia. The FDA said the ad failed to present certain risk information and presented other risk information in a confusing way. The company pulled the ad to make changes.

◆ A key legislator in the health arena — William Thomas (R-Calif.), chairman of the House Ways and Means Committee — said in August 2001 that he was considering adding restrictions on DTC advertising to any legislation adding a prescription drug benefit to Medicare. Among the restrictions he said he was considering are higher co-pays for drugs that are advertised to consumers and outright prohibitions on advertising some kinds of drugs.

◆ An FDA official in July 2001 told a congressional committee that the agency had so far seen no evidence DTC ads were "doing any harm" to consumers. The official, Nancy Ostrove, said further research was needed on the impact of DTC ads. Her written testimony stated that since 1997 the agency had issued 45 "notices of violation" and three "warning letters" to drug companies regarding their broadcast prescription drug ads, and 44 "notices of violation" and one "warning letter" regarding DTC print ads. Most of the violations cited were because the ad "overstated of guaranteed the product's efficacy...or minimized the risk of the product," her testimony stated. A notice of violation asks a company to correct the problem immediately. A warning letter requires a remedial campaign by the company to correct impressions left by an ad.

◆ The American Medical Association's governing body approved in June 2001 a resolution asking the pharmaceutical industry to voluntarily place disclaimers on all DTC prescription drug ads. The disclaimers would state: "Your physician may recommend other appropriate treatments." The AMA intends to lobby regulators to press companies to include the disclaimer. In its resolution, the AMA's governing body stated: "Currently, we do not know how DTC advertising affects the patient-physician relationship, whether it provides educational value, how it affects consumer perceptions of prescription drugs and whether it results in cost effective health outcomes...Many broadcast ads are misleading, using imagery to suggest effectiveness far beyond what clinical evidence supports."

◆ A pharmaceutical industry study released in June 2001 found no relationship between the price increases of 20 drugs from 1999 to 2000 and the amount spent on DTC ads for those drugs. The study used price data from Scott Levin. It was funded by GlaxoSmithKline.

◆ The FDA in June 2001 asked Merck, in a letter, to revise the information on its website pertaining to Fosamax, used to treat osteoporosis. The agency said the site did not give enough information to consumers on the potential side effects of the drug. The company complied.

◆ *Prevention* magazine in June 2001 released its third annual report on "wellness and consumer reaction to DTC advertising of Rx drugs." The survey of 1,222 consumers (conducted in June 2000) found a high level of awareness (over 90%) of DTC ads. Among the key findings are that DTC ads may be increasing patient compliance with prescribed drugs.

◆ The FDA in May 2001 sent letters to eight manufacturers of drugs to treat HIV/AIDS, warning them that DTC ads for their drugs were not balanced. Specifically, the FDA said the ads lacked sufficient information on the limitations of the drugs in treating HIV/AIDS and that people portrayed in the ads were not representative of the population with HIV/AIDS. The companies agreed to comply.

◆ Ethicad, a non-profit group established in 2000, in May 2001 released voluntary standards for DTC prescription drugs ads. Among other things, the group calls on pharmaceutical companies to (1) seek assistance from health care professionals when creating drugs ads, (2) conduct formal assessments of the educational needs of persons with the disease being targeted, and (3) test DTC ads in advance with consumer focus groups to assure they convey balanced information. Ethicad is based in Atlanta, Georgia. Its stated goal is to "maximize the public health benefits of DTC information by providing the consumer with substantive, understandable and reliable information about pharmaceutical products."

◆ The U.S. Department of Health and Human Services in May 2001 held a conference on the issue of DTC advertising. A series of papers prepared for the conference by academic

What Are the Rules?

Confusion exists about the different types of prescription drug ads and FDA regulation of DTC ads. The full set of regulations covering DTC ads are quite specific. What follows is a brief synopsis of the most important rules.

The three types of DTC ads

• **Help seeking:** These ads aim to alert consumers about a disease or condition and its symptoms and let them know that treatment is available. A drug's brand name can not be used, but the company sponsoring the ad is identified. People are exhorted to see their doctor.

• **Reminder:** These ads give the name of a drug but do not mention any disease or condition to be treated. They are designed to build brand recognition and prompt people to ask their doctors about the drug.

• **Product claim:** These ads mention both a drug's brand name and its intended use. They aim explicitly to prompt people with a specific disease or condition to go to the doctor to inquire about the drug. Such ads must meet more exacting requirements. Most DTC drug ads today are product claim ads.

The requirements

All types of DTC drug ads:

• Must comply with FDA and other federal rules regarding advertising fairness and accuracy and "false advertising." In addition, no drug ad can (a) falsely report scientific data, (b) declare clinical superiority for a drug without scientific data to back it up, or (c) represent a drug as a treatment for a disease for which it has not been FDA approved.

Help seeking and reminder ads:

• Do not have to contain detailed information – or give a source where consumers can get such information – on a drug's effectiveness or potential side effects

Product claims ads:

• Must present a "fair balance" of benefit and risk information. This means, for example, that a print ad is not supposed to have huge type touting a drug's benefits and small type listing major side effects. Likewise, a 60-second TV ad can't spend 50 second on benefits and 10 seconds on potential problems.

• Must, if they are in print (newspapers, magazines, internet), contain a "brief summary" of a drug's side effects, indications and effectiveness as well as any precautions and warnings about its use. This information must be consistent with and derive from a drug's official product labeling. The FDA in consultation with manufacturers dictates such labeling. In practice, this summary information is not brief at all. It can run to 1,000 words or more and usually takes up a sizeable chunk of space even when small print is used (which it almost always is). However, this information may be, and usually is, printed on an adjacent page. In practice then, it is usually far less visible.

• Must, if they are broadcast (TV or radio), include prominent mention of a drug's "major" side effects or limitations and any important contraindications. In addition, such ads must give a toll free telephone number, a web site or internet address, and reference to print ads or available written material on a drug that can be obtained in a public place. Information sought from these sources must be sent out within two business days. Thus, DTC drug ads in broadcast media are exempted from airing the detailed "brief summary" information that is required in print ads.

researchers concurred that data suggests DTC ads are playing an increasingly important role in the pharmaceutical marketplace. But the papers agreed that not enough data exists to quantify that role or render a judgement on whether the ads are, on balance, beneficial or harmful to the health of the population. (See note 12)

◆ A study released in May 2001 found that many Americans who take prescription allergy medicines to relieve symptoms (such as runny nose and congestion) may not have allergies at all. The study evaluated 246 people who had been prescribed one of the three leading prescription allergy drugs — Claritin, Allegra or Zyrtec. It found that 65% did not have allergies based on a blood test that measures immune response to potential allergy causing substances. But the Ohio State University researchers who conducted the study reported that the test is not 100% reliable and may have missed some subjects people who did have allergies. The researchers and other allergy specialists

estimate that between a third and half of patients taking prescription allergy medicines may have other conditions, such as sinusitis, which were causing their symptoms. Such patients would be helped only by versions of the three drugs that also contain a decongestant. Pharmacia Diagnostics, the company that makes the immune test, funded the study. The study is relevant to DTC advertising because Claritin, Allegra and Zyztec have been among the most widely advertised drugs over the past three years. Many doctors believe patients who have allergy symptoms are prompted by the ads to ask for these drugs.

◆ The FDA in April 2001 said it was studying a TV ad campaign for Xenical, a weight loss drug. The drug's maker, Hoffman-La Roche, aired ads that failed to mention side effects by splitting one ad into two parts. Technically, ads that do not mention both the name of a drug and the condition it treats do not have to mention possible side effects. (See box on page 14) Some ads only mention a medical condition *or* the name of a drug, but not both, and then advise viewers to see their doctor. Roche earlier this year aired two such ads (one naming the drug and the other the condition, excessive weight gain) within minutes of each other, not naming any side effects. In addition, the FDA in March 2001 sent a warning letter to Hoffman-La Roche ordering the company to alter its print and TV DTC ads for Xenical. The letter said the company's DTC ads did not adequately present information on the side effects of the drug. Since Xenical's launch in 1999, Roche has received four warning letters from the FDA regarding DTC ads for the drug. The company has since altered the ads.

◆ The FDA in March 2001 said it had launched an internal review of its rules on DTC advertising of prescription drugs. As part of the review, the agency will conduct two surveys — one of physicians and one of consumers — to help it decide whether any changes in its rules are in order. The review is to be completed by the end of 2001.

◆ A study published in the *Journal of Family Practice* (December 2000) found that print ads for 101 prescription drugs appearing in 320 ads in 18 mass media magazines over 10 years "seldom provided information about the drugs' mechanism of action, success rate, treatment duration, alternative treatments and behavior changes that could enhance the health of affected patients." Researchers at the University of California, Los Angeles and Davis conducted the study.

◆ The FDA in November 2000 asked G.D. Searle, a unit of Pharmacia, to revise a TV ad for the arthritis drug Celebrex. The agency said the ad was "misleading because the totality of the music and the audio statements...overstate the efficacy for Celebrex." The company pulled the ads.

◆ In October 2000, a congressman who blamed the suicide of his 17-year old son on the psychiatric side effects from the acne drug Accutane called on the drug's maker, Hoffman La Roche, to stop advertising the drug to consumers. Though the ads don't mention the name of the drug, the congressman, Bart Stupak (D-Mich), alleged that the ads target young people and urge them to see a doctor to get treated, but do not warn of potential side effects. Accutane is the most popular prescription drug used to treat acne.

◆ The FDA in September 2000 issued a notice of violation to Alza Corp., requesting that the company alter its TV ads for Ditropan XL. The drug is used to treat urinary incontinence or "overactive bladder." The agency said the ads understated the risk of certain side effects, particularly dry mouth.

Discussion

As highly visible as they are, there are still many unknowns about the impact of DTC drug ads — on prescribing trends, the public's health and drug costs. Consensus has emerged in the last year that more research is needed to measure and clarify this impact. Our results do not address the affect of DTC ads on the public's health. But they add to the growing circumstantial evidence that such ads are one element — and perhaps an increasingly important one — in the recent trend to the expanded use of newer prescription drugs and the resultant increased overall spending on pharmaceuticals.

Political pressure could build in the next year or two to put further requirements or restrictions on DTC ads — such as a requirement that they carry disclaimers or specific types of information. But definitive political action imposing additional requirements or limits on DTC ads could be thwarted by debate over the legality of such moves. Many legal analysts believe it will be difficult to put more restrictions on DTC ads due to the protected rights of companies to promote their products in a free society — now that the regulatory door to such ads have been opened.

The debate over DTC ads also comes amid heightened scrutiny of the pharmaceutical industry in general and Congress' consideration of a Medicare drug benefit. If analysis begins to emerge over the next year or two that DTC ads are leading to inappropriate prescriptions or are a prime cause of an inappropriate shift to newer drugs, Congress could look more seriously at how to minimize this affect.

In the meantime, DTC advertising is likely to continue to grow — subject to political and economic conditions in the nation. Drug companies will likely continue to experiment with innovative ways to promote their products, especially via the internet. Sponsorship of sporting events and concert

series, for example, could also increase. Pfizer in September 2001 sponsored the "Viagra Concert Series" — a national tour headlined by the band Earth, Wind and Fire.

Many DTC campaigns have been high profile and large in scope — with TV ads complemented by print and billboard ads. The industry may try more targeted ads in the future. For example, future drugs to treat Alzheimer's disease could be advertised selectively in publications purchased by older Americans. Likewise, drugs to treat obesity or curb appetite could be advertised on cable TV shows featuring exercise regimes.

DTC ads in the U.S. could also be coordinated more closely to worldwide campaigns — if barriers to DTC advertising fall in other countries. Currently only the U.S. and New Zealand permit DTC advertising. But Canada, Australia and all of Europe are watching the American "experiment." Proponents of DTC ads have begun to press their case in Canada, and the government is weighing changes in Canada's Food and Drugs Act.[19] The European Union is also debating a recommendation to EU members to permit DTC ads for drugs to treat a limited number of conditions. Asthma, AIDS and diabetes were on an initial list.[20]

The issues raised by DTC advertising are serious. They involve questions of public health, corporate responsibility, advertising ethics, and consumers' capacity to understand complex medical and pharmaceutical information. The ads and their impact warrant continued study and public policy attention.

Credits

Steven Findlay, MPH, director of research and policy at the NIHCM Foundation, wrote this report. Daniel Sherman, Ph.D., principal economist at the American Institutes for Research in Washington D.C., provided data analysis and chart preparation. Nancy Chockley, MBA, president of the NIHCM Foundation, edited the report. Jennifer Montoya of the NIHCM Foundation provided research assistance.

About the NIHCM Foundation

The National Institute for Health Care Management Research and Educational Foundation is a non-profit organization whose mission is to promote improvement in health care access, management and quality.

Relevant NIHCM Foundation Publications

- *Prescription Drug Expenditures in 2000: The Upward Trend Continues* — May 2001
- *Prescription Drugs and Mass Media Advertising* — September 2000
- *Prescription Drugs and Intellectual Property Protection: Finding the Right Balance Between Access and Innovation* — August 2000
- *Factors Affecting the Growth of Prescription Drug Expenditures* — July 1999

Notes

1. The National Institute for Health Care Management Foundation, *Prescription Drug Expenditures in 2000: The Upward Trend Continues* (May 2001). Available at www.nihcm.org.

2. Steven D. Findlay, "Direct-to-Consumer Promotion of Prescription Drugs: Economic Implications for Patients, Payers and Providers," *PharmacoEconomics*, Vol. 19. No 2 (February 2001), pages 109-119. Also see papers from a May 30, 2001 conference convened by the U.S. Department of Health and Human Services, "Assessing the Impact of DTC Advertising on Health Care Use, Costs, and Outcomes." Papers available at www.hsrnet.com/ASPE/991/papers.

3. Donald K. Cherry et al, National Ambulatory Medical Care Survey: 1999 Summary, (July 17, 2001), Advance Data Report No 322, National Center for Health Statistics/Centers for Disease Control. Available at www.cdc.gov/nchs.

4. All data are from IMS Health (Westport, Conn) and CMR, Inc, (New York), communicated to author from IMS Health on June 19, 2001.

5. "Meeting with Physicians," *Med Ad News* (November 2000), page 4. www.medadnews.com.

6. Physician Meeting and Event Audit, Scott Levin Inc. March 23, 2001 and May 2, 2001 press releases. www.scottlevin.com.

7. Figures were obtained from IMS Health. They include the retail value of samples in its data for promotional spending. We present DTC spending as a percentage of total promotional spending with and without the retail value of samples because the retail value is calculated; it is not real money spent. The actual costs to pharmaceutical companies of distributing such samples is far less than the calculated retail value of the drugs.

8. Data are from CMR, Inc. www.cmr.com. CMR tracks ad spending for all TV, radio, major mass marketed magazines, newspapers and billboards. Interpublic Group tracks total ad spending in all lines of media and promotion. Their estimate of overall ad spending in all media (including such outlets as the telephone yellow pages) for the year 2000 was $243.7 billion, as reported June 15, 2001 in *The Wall Street Journal* (Suzanne Vranica, "Ad Spending Growth is Forecast to Slow to 2.5% in 2001.")

9. All data from CMR, Inc. See note 8. These figures, as noted above, are primarily for national ad spending. They do not included some streams of promotional spending, such as sponsorship of sporting events.

10. Center for Drug Evaluation and Research, Food and Drug Administration, *Attitudes and Behaviors Associated with Direct-to-Consumer Promotion of Prescription Drugs*, (Spring 1999). Available at www.fda.gov/cder/ddmac/research.htm.

11. *Prevention*, Rodale Inc. *International Survey on Wellness and Consumer Reaction to DTC Advertising of Rx Drugs*, Vol. 1 (Winter 2001). Requests for information should be directed to Ed.Slaughter@rodale.com.

12. This was the general consensus of attendees at a government-sponsored conference, "Assessing the Impact of DTC Advertising on Health Care Use, Costs, and Outcomes," held May 30, 2001 in Washington D.C. Papers available at www.hsrnet.com/ASPE/991/papers.

13. Cherry et al as cited in note 3.

14. Frank Scussa, "Getting Noticed: The Future of Consumer Promotion is Being Challenged by Government Agencies and the Public," *Med Ad News* (June 2001): page 1. www.medadnews.com.

15. *Prescription Drug Expenditures in 2000: The Upward Trend Continues*. As cited in note 1.

16. Ibid.

17. "Abbott Shifts Meridia Marketing Focus from Consumer to Physicians," *The Pink Sheet, FDC Reports* (June 25, 2001), page 13.

18. As explained in the Methodology section, CMR Inc generated the list of 103. It cuts off at a DTC spend of $12,000. Some companies may have spent less than that on a handful of other drugs. We present data in Figures 4 and 5 for the top 50 drugs on this list.

19. Barbara Mintzes, *Pills, Persuasion and Public Health Policies: Report of an Expert Survey on Direct-to-Consumer Advertising of Prescription Drugs in Canada, the United States, and New Zealand*. A report from the Center for Health Services and Policy Research, University of British Columbia (June 2001).

20. Joseph Brown, "Brands without Borders," *Med Ad News*, (August 2001): page 1. www.medadnews.com.

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Exhibit 41

appeared to have a higher rate of cases, the side effect ppears to be class related.

"In the entire ezetimibe program, *Phase III*, there have been no cases of rhabdomyolysis," Scolnick said. The product will allow prescribers to stay within "the safe range for statins," he suggested.

Merck and Schering have a separate joint venture to develop a fixed combination of Merck's asthma agent ***Singulair*** and Schering's antihistamine ***Claritin***. During the Dec. 11 meeting, Merck did not highlight that aspect of the joint venture.

The Singulair/Claritin project was not formally discussed, and when asked to provide an update, Scolnick refused to comment beyond saying that clinical research is ongoing.

Schering's manufacturing difficulties may have more of an impact on that aspect of its agreements with Merck. Schering's top priority is gaining approval of the Claritin successor agent ***Clarinex*** (desloratadine).

Merck did present data on Singulair for allergic rhinitis, which the company is developing apart from the joint venture. Merck counts the line extension as one of its "breakthrough" projects in development.

Data presented by Merck during the meeting suggest that Singulair is as effective as Claritin in controlling nighttime symptoms of seasonal allergic rhinitis, but not as effective in daytime symptoms.

The company said it intends to file for the new indication in early 2002.

Merck does not expect that an OTC switch for Claritin or the other prescription antihistamines would affect Singulair. "Patients that suffer from allergic Rhinitis are dissatisfied patients," Merck President-Human Health Europe, Africa and the Middle East Per Wold-Olsen said.

"They seek new treatment opportunities. Even if some of the antihistamines would go OTC, they don't do the job, you go to see your doctor and seek better and alternative options. And we fundamentally believe that Singulair would have a lot to offer. Whether antihistamines go OTC or not shouldn't influence our ability to commercialize Singulair in allergic rhinitis." ♦♦

Merck COX-2 Cardiovascular Safety Studies Will Enroll 30,000 Subjects

Merck plans to enroll approximately 30,000 subjects in cardiovascular safety trials to resolve issues raised about the CV effects of its COX-2 inhibitors ***Vioxx*** (rofecoxib) and ***Arcoxia*** (etoricoxib).

Although a final protocol has not yet been completed, Merck expects to conduct separate event-driven studies for each product. Merck will compare Vioxx and Arcoxia's relative benefits to standard NSAIDs, and compare each CV profile to placebo.

Merck is conducting the outcome studies in response to cardiovascular safety concerns raised during the FDA Arthritis Advisory Committee's February review of the Vioxx VIGOR gastrointestinal safety trial ("The Pink Sheet" Feb. 12, p. 3).

During VIGOR, the incidence of myocardial infarctions was .5% for Vioxx and .1% for naproxen. Arcoxia trials indicate a similar MI incidence; a pivotal osteoarthritis trial had a 3.2% rate of thrombotic events for etoricoxib versus .8% for naproxen ("The Pink Sheet" Nov. 26, p. 9).

The comparator NSAIDs have not yet been chosen for the Vioxx and Arcoxia outcome studies. The multi-year studies are slated to commence in 2002 and Merck is expecting at least a 12-month patient follow-up.

Patients will be able to use concomitant aspirin during the trials, and Merck will track those patients versus non-aspirin users. VIGOR excluded patients on aspirin; the decision has been offered as one reason why the rate of CV events was higher in the Vioxx group.

The "lingering concerns" regarding Vioxx' potential safety effects "will not dissipate completely until we finish the cardiovascular outcomes studies," Merck Research Labs President Edward Scolnick, MD, told analysts during Merck's annual business update Dec. 11 in Whitehouse Station, N.J.

"It's understandable why some people have concerns about it, based on all the publicity that hit the newspapers a couple of months ago," Scolnick acknowledged. "Because of the questions that are there, we're going to do additional studies to allay those concerns."

Vioxx sales are tracking well below Merck's forecast for the year, and the company no longer believes it can grow earnings in 2002 *(see related story, p. 9)*.

Merck also is conducting CV surveillance in ongoing Vioxx trials, "some of the most important of which are placebo-controlled studies, especially in colon cancer,"

Scolnick said. By 2004, Merck will "accumulate 9,000 patient years of placebo-controlled data."

An FDA warning letter may have served as an added incentive to conduct a large cardio safety trial ("The Pink Sheet" Oct. 1, p. 22).

The Sept. 17 letter cited Merck for minimizing Vioxx' CV side effects in promotions. While Merck suggested that the VIGOR data reflect a cardioprotective effect of naproxen, FDA said another "reasonable explanation" is that "Vioxx may have pro-thrombotic properties."

Scolnick offered analysts a comprehensive defense on the difference in myocardial infarctions between Vioxx and naproxen in the VIGOR trial.

Scolnick acknowledged that a "possible explanation" is that Vioxx increased the rate of myocardial infarctions. However, he said, "you can't tell from the study, because you're dealing with a two-arm study when the rates are different."

He pointed to data from a thrombotic cardiovascular study comparing 25 mg rofecoxib and placebo in Alzheimer's patients. "We did not detect an increased rate of myocardial infarctions against placebo in an elderly, fragile patient population with underlying heart disease," he maintained.

Scolnick also superimposed the VIGOR data over an osteoporosis study using non-naproxen NSAIDs; the number of naproxen events fell below the NSAID curve. "That suggests strongly – not unambiguously proves – but suggests strongly that what happened in VIGOR is [that] naproxen lowered the rate" of MIs.

Merck is continuing to hold discussions with FDA over GI safety changes to the Vioxx label after receiving an "approvable" letter April 6. Merck expects the VIGOR data will be added to the clinical studies section rather than lead to an elimination of the GI warning.

While controversy surrounding an August *Journal of the American Medical Association* article caused a "dip" in Vioxx share, "growth has now resumed," Human Health/Americas President David Anstice said. The *JAMA* article suggested an adverse cardiovascular effect with COX-2s ("The Pink Sheet" Sept. 3, p. 3).

Vioxx' new prescription market share remains virtually even with Pfizer/Pharmacia's *Celebrex* (celecoxib). Vioxx reclaimed a slim edge in November, based on IMS Health's rolling four-week average ended Nov. 16, Merck said.

One reason for the rebound in Vioxx' share was the recent release of comparative data versus Endo's *Percocet* (oxycodone/acetaminophen), Merck said. Vioxx sales reps began distributing the data in October ("The Pink Sheet" Oct. 22, p. 30).

Merck is positioning the Vioxx follow-on Arcoxia as a COX-2 inhibitor that delivers "fast and sustained pain relief" with a 24-minute onset of action and 24-hour duration of action. Filings in osteoarthritis, rheumatoid arthritis, acute pain, chronic pain and dysmenorrhea were accepted by FDA in October.

"We have filed for a broad set of indications, and we expect to be approved for a broad set of indications," Scolnick declared. Pharmacia/Pfizer's follow-on COX-2 *Bextra* (valdecoxib) cleared FDA in November, but did not receive approval for an acute pain indication ("The Pink Sheet" Dec. 3, p. 23).

When asked if Merck expected to have the 24-minute onset of action in labeling, Anstice said: "That is our hope at this stage. Obviously, until the label is decided, we won't be able to confirm that, but that's what our clinical studies to date show us." Bextra and Vioxx are labeled for 60- and 45-minute onsets of action, respectively.

Merck showed analysts one slide of Arcoxia efficacy data from a chronic lower back pain trial. After 12 weeks, etoricoxib 60 mg patients reported a greater change from baseline in back pain intensity.

Regarding safety data, Arcoxia did show "tiny" dose-related increases in systolic blood pressure in the 60 mg and 90 mg doses, comparable to naproxen, Scolnick said. There was also "nothing serious going on" in hypertension and edema, he added.

Merck will market Vioxx and Arcoxia via two separate sales forces. "There are two enormous opportunities for each brand," Anstice said. "We think we will maximize each brand individually by having different sales people...supporting each of those brands."

Since Vioxx and Arcoxia have different metabolic pathways, they can be used by "incredibly diverse patient populations with very different pharmacogenetic backgrounds," Scolnick said.

One indication Merck will not be pursuing for Vioxx is Alzheimer's disease. Two of the three rofecoxib studies in Alzheimer's have been completed; "so far we've seen no evidence for efficacy," Scolnick said. "We are going to finish the third study – the design is a little different – but it's not a promising area right now." ♦♦

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Exhibit 42

To: Spritzler, Christine M.
From: Braunstein, Ned S.
Cc Goldmann, Bonnie J; Gertz, Barry J.; Reicin, Alise S.; Silverman, Robert E.
Bcc:
Date: 2002-01-21 17:06:02
Subject: VIOXX CV Document for Peter Kim

Christine,
Thanks for printing this and delivering to Dr. Kim.

Peter,
This draft incorporates comments from you, Doug, Ed, and Alan as well as comments from Bonnie, Barry, Alise, and Bob. Shaded text (yellow in the document, light grey when printed) shows text that changed from the version sent on Friday. Darker shaded text (green in the document) are the few references I need to get or other minor changes I need to do.

Thank you for reviewing on short notice.
Ned

Attachments:

CV Memo for FDA ManagementC1.doc

DRAFT

Executive Summary

This document provides a comprehensive review of the cardiovascular data from the rofecoxib development program as well as relevant preclinical, clinical pharmacology, and epidemiologic data. Information from the etoricoxib program is also included to complement and expand on the findings with rofecoxib. Part I of this document summarizes the data which are detailed in Part II. All of the data in this document have previously been submitted to FDA or are in the public domain.

As is evident from these studies, the field of eicosanoid biology is currently undergoing a period of rapid evolution. As in any changing field, there are many hypotheses being tested and consequently an element of uncertainty as to the significance of individual findings. In this setting, the observation in VIGOR of a difference in rates of thrombotic events [redacted], in the absence of a placebo control group, has led to several [redacted] as explanations:

A. A prothrombotic effect of selective COX-2 inhibitors as a class

B. Mechanism-based toxicity of rofecoxib greater than others in the class (eg: related to the degree of selectivity for COX-2)

C. Molecule-specific and non-mechanism-based toxicity of rofecoxib

D. Relative cardioprotective benefit of naproxen

As discussed in Part I and further documented in Part II, hypothesis D is [redacted] the various hypotheses proposed as explanations of the VIGOR results:

Hypothesis A: A prothrombotic effect of selective COX-2 inhibitors as a class

Evidence in favor

- First raised as a theoretical possibility by authors of clinical pharmacology experiments done with celecoxib and rofecoxib that show that selective COX-2 inhibitors partly inhibit the production of systemic prostacyclin and do not inhibit platelet thromboxane synthesis {1445, 1116}.
- [redacted]

REDACTED

Evidence against

- No difference in thrombotic events between rofecoxib and placebo in over 3000 patient-years of experience [redacted] (Rofecoxib Alzheimer's Disease Studies)
- No difference in thrombotic events between rofecoxib and the non-selective NSAIDs ibuprofen, diclofenac and nabumetone in over 3400 patient-years of experience [redacted] (Rofecoxib OA Phase IIb/III Studies)
- No difference in thrombotic events between celecoxib and the non-selective NSAIDs ibuprofen and diclofenac in CLASS [redacted]

REDACTED

[redacted]

Hypothesis B: Mechanism-based toxicity of rofecoxib greater than others in the class (eg: related to the degree of selectivity for COX-2 [redacted])

Evidence in favor

- Rofecoxib and etoricoxib have different pharmacokinetic properties as compared with celecoxib and valdecoxib.
- Celecoxib and valdecoxib clinical studies have been reported to show no differences in thrombotic events from any other NSAIDs (including naproxen).

Evidence against

[redacted]

- Despite differences in selectivity for COX-2 defined *in vitro* (etoricoxib>rofecoxib=valdecoxib>celecoxib) {1204}, none of the selective COX-2 inhibitors, when taken at their clinical doses, inhibit COX-1 *in vivo*. [redacted]
- [redacted] Rofecoxib (in the Phase IIb/III OA studies) and celecoxib (in the CLASS study) both demonstrated cardiovascular safety profiles based on investigator-reported events similar to ibuprofen and diclofenac. Thus, the premise that rofecoxib and celecoxib have intrinsically different cardiovascular safety profiles is not supported [redacted]
- MRL clinical data [redacted] acquired according to an SOP and are based on events confirmed by an outside panel of experts with access to source documentation. Pharmacia data are based on investigator reports. Investigator-reported data have greater noise than confirmed data and, in some MRL databases (eg: RA Phase IIb/III), are

discordant with confirmed data (ie: investigator reported events show no difference from naproxen whereas confirmed events show a difference).

- [redacted] Rofecoxib and etoricoxib databases that show a difference from naproxen contain several thousands of patients-years of exposure in naproxen studies; rofecoxib databases with less exposure show inconsistent findings against naproxen. Overall exposures in celecoxib and valdecoxib studies versus naproxen are less than rofecoxib and etoricoxib studies versus naproxen.

- [redacted]

- Identification of thrombotic events in SLE patients was noted on Celecoxib {1732}

Hypothesis C: Molecule-specific and non-mechanism-based toxicity of rofecoxib

Evidence in favor

- None

Evidence against

- Etoricoxib data on thrombotic events shows similar pattern of difference with naproxen as in rofecoxib data. Etoricoxib and rofecoxib have distinct molecular structures [redacted]

- No difference in thrombotic events between rofecoxib and placebo in over 3000 patient-years of experience in elderly patients not selected on the basis of arthritis (Rofecoxib Alzheimer's Disease Studies)

- See additional points in *Evidence Against* Hypothesis B

Hypothesis D : Relative Cardioprotective Benefit of Naproxen

Evidence in favor

- Clinical Pharmacology Studies:
  - Naproxen 500 mg twice daily provides near-maximal inhibition of platelet function that is sustained throughout the twice-daily dosing interval in accord with its long plasma half-life {1731}.
  - Ibuprofen, diclofenac, and nabumetone have less pronounced and/or less sustained antiplatelet effects {1731, 1882}.
  - Selective COX-2 inhibitors do not inhibit COX-1-mediated platelet aggregation {1445, 1731}
- Epidemiology Studies:
  - Several studies have demonstrated a relationship between the use of naproxen and reduction in CV outcomes {3076, 3081, 3083, 3079} (however, one study does not {3077}).

- VIGOR was conducted exclusively in patients with RA [redacted]. RA patients have an increased risk for coronary artery disease {1477, 1504, 1481, 3110}; the magnitude of the effect of anti-platelet drugs is higher in patients at highest risk for coronary artery disease {3096} [redacted] {1744}.

- Clinical studies (NSAIDs)
  - Clinical studies with flurbiprofen and indobufen serve as evidence that reversible but highly effective COX-1 inhibitors can be cardioprotective {1471, 1410, 1503, 1505}.
- Clinical studies (rofecoxib)
  - Alzheimer's disease studies and OA Phase IIb/III Studies with rofecoxib do not demonstrate a difference in thrombotic events between rofecoxib and placebo or between rofecoxib and the non-naproxen-NSAIDs studied.
  - Ninety-five percent confidence interval for the "reduction" in risk of thrombotic events by naproxen in VIGOR contains the average effect for aspirin reported in a large meta-analysis of anti-thrombotic trials {3096}.

Hypothesis D : Relative Cardioprotective Benefit of Naproxen (cont.)

Evidence Against

- Magnitude of the effect for naproxen is larger than the average effect for aspirin reported in a large meta-analysis of anti-thrombotic trials {3096}.
- There is no prospectively defined cardiovascular outcomes study that shows that naproxen can provide cardioprotective benefit.

Part I – Overview

Clinical Pharmacology of NSAIDs With Respect to Platelet Thromboxane and Systemic Prostacyclin Inhibition and Preclinical Data With Respect to Cardiovascular Effects

The relationship between the platelet and the vascular endothelium is delicate and provides a balance between inhibiting platelet aggregation in healthy tissue and facilitating aggregation after vessel injury. Both prostacyclin (PGI_2) produced by the endothelium and thromboxane (TxA_2) produced by the platelets, are among the factors that participate in this balance.

[redacted]

Platelets contain predominantly, if not exclusively, the COX-1 enzyme; in the absence of nuclei in platelets there can be no induction of COX-2 enzyme synthesis. TxA_2, the major COX-1 product of arachidonic acid metabolism in platelets, causes irreversible platelet aggregation, vasoconstriction and smooth muscle proliferation {3092}. TxA_2 production is important for hemostasis. However, in pathologic situations, such as with a ruptured atherosclerotic plaque, platelet aggregation can produce a vascular thrombosis.

The sustained inhibition of COX-1 mediated thromboxane synthesis in platelets underlies the efficacy of aspirin in significantly reducing the incidence of cardiovascular death, myocardial infarction, and stroke in high-risk patients {1507, 1061, 1059, 1061}. By virtue of covalent acetylation of the COX-1 enzyme, aspirin produces irreversible inhibition of platelet COX-1 even at low doses (81-325 mg/day). This inhibition is extensive (>90%), cumulative, and sustained for the life of the platelets {1731}. In contrast to aspirin, non-selective NSAIDs are reversible inhibitors of COX-1; the extent and duration of inhibition reflects both the potency of the drug as an inhibitor of COX-1 and the systemic plasma drug concentrations {1731}. Thus, the ability of the non-selective NSAIDs to provide sustained inhibition of platelet COX-1 is a function of intrinsic potency, concentration achieved, and plasma pharmacokinetics across the dosing interval.

Whether reversible inhibitors of COX-1 could act as cardioprotective agents has been a matter of debate. {3084}. Naproxen is among the few nonselective NSAIDs with potent antiplatelet effects that are sustained throughout the twice-daily dosing interval in accord with its long plasma half-life {1731}. Ibuprofen, diclofenac, and nabumetone have less pronounced and/or less sustained antiplatelet effects {1731}. Selective COX-2 inhibitors do not inhibit COX-1-mediated platelet aggregation {1445, 1731}.

These clinical pharmacology data, discussed in greater detail in Part II – Section 1, support the possibility that certain nonselective NSAIDs such as naproxen with both potent and sustained antiplatelet effects might provide aspirin-like protection from thrombotic cardiovascular events and could result in a lower incidence of thrombotic cardiovascular serious adverse experiences as compared with the selective COX-2 inhibitors.

[redacted]

In contrast to the well-recognized effects of NSAIDs on platelet[redacted], the influences of NSAIDs on the endothelium have not been as well characterized. [redacted]

[redacted] PGI_2 is a physiologic counter-regulatory influence to platelet-derived thromboxane. Based on older studies involving vascular tissue, isolated cells, and immunohistochemistry, COX-1 was thought to be the cyclooxygenase isoenzyme controlling systemic, presumably vascular endothelial, prostacyclin synthesis {[redacted]}. However, during the rofecoxib and celecoxib development programs, the surprising discovery was made that these selective COX-2 inhibitors reduced the urinary excretion of a major metabolite (2,3 dinor 6 keto $PGF_{1\alpha}$ [PGI-M]) of prostacyclin {1445, 1116}. This finding has been interpreted as a direct effect of COX-2 inhibition on systemic prostacyclin synthesis {1445}. Rofecoxib, celecoxib, and the non-selective NSAIDs that were studied all produced similar, 50-60% reductions in prostacyclin synthesis (as measured by urinary excretion of PGI-M) {1445,1116} (See Part II – Section 1). It is unclear why the selective inhibition of COX-2 and the nonselective inhibition of both COX-1 and COX-2 should result in similar levels of inhibition of PGI-M if the urinary excretion of PGI-M quantitatively reflects the [redacted] synthesis of [redacted] prostacyclin. [redacted]

Despite the uncertainty as to the cellular source of the PGI-M measured in these experiments, McAdam *et al.* proposed the theoretical possibility that a selective COX-2 inhibitor might alter the balance between [redacted] prostacyclin and platelet thromboxane and might be prothrombotic. However, if this hypothesis is correct for selective COX-2 inhibitors, it would also likely apply to nonselective NSAIDs (eg: ibuprofen and diclofenac) that inhibit PGI-M but do not provide sustained and near-maximal antiplatelet effects throughout their dosing interval. Moreover, the clinical importance of this 60% reduction in systemic prostacyclin synthesis is in fact not known; there is no direct evidence that the degree of inhibition of [redacted] PGI_2 synthesis reported with these compounds would overwhelm the ability of endothelial-derived [redacted] prostacyclin to prevent the formation of a platelet thrombus. This system is reported to have enormous reserve; Jaffe and Weksler calculate that even with 90% inhibition of PGI_2 synthesis, there is sufficient prostacyclin to prevent platelet aggregation *in vivo* {3086}. While the complete absence of the prostacyclin receptor produces a mouse with a propensity for thrombosis following vascular injury, the effect in a heterozygote is not known {3087}. The clinical impact of alterations in cyclooxygenase mediated platelet-endothelial interactions is further complicated by the fact that the endothelium also produces other potent antiplatelet factors, the most well-known of which is nitric oxide {3093}, which does not depend on cyclooxygenase. This redundancy in the system to prevent aggregation may minimize the importance of any single factor. Nonetheless, such findings could have important implications for the use of selective COX-2 inhibitors in patients at risk for a thrombotic cardiovascular event[redacted].

The effects on platelet aggregation and prostacyclin/thromboxane balance are not the only influences that COX-2 expression may have on cardiovascular health. Over the past decade, our understanding of atherogenesis has evolved from one of occlusive lipid accumulation to one of chronic inflammation involving cellular proliferation {3085,3088}. In both animal models and human tissue, COX-2 expression has been found in each of the cell types (endothelial,

monocyte/macrophage, and vascular smooth muscles cells) involved in atheromatous plaque generation {3090,3091,1735}. Similarly, COX-2 can be induced in these cells by many, if not all, of the same pro-inflammatory mediators implicated in the development of atherosclerosis [redacted] {3088,3091[redacted]}.

[redacted]

The current body of preclinical animal studies with a variety of COX-2 inhibitors or knock out animals are inconsistent [redacted] COX-2 inhibition and cardiovascular effects. Assessments of COX-2 inhibition [redacted]) or deletion in myocardial ischemic-reperfusion injury (MI-RI) studies have yielded inconsistent and potentially conflicting results {3097, 3098, 3099, 3100, 3101, 3102, 3103}. [redacted].

NSAID-aspirin Interactions

[redacted] Rofecoxib did not interfere with aspirin in these studies, confirming the earlier work at Merck {1733}. The authors raised the question whether patients receiving such non-selective NSAIDs would receive adequate cardioprotection when ibuprofen and aspirin are co-administered. *In vitro* work suggests this effect may extend beyond ibuprofen {2996}. Such findings would have important implications for the concomitant use of aspirin with nonselective NSAIDs in patients at risk for thrombotic cardiovascular events and might suggest that selective COX-2 inhibitors [redacted] the preferred agents to use in patients who need both an NSAID and low-dose aspirin.

As is evident from these studies, the field of eicosanoid biology is currently undergoing a period of rapid evolution, in part due to the availability of selective COX-2 inhibitors as tools. At the same time, there are emerging clinical data on the use of selective COX-2 inhibitors in humans. As in any changing field, there are many hypotheses being tested and consequently an element of uncertainty as to the significance of individual findings.

Clinical Data on Thrombotic Cardiovascular Safety with Rofecoxib

Phase IIb/III OA Studies with Rofecoxib

An analysis of [redacted] cardiovascular safety outcomes in the Phase IIb/III OA program was presented at the 1999 Advisory Committee Meeting for rofecoxib [redacted] taking rofecoxib or the comparator nonselective COX-1/COX-2 inhibitors ibuprofen, diclofenac, or nabumetone (and not taking low-dose aspirin) had similar incidences of thrombotic cardiovascular serious adverse experiences (only Protocol 058, a study of 341 patients 80 years or older, included patients who used low-dose aspirin, 70 of whom were in the rofecoxib group). The Phase IIb/III OA data [redacted] consists of over 4900 patients treated over a period of ~3400 patient-years. The updated data continue to show a similar incidence of thrombotic cardiovascular serious adverse experiences in patients taking rofecoxib (49 of 3358 patients had events reported by investigators as potential thrombotic cardiovascular serious adverse experiences; rate = 2.07 per 100 patient years) compared with the non-selective NSAIDs (21 out of 1565 patients had events; rate = 2.05 per 100 patient-years).

Initiation of Adjudication Procedures for CV Events – SOP Rationale and History

[redacted] a Cardiovascular Adjudication Standard Operating Procedure (Adjudication SOP) [redacted] in the second quarter 1998 (more than a year prior to the initiation of VIGOR) to further evaluate whether there were any differences in the incidence of these events during chronic therapy with rofecoxib versus nonselective NSAIDs or placebo. The purpose of the Adjudication SOP was: [redacted] to standardize the evaluation of thrombotic cardiovascular serious adverse experiences across ongoing clinical studies of rofecoxib; and [redacted] to improve accuracy in diagnosis across a heterogeneous group of study investigators in different nations and having different clinical specialties. A description of the Adjudication SOP and the procedures involved is in Part II – Section 2 and a description of the different endpoints is in Part II – Section 3. The analysis of cardiovascular outcomes in trials of rofecoxib as described in the Adjudication SOP did not envision a separate analysis of individual trials. Individual trials would likely be underpowered with respect to subgroup and exploratory analyses necessary to understand any observed differences in event rates. Instead, the SOP was designed to examine the combined incidence of cardiovascular outcomes across a broad range of patients in all post-Phase III OA trials of rofecoxib initiated by or after the second quarter 1998. However, based on a request from the VIGOR Data Safety Monitoring Board, a separate analysis of thrombotic cardiovascular serious adverse experiences in VIGOR was performed.

Cardiovascular Results of VIGOR

The Vioxx GI Outcomes Research Study (VIGOR) was designed primarily to assess the GI safety of rofecoxib versus naproxen. Over 8000 patients [redacted] were randomized. Median duration of exposure was 9 months. Total exposure was ~2700 patient-years in each group. The cardiovascular results of VIGOR are presented in Part II – Section 4. In VIGOR, 45 of 4047 patients taking rofecoxib had confirmed thrombotic cardiovascular serious adverse experiences (rate = 1.67 per 100 patient years) whereas 19 of 4029 patients taking naproxen had confirmed thrombotic cardiovascular serious adverse experiences (rate = 0.70 per 100 patient years). The relative risk, 2.37 for rofecoxib compared to naproxen, was statistically

significant (p=0.002) This difference was mostly attributable to a difference in the incidence of myocardial infarction (MI) between the groups.

Exploratory analyses did not identify particular subgroups of patients with relative risks that were significantly different from the entire cohort. As one might have expected, the absolute incidence of CV events was increased in patients with traditional risk factors for cardiovascular disease. In particular, 4% of the patients in VIGOR had a previous history of symptomatic cardiovascular disease retrospectively identified (and therefore an indication at study entry for concomitant use of low-dose aspirin for cardioprotection). A total of 28% of CV events occurred in this subgroup of patients. There was no treatment-by-subgroup interaction for thrombotic events (p=0.177) in the subgroups of patients with or without an indication for aspirin. However, consistent with the higher overall incidence of events in the aspirin-indicated subgroup, the numeric difference between rofecoxib and naproxen in the incidence of CV events was greater in patients with an indication for aspirin therapy that in patients without this indication for aspirin. Furthermore, there was no correlation in VIGOR between patients who experienced hypertension adverse experiences or blood pressure elevations and patients who had thrombotic cardiovascular serious adverse experiences. Moreover, there was no significant difference in overall mortality or cardiovascular mortality between the rofecoxib and naproxen groups. [See Section 10 for a complete discussion of mortality in the rofecoxib and etoricoxib programs.] Analyses based on investigator-reported events or using the Antiplatelet Trialists' Collaboration (APTC) combined endpoint (defined in Part II – Section 3) yielded consistent results.

[redacted] APTC combined endpoint for the VIGOR data allows one to compare the effect size in VIGOR with the effects of antiplatelet drugs reported in a large meta-analysis {3096} and thus determine if it is reasonable to hypothesize an antiplatelet and therefore cardioprotective effect of naproxen in VIGOR. The risk reduction for the APTC combined endpoint in the meta-analysis of antiplatelet drugs was 25% (overall combined data). The "risk reduction" and 95% CI of the APTC combined endpoint for naproxen versus rofecoxib was 49% (95% CI: 9, 71%). Although the point estimate for "risk reduction" in VIGOR is greater than in the meta-analysis, the meta-analysis result is within the 95% CI of the VIGOR result.

Recent studies have suggested that aspirin has a larger relative benefit in higher risk patients defined either by levels of C-reactive protein (CRP) {1744} or as defined clinically {3096}. In the Physician's Health Study, the risk reduction for myocardial infarction ranged from 13.9% in the quartile of patients with the lowest level of CRP to 55.7% in the quartile with the highest CRP levels {1744}. In the antiplatelet drugs meta-analysis, a greater risk reduction was seen in higher risk patients (37% reduction of the APTC combined endpoint in patients with coronary artery disease and ~50% reduction in patients with unstable angina or post-angioplasty) {3096}. The patients in VIGOR all had RA, RA patients generally have higher CRP levels than patients without inflammatory disease, and RA patients have an increased risk of coronary artery disease and are a recognized high risk group for coronary artery disease {1477, 1504, 1481}.

Thus, the results in VIGOR were thought to be consistent with an antiplatelet and therefore cardioprotective effect of naproxen. However, whether the difference in the incidence of thrombotic cardiovascular serious adverse experiences between the rofecoxib and naproxen groups in VIGOR represented a relative cardioprotective effect due to inhibition of platelet

function by naproxen or a prothrombotic effect of rofecoxib could not be determined by the evaluation of the VIGOR results in isolation. As discussed above, no difference was seen in the incidence of thrombotic cardiovascular serious adverse experiences (in general) or myocardial infarction (in particular) between rofecoxib and the non-naproxen, nonselective NSAIDs studied in the Phase IIb/III OA studies (see Part II – Section 5). A review of other rofecoxib studies was undertaken.

Comparison Between Rofecoxib and Placebo – Data from the Alzheimer's Disease Program

To assess whether the risk of thrombotic cardiovascular events with rofecoxib differs from placebo, an analysis of thrombotic cardiovascular serious adverse experiences was performed on data from 2 recently completed and 1 ongoing placebo-controlled trials of rofecoxib in elderly patients with early Alzheimer's Disease. Patients were to be excluded from enrollment in these studies if they either were taking or had an indication for low-dose aspirin at baseline. However, because these patients are elderly and may be at risk for atherosclerotic cardiovascular disease complications, patients were allowed to initiate therapy with aspirin or clopidogrel during the study period if the investigator determined that it was indicated. [See Part II – Section 6 for details on aspirin usage in these studies.] The data from the Alzheimer's Disease studies indicate, despite the high rate of events in these elderly, susceptible individuals, that the incidence of confirmed thrombotic cardiovascular serious adverse experiences is similar in patients taking rofecoxib (25 of 1448 patients had confirmed events; rate = 1.71 per 100 patient years) or placebo (39 of 1451 patients had confirmed events; rate = 2.39 per 100 patient years) (Part II – Section 6). Analyses based on investigator-reported events, using the [redacted] APTC combined endpoint, [redacted] comparing the incidence of myocardial infarction also yielded similar results: that is, no evidence of an increased incidence on rofecoxib compared with placebo.

Other Rofecoxib Studies – Phase IIb/III RA Program and ADVANTAGE trial

Additional data obtained since the VIGOR trial on the incidence of thrombotic cardiovascular serious adverse experiences for rofecoxib versus naproxen are available from the Phase IIb/III RA development program (Part II – Section 7) and from the ADVANTAGE study in OA patients (Part II – Section 8). In the RA program in which there were ~2100 patient-years of exposure to rofecoxib or naproxen, the data demonstrate a difference between rofecoxib and naproxen that was consistent with the VIGOR results. Thrombotic cardiovascular serious adverse experiences occurred in 28 patients in the rofecoxib group (1643 patient-years at risk; rate = 1.70 per 100 patient-years) and 6 patients in the naproxen group (522 patient-years at risk; rate = 1.15 per 100 patient-years). Aspirin use in the RA program was limited; overall, there were only 65 patients who used low-dose aspirin both at baseline and also concomitantly during studies. ADVANTAGE was a 12-week study comparing rofecoxib 25 mg to naproxen 1000 mg daily in OA patients (N=5557). Patients taking low-dose aspirin were allowed to enroll in ADVANTAGE and approximately 13% of patients were low-dose aspirin users. In ADVANTAGE, there was no consistent difference in the overall incidence of thrombotic cardiovascular serious adverse experiences between the 2 groups. There were 9 patients with confirmed thrombotic cardiovascular serious adverse experiences in the rofecoxib group (640 patient-years at risk; rate = 1.41 per 100 patients-years) and 12 in the naproxen group (629 patient-years at risk; rate = 1.91 per 100 patient-years). Although the overall incidence of thrombotic events was similar between the groups, there were imbalances in individual types of events. In ADVANTAGE, there were 5 confirmed myocardial infarction in the rofecoxib group

and 1 in the naproxen group. There was 1 confirmed ischemic stroke in the rofecoxib group and 6 in the naproxen group. The relatively small databases from these 2 studies limit the ability to draw conclusions.

Pooled-analysis of Cardiovascular Outcomes in the Rofecoxib Program

As discussed above, the Adjudication SOP provided for a [redacted], combined analysis of thrombotic events to provide a global assessment of cardiovascular outcomes in the rofecoxib clinical program. Such a pooled-analysis of all relevant ongoing and completed studies of rofecoxib was performed on data available in September-2000 {2919}[provided as Attachment #1]. The focus of the pooled-analysis was to improve precision in the estimate of relative risks for the development of a cardiovascular serious adverse experience between rofecoxib and naproxen, rofecoxib and placebo, and rofecoxib and non-naproxen nonselective NSAIDs, and to determine if the conclusions from the individual studies described above (VIGOR, OA Phase IIb/III, Alzheimer's Disease) would be either altered or strengthened by inclusion of all relevant data. The pooled-analysis utilized data on the APTC combined endpoint to mirror the approach taken in the other published meta-analysis of cardiovascular outcomes trials.

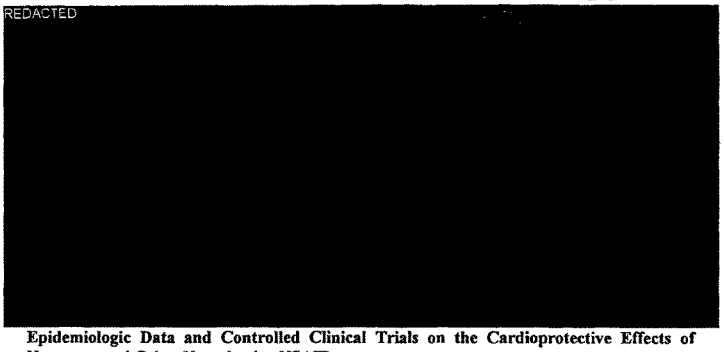
The results of the pooled-analysis fully support the results of each of the large programs described above. The relative risk of an APTC combined endpoint event for rofecoxib with respect to naproxen was 1.69 (95% CI 1.07, 2.69). The relative risk of an APTC combined endpoint event for rofecoxib with respect to placebo was 0.84 (95% CI 0.51, 1.38). The relative risk of an APTC combined endpoint event for rofecoxib with respect to the non-naproxen NSAIDs studied (ibuprofen, diclofenac, or nabumetone) was 0.79 (95% CI 0.40, 1.55) {2919}[provided as Attachment #1].

Several subanalyses were performed. The analysis was repeated in the subgroup of patients at high risk for cardiovascular thrombotic events (defined as either ≥2 major risk factors for coronary artery disease or a history of a prior symptomatic cardiovascular disease.). The results were highly consistent with the primary analysis. To ensure that studies of short duration did not unduly influence these results, the analyses were repeated using studies ≥6 months duration and again yielded results consistent with the primary analysis. Finally, attempts to identify dose-related trends for rofecoxib yielded risks for each dose that varied in an inconsistent way {2919}[provided as Attachment #1]. Some of the studies in the pooled-analysis allowed the use of aspirin/clopidogrel. A sensitivity analysis described in the initial report of the pooled-analysis sent to FDA and conducted only in patients who were not taking aspirin/clopidogrel prior to study start also provided results consistent with the primary analysis. The July-2001 update to the pooled-analysis provided results consistent with these. The pooled-analysis is a prespecified ongoing project; the results will be periodically updated as additional sets of data become unblinded.

Use of Rofecoxib with Low-Dose Aspirin

Rofecoxib has been used concomitantly with low-dose aspirin in over 500 patients in the completed nabumetone studies (Protocols 058, 085, and 090) and ADVANTAGE study (Protocol 102). In addition, cardiovascular data on aspirin users in the Alzheimer's Disease program has been provided to the Agency. No consistent differences in adverse experience profiles have been observed between the groups of patients taking rofecoxib with or without low-dose aspirin. In the nabumetone studies (Protocols 058, 085 and 090), there was 1 APTC combined endpoint event in 161 patients taking rofecoxib with low-dose aspirin and 1 in 141

patients taking nabumetone with low-dose aspirin. In ADVANTAGE, there were 3 APTC endpoint events in 352 patients taking rofecoxib with low-dose aspirin and 0 events in 367 patients taking naproxen with low-dose aspirin. In the Alzheimer's Disease studies, based on the September-2000 dataset used for the pooled-analysis, there was 1 APTC event in 108 patients taking rofecoxib with low-dose aspirin and 4 events in 92 patients taking placebo with low-dose aspirin. Although the data are sparse with regard to cardiovascular (or GI) outcomes when rofecoxib and aspirin are used concomitantly, as discussed above, rofecoxib has been shown in biochemical studies {2996} and in clinical pharmacology studies {1733, 3060} not to interfere with the antiplatelet effects of aspirin. In contrast, nonselective NSAIDs such as ibuprofen, as noted above, have been shown to interfere with the antiplatelet effects of aspirin {[redacted]}.



Epidemiologic Data and Controlled Clinical Trials on the Cardioprotective Effects of Naproxen and Other Nonselective NSAIDs

Whether reversible inhibitors of COX-1 could act as cardioprotective agents has been a matter of debate. {3084}. Studies that investigated the non-aspirin NSAIDs as a class have mostly shown no relationship between exposure and cardiovascular outcome {3074, 3079, 3080, 3082, 3077}, although [redacted] retrospective analysis of clinical trials data identified a trend that the authors found compelling {3078}. Data on the effects of individual NSAIDs are more limited. For naproxen, [redacted] studies showed a relationship between the use of naproxen and a reduction in cardiovascular outcome {3076, 3081, 3083}, [redacted] identified a trend in favor of naproxen {3079}, and [redacted] showed no effect of naproxen {3077}. [redacted]

Furthermore, two other reversible inhibitors of COX-1 with both potent and sustained antiplatelet effects have been studied in randomized clinical trials. Flurbiprofen 50 mg twice daily has been shown to reduce the incidence of recurrent myocardial infarction by 70% compared to placebo {1471}. Indobufen {1410} was shown to be similar to aspirin in preventing saphenous vein graft occlusion in patients undergoing cardiac bypass graft surgery {1503} and to significantly reduce, compared to placebo, thrombotic events in patients with atrial fibrillation or ischemic heart disease {1505}.

The data on naproxen, flurbiprofen, and indobufen suggest that reversible nonselective COX-1/COX-2 inhibitors with both potent and sustained antiplatelet effects can demonstrate vascular-protective properties similar to those observed with aspirin and support the hypothesis that, in VIGOR, naproxen provided a cardioprotective benefit.

Discussion and Conclusions

The observation in VIGOR of a difference in the rates of thrombotic events between rofecoxib and naproxen, in the absence of a placebo control group, has led to several hypotheses as explanations:

A. A prothrombotic effect of selective COX-2 inhibitors as a class

B. Mechanism-based toxicity of rofecoxib greater than others in the class (eg: related to the degree of selectivity for COX-2)

C. Molecule-specific and non-mechanism-based toxicity of rofecoxib

D. Relative cardioprotective benefit of naproxen

Although the data support the concept in Hypothesis A that the difference from naproxen in the relative risk of thrombotic events is common to all members of the class of selective COX-2 inhibitors, the data do not support the proposition that this difference is a prothrombotic effect of the class. Instead, the clinical pharmacology data suggest that such a "class effect" is most likely that the selective COX-2 inhibitors all lack anti-platelet activity [redacted] Hypothesis D is most consistent with the totality of the data.

Hypothesis A: A prothrombotic effect of selective COX-2 inhibitors as a class

This hypothesis was originally proposed by the authors of some of the preclinical and clinical pharmacology studies referred to in this document. [redacted] Although the preclinical data are inconsistent [redacted] COX-2 inhibition and cardiovascular effects, the homozygous prostacyclin receptor deletion-mutant (knock-out) mouse has increased propensity for thrombosis and atherosclerosis, indicating that the complete inhibition of systemic prostacyclin synthesis could be prothrombotic. [redacted] Thus, Hypothesis A has engendered a lot of scientific interest. [redacted]

Importantly, the clinical data [redacted] to a prothrombotic effect of the selective COX-2 inhibitors. The finding that there are similar rates of thrombotic events in elderly patients taking rofecoxib and placebo in over 3000

patient-years of experience in the Alzheimer's disease studies provides strong evidence against a prothrombotic effect of the class. [redacted] The overall number of cardiovascular events in each of these databases is similar to that in the VIGOR dataset; therefore, if the VIGOR results were consistent with a prothrombotic effect of rofecoxib (ie, a 2.5 increase in incidence), it is highly unlikely that this signal would have been missed in both the Alzheimer's Disease and OA databases. In the etoricoxib program, based on limited data, there was no discernible difference in the rates of thrombotic cardiovascular serious adverse experiences in patients taking etoricoxib or placebo. Furthermore, in the CLASS study, there was no difference in thrombotic events between celecoxib and the non-selective NSAIDs ibuprofen and diclofenac. Thus, the clinical data argue against a prothrombotic effect of the class.

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Hypothesis B: Mechanism-based toxicity of rofecoxib greater than others in the class (eg: related to the degree of selectivity for COX-2)

This hypothesis implies that only certain selective COX-2 inhibitors would show a difference from naproxen; ie, the more selective an agent the more likely it would be to demonstrate prothrombotic effects. In favor of this hypothesis is the observation that the celecoxib and valdecoxib clinical studies have been reported to show no differences in thrombotic events from any other NSAIDs (including naproxen) whereas the rofecoxib and etoricoxib programs show a difference from naproxen. In *in vitro* assays, etoricoxib is the most selective agent, followed by valdecoxib and rofecoxib which have similar selectivity, and finally by celebrex which is the least selective. However, despite these differences in selectivity *in vitro*, none of the selective COX-2 inhibitors inhibit COX-1 *ex vivo* at their clinical doses. Thus greater selectivity demonstrated in *in vitro* assays would only be relevant at doses higher than those used therapeutically. [redacted]

Etoricoxib and rofecoxib [redacted] Moreover, there was no correlation between the incidence of mechanism-

based renal-vascular adverse experiences (ie, edema and hypertension) and thrombotic cardiovascular adverse experiences in VIGOR or in the etoricoxib program. Thus, the data do not support a mechanism-based difference between rofecoxib and celecoxib that would support a difference in cardiovascular safety.

With regard to the clinical data, the rofecoxib and etoricoxib programs provide the most patient-years of experience for comparing a selective COX-2 inhibitor with naproxen. Although individual studies [redacted] of short duration may not reveal a difference in thrombotic cardiovascular serious adverse experiences with naproxen, a difference is readily demonstrable when the database of events is sufficiently large. Moreover, the presence of a prospectively-defined Adjudication SOP has ensured the collection of high quality data that are handled using standardized procedures and that are amenable to analysis. The lack of comparable data with other COX-2 selective inhibitors [redacted]. Indeed, the rofecoxib Phase IIb/III OA studies and the celecoxib CLASS study both demonstrated cardiovascular safety profiles of investigator reported events similar between each of the selective COX-2 inhibitors and the nonselective NSAIDs studied (ibuprofen, diclofenac, and nabumetone). [redacted] a difference in cardiovascular safety amongst the selective COX-2 inhibitors is not compelling.

Hypothesis C: Molecule-specific and non-mechanism-based toxicity of rofecoxib

This hypothesis [redacted] the demonstration in the etoricoxib program of a similar difference from naproxen as was first observed with rofecoxib in VIGOR. Etoricoxib and rofecoxib have distinct chemical structures and differ from each other to the same extent as they differ from celecoxib and valdecoxib. Thus, the clinical data along with the structural data directly refute this hypothesis. Hypothesis C is also inconsistent with the clinical pharmacology and preclinical studies that have been done with celecoxib and rofecoxib. [redacted] The similar cardiovascular safety profiles versus ibuprofen and diclofenac seen in the rofecoxib OA studies and the celecoxib CLASS, and the placebo-controlled data from the rofecoxib Alzheimer's Disease program [redacted]. Thus, the hypothesis that the cardiovascular observation in VIGOR was due to a molecular-specific, non-mechanism-based toxicity seems [redacted].

Hypothesis D : Relative Cardioprotective Benefit of Naproxen

The totality of the data are most consistent with this hypothesis [redacted] in the rofecoxib and etoricoxib clinical trials. Clinical pharmacology and epidemiologic data are consistent with the hypothesis that naproxen can provide a cardioprotective benefit and the data on flurbiprofen and indobufen serve as evidence that other reversible but highly effective COX-1 inhibitors can be cardioprotective. In contrast to naproxen, the nonselective NSAIDs ibuprofen, diclofenac, and nabumetone (and others) do not provide potent and sustained antiplatelet effects throughout their dosing interval and epidemiologic studies do not support a cardioprotective effect of these agents. In contrast to these agents, selective COX-2 inhibitors do not inhibit COX-1-mediated platelet aggregation within their clinical dose range. Thus, it is reasonable to hypothesize a relative cardioprotective benefit of naproxen with respect to the selective COX-2 inhibitors.

Although the magnitude of a proposed cardioprotective effect of naproxen in VIGOR was larger than the average effect of aspirin reported in a large meta-analysis of anti-thrombotic trials, the average effect of aspirin in the meta-analysis result is within the 95% CI of the VIGOR result. [redacted] Moreover, VIGOR was conducted in patients with RA, a chronic inflammatory disease [redacted] RA patients have an increased risk of coronary artery disease, and the magnitude of the effect of antiplatelet drugs [redacted] higher in patients at increased risk for coronary artery disease and in patients with elevated CRP. Finally, the lack of difference between rofecoxib and placebo in the Alzheimer's studies and between rofecoxib and the non-selective NSAIDs studied (ibuprofen, diclofenac, and nabumetone) in the Phase IIb/III OA studies argue against a clinically important prothrombotic effect of rofecoxib [redacted].

Thus, in VIGOR and in the etoricoxib program, the totality of the data is most consistent with naproxen having provided a relative cardioprotective benefit and argue against a prothrombotic effect of rofecoxib or etoricoxib. To confirm and extend the results and conclusions drawn from the current databases, MRL is committed to conducting further cardiovascular studies. Protocol development is currently in progress and we look forward to discussing these proposals with the agency in the near future.

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Part II — Data

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1. Clinical Pharmacology Data

1.1 The Effects of Aspirin, Selective COX-2 Inhibitors, and Nonselective NSAIDs on Platelet Thromboxane Metabolism and Function

Cyclooxygenase and its prostanoid products have important roles in hemostasis. [redacted]

Serum thromboxane A_2 (TXA_2), largely a product of platelet COX-1, is a vasoconstrictor and promotor of platelet aggregation. Aspirin, a well recognized antiplatelet agent and inhibitor of platelet TXA_2 synthesis, is effective in decreasing the risk of cardiovascular thrombotic events in patients at risk for such events. Aspirin's antiplatelet effect is mediated through its near complete, irreversible inhibition of platelet COX-1 activity. Even low-dose aspirin (≥81 mg/day) achieves nearly complete inhibition of platelet TXA_2 production. This effect on platelets is irreversible because these nonnucleated cells cannot replace the COX-1 enzyme that is permanently acetylated and inactivated by aspirin.

It is thought that, to serve as a vascular-protective agent, near-complete inhibition of TXA_2 synthesis sustained over time is needed {585}. The effect of chronic therapy with non-aspirin COX-1/COX-2 inhibitors (the nonselective NSAIDs) on the incidence of cardiovascular thrombotic events has not been well characterized. Although nonselective NSAIDs inhibit platelet COX-1 activity, this inhibition is reversible. Thus, the ability of a nonselective NSAID to provide potent and sustained antiplatelet effects that mimic aspirin's antiplatelet properties (and thus potentially to effect aspirin-like vascular-protection) is highly dependent on the unique COX-1/COX-2 potency and pharmacokinetic profiles of each of these compounds. In contrast to the nonselective NSAIDs or aspirin, COX-2 selective inhibitors such as celecoxib and rofecoxib do not have these platelet inhibitory effects because platelets do not express COX-2.

Several studies have demonstrated that the nonselective COX-1/COX-2 inhibitors vary in the magnitude and time course of their effects on platelet function. These studies evaluated the effects of the NSAIDs on prostaglandin metabolism and platelet aggregation in normal subjects. TXA_2 and PGI_2 synthesis were monitored by measuring their stable metabolites, serum TXB_2 generated in clotted whole blood and urinary PGI-M (2,3-dinor $PGF_{1\alpha}$), respectively. As blood coagulates, platelets synthesize and release TXA_2. The synthesis of TXA_2 is dependent on COX-1. TXA_2 is converted spontaneously and non-enzymatically to TXB_2 which is measured. Prostacyclin (PGI_2) is synthesized systemically but is unstable and converted rapidly (and non-enzymatically) to 6-Keto-$PGF_{1\alpha}$ which itself undergoes metabolism to PGI-M. In addition to the measurement of these prostanoid metabolites, effects on platelet aggregation and bleeding time were studied. The MRL studies discussed in this section were presented in the original NDA for rofecoxib.

Studies reported in the original NDA explored the platelet effects of rofecoxib 12.5 to 50 mg. Protocol 063 investigated the effects of rofecoxib 50 mg daily on peak TXB_2 inhibition and on

platelet aggregation. Therapy with rofecoxib 50 mg did not result in statistically significant inhibition of serum TXB_2 or platelet aggregation compared to placebo. Protocol 061 compared the effects of lower doses of rofecoxib and several nonselective COX-1/COX-2 inhibitors on thromboxane generation and platelet function {1731}. Patients were randomized to receive 6 days of therapy with either placebo, rofecoxib 12.5 or 25 mg daily, diclofenac 50 mg 3 times daily, ibuprofen 800 mg 3 times daily, or naproxen 500 mg 2 times daily. The effects of therapy on COX-1 activity were assessed by measurement at steady state of the peak and time-weighted average inhibition (WAI) of TXB_2 generation. Time averaged inhibition of platelet aggregation was also determined. The use of time-averaged measurements allowed for determination of platelet effects across the entire dosing interval for each compound. As a point of reference for this study, 120 mg aspirin daily is reported to decrease TXB_2 generation by 94 ± 1% throughout the dosing interval {585}. Eighty-one (81) mg aspirin has similar effects {1733}. In multiple studies in vivo, aspirin has been shown to significantly prolong bleeding time {1598}.

In Protocol 061, therapy with rofecoxib did not meaningfully inhibit platelet TXB_2 formation. Peak TXB_2 inhibition was similar among the nonselective NSAIDs. However, the nonselective NSAIDs differed in their effects when the entire dosing interval was taken into account. Therapy with diclofenac resulted in a 50% reduction in time-weighted average TXB_2 levels, ibuprofen in a 87% reduction in time-weighted average TXB_2 levels, and naproxen in a 95% reduction in time-weighted average TXB_2 levels (Figure 1). Similarly, platelet aggregation on Day 6 was not inhibited by therapy with rofecoxib or placebo. Therapy with naproxen resulted in substantial inhibition of platelet aggregation (88% mean time-averaged inhibition; SD = 1.9%) whereas therapy with diclofenac resulted in a modest 21% time-averaged inhibition of platelet aggregation (Figure 2).

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Figure 1

Weighted Average Inhibition of TXB_2 WAI (%) by Different Nonselective NSAIDs or by the Selective COX-2 Inhibitor Rofecoxib (Mean ±SE)

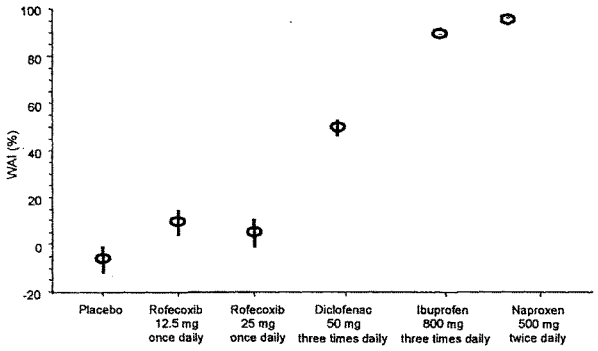
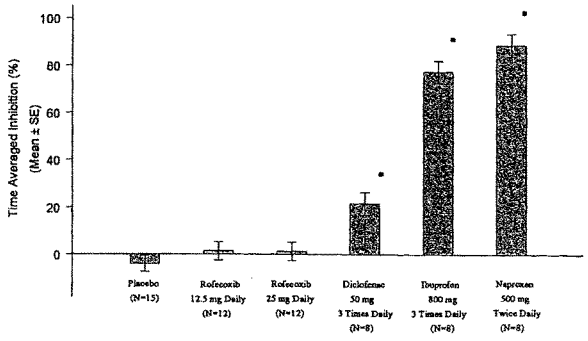


Figure 2

The Differential Effects of Nonselective COX-1/COX-2 Inhibitors and a COX-2 Selective Inhibitor on Ex Vivo Platelet Aggregation to 1 mM Arachidonic Acid



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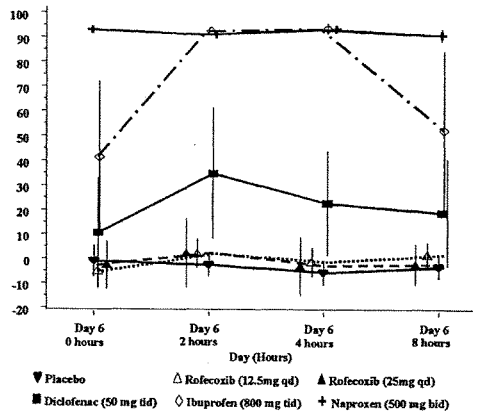
* p<0.001 versus placebo.

Inspection of the individual time points for the inhibition of TXB_2 and platelet aggregation from Protocol 061 further demonstrates the difference between these drugs (Figure 3). Note, in this figure, because drug effect was studied at steady state, the 0 hour time point is also the trough, i.e., 8 or 12 hours since the previous dose depending on the regimen. Only naproxen 500 mg twice daily (the top curve in the figure; symbol = ı) showed ~90% inhibition of platelet aggregation consistently throughout its 12-hour dosing interval. The next most effective agent, ibuprofen 800 mg 3 times daily (the second curve; symbol = ≈), only provided maximal inhibition of platelet function at 2 and 4 hours after a dose and not at 8 hours (its trough time point). The maximal inhibition of platelet aggregation with diclofenac (third curve from the top; symbol = ■) was ~35% at 2 hours after dosing. At trough (12 hours after the prior dose), the mean inhibition of platelet aggregation by naproxen was 93.0% (range 89.7, 96.4%). In a separate study (Protocol 063), the mean inhibition of platelet aggregation by aspirin 81 mg daily at trough was 92.1% (range 84.1, 95.0). Thus, naproxen, but not ibuprofen or diclofenac, resulted in high-level inhibition of platelet aggregation throughout its dosing interval similar to that achieved by aspirin.

Figure 3

Percent Inhibition From Baseline Platelet Aggregation by
Time Point* on Day 6 Using Arachidonic Acid as Agonist (Mean ±90% CI)



*Study was performed at steady-state
0 hours was 8 hours post-previous dose for ibuprofen and diclofenac
0 hours was 12 hours post-previous dose for naproxen

Consistent with these data, therapy with placebo, rofecoxib, and diclofenac did not result in a prolongation of bleeding time whereas therapy with naproxen prolonged bleeding time by ~79% {1731}. This effect of naproxen on bleeding time is similar to the reported effect of aspirin (~50% prolongation).

These studies thus demonstrated a gradient of antiplatelet effects among the NSAIDs. Therapy with naproxen was associated with antiplatelet effects similar to aspirin, diclofenac which does not provide sustained high level inhibition of platelet COX-1 resulted in modest antiplatelet effects, and rofecoxib was similar to placebo. The different effects of these drugs on hemostasis are reflected in their distinctive U.S. product labels.

These results demonstrate that nonselective NSAIDs differ in their magnitude and/or duration of antiplatelet effects. They support the possibility that certain nonselective NSAIDs such as naproxen with both potent and sustained antiplatelet effects might provide aspirin-like protection from thrombotic cardiovascular events.

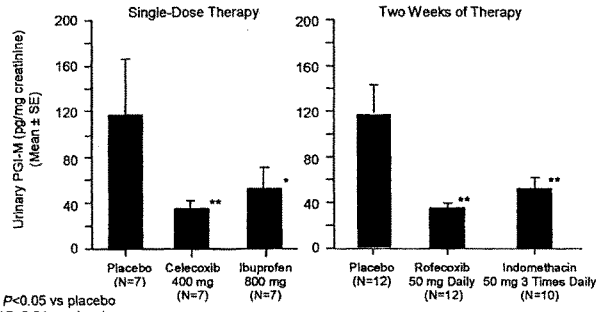
1.2 The Effects of Selective COX-2 Inhibitors and of Nonselective NSAIDs on Prostacyclin Synthesis

The effects of nonselective NSAIDs and COX-2 selective inhibitors on systemic PGI_2 (prostacyclin) synthesis have also been studied. The effect of a single dose of celecoxib, ibuprofen, or placebo on this parameter was evaluated by FitzGerald et al. {1445}. The effect of 14 days of therapy with rofecoxib 50 mg daily, indomethacin 50 mg 3 times daily, or placebo on this parameter was evaluated in Protocol 023 {1116}. Results of these studies are shown in Figure 4. As measured by urinary PGI-M levels, PGI_2 synthesis was reduced ~45 to 70% for rofecoxib, indomethacin, ibuprofen, and celecoxib.

DRAFT

Figure 4

Systemic Prostacyclin Synthesis as Assessed by Urinary PGI-M Levels Following Therapy With COX-2 Selective Inhibitors and Nonselective NSAIDs



* $P<0.05$ vs placebo
** $P<0.01$ vs placebo

[redacted] selective COX-2 inhibitors and nonselective NSAIDs inhibit the production of the urinary metabolite of prostacyclin (PGI-M) and do so to a similar extent. [redacted]

Nonetheless, as previously alluded to, because prostacyclin is a vasodilator and an inhibitor of platelet aggregation, the theoretical possibility was suggested that therapy with COX-2 selective inhibitors, because they have no effect on platelet function yet lower prostacyclin synthesis, might result in proaggregatory effects. If this were true, patients taking selective COX-2 inhibitors might be expected to have an increased incidence of thrombotic events relative to placebo. In this situation, the presence of COX-2 inhibition and the lack of COX-1 inhibition within the therapeutic dose range would be relevant and not the degree of selectivity as measured in ***in vitro*** assays. Thus the class of COX-2 inhibitors would be expected to have similar prothrombotic effects.

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[redacted]

[redacted]

4.2 Preclinical Models on the Effects of Selective COX-2 Inhibitors on Myocardial Ischemia/Reperfusion Injury, Cardiac Function, and Atherosclerosis

[redacted]

[redacted]

[redacted]

[redacted]

2. The Adjudication SOP

The Adjudication SOP was initiated in the second quarter, 1998 after the conclusion of the OA Phase IIb/III program and more than 1 year before the initiation of VIGOR. All MRL studies that initiated after the second quarter 1998 were subject to the procedures specified in the SOP as outlined here.

The basis of the Adjudication SOP is a blinded systematic review by an expert panel of cardiologists, neurologists, and vascular medicine internists of serious adverse experiences reported by site investigators that are prespecified in the Adjudication SOP as potential thrombotic cardiovascular serious adverse experiences. The report of such an event triggers a procedure whereby additional information is collected and the event is adjudicated.

A list of >100 adverse experience terms representing potential cardiovascular thrombotic events were chosen from the Merck Adverse Experience Dictionary and are identified in the Adjudication SOP. Serious adverse experiences reported by investigators and that occur while on study therapy or within 14 days of study drug discontinuation and include one or more of the preferred terms listed in the Adjudication SOP are identified by Merck personnel, and the study site is notified that the event is eligible for adjudication. The study site then sends all blinded study documentation (case report forms, adverse experience reporting forms), as well as any supporting nonstudy documentation (clinic notes, hospital records, death certificates) to the clinical team, who review the forms and documents for completeness and consistency based on guidelines described in the Adjudication SOP. Completed packages are then forwarded for adjudication.

A Vascular Events Coordination Center and a Vascular Events Adjudication Committee support this process. The Vascular Events Coordination Center is responsible for the overall administration of the process described in the Adjudication SOP. Specifically, the coordinating center participates in the surveillance for serious adverse experiences eligible for adjudication, assembly of adjudication packages, distribution, tracking, and logging of adjudication results, maintaining the official adjudication database, and communication with the clinical team and the Adjudication Committee regarding the process. The coordinating center is staffed by individuals within the Epidemiology Department at Merck Research Laboratories who are not directly involved with any of the rofecoxib or etoricoxib clinical trial programs.

The Vascular Events Committee is responsible for assigning potential thrombotic cardiovascular serious adverse experiences to one of the diagnostic categories established in the Adjudication SOP. This committee is composed of 3 separate subcommittees: 1 each for cardiac events, cerebrovascular events, and peripheral vascular events. The members of the 3 subcommittees are, respectively, cardiologists, neurologists, and vascular specialists who were expert in the treatment of ischemic syndromes as well as the medical aspects of clinical trials. Each subcommittee consists of 3 physicians. None of the members of this committee is a Merck employee or a site investigator for any of the rofecoxib or etoricoxib studies.

3. Definition of Endpoints Used in the Analysis of Thrombotic Cardiovascular Serious Adverse Experiences

3.1. Confirmed Thrombotic Cardiovascular Serious Adverse Experiences Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences

The data analysis section for the Adjudication SOP specifies that the primary analysis of cardiovascular events would utilize only events that were confirmed to be thrombotic cardiovascular serious adverse experiences by the Vascular Endpoint Adjudication Committee. In all studies that initiated after the second quarter 1998 (that is, VIGOR and all studies in this report except for the OA Phase IIb/III studies and the RA Phase IIb study,) data on confirmed thrombotic cardiovascular serious adverse experiences are considered primary and analyses of investigator reported thrombotic cardiovascular serious adverse experiences (i.e., events eligible for adjudication based on the predefined list of >100 serious adverse experience terms in the Adjudication SOP) are provided as supportive information. The OA Phase IIb/III studies and the RA Phase IIb study were completed prior to the initiation of the Adjudication SOP; therefore, data are only provided for investigator-reported events.

3.2. Antiplatelet Trialists' Collaboration (APTC)Combined Endpoint

Data from these adjudicated events are being analyzed as part of an ongoing pooled-analysis of all Merck COX-2 inhibitor trials. The primary endpoint used in the pooled-analysis is the Antiplatelet Trialists' Collaboration (APTC) combined endpoint. This endpoint is the most common and widely accepted method to quantify the overall cardiovascular impact of antithrombotic compounds in cardiovascular clinical trials and represents the incidence of fatal and irreversible morbid cardiovascular events {1061,1385}. The APTC combined endpoint is the combined incidence of cardiovascular, hemorrhagic, and unknown death, myocardial infarction, and cerebrovascular accident. In order to provide adjudicated data for the APTC combined endpoint, all deaths reported during etoricoxib clinical trials were also adjudicated (See Table 1 for the different terms included in the APTC endpoint and the confirmed thrombotic cardiovascular serious adverse experience endpoint).

Table 1

Serious Adverse Events Included in the Thrombotic Cardiovascular Serious Adverse Experience and APTC† Combined Endpoints

Adjudication Committee Categories for Cardiovascular Events	Confirmed Thrombotic Cardiovascular Event	APTC† Combined Endpoint
Thrombotic Events		
Cardiac Events		
Acute MI	√	√
Fatal: Acute MI	√	√
Unstable Angina Pectoris	√	
Sudden and/or Unexplained Death	√	√
Resuscitated Cardiac Arrest	√	√
Cardiac Thrombus	√	
Peripheral Vascular Events		
Pulmonary Embolism	√	
Fatal: Pulmonary Embolism	√	
Peripheral Arterial Thrombosis	√	
Fatal: Peripheral Arterial Thrombosis	√	√
Peripheral Venous Thrombosis	√	
Cerebrovascular Events		
Ischemic Cerebrovascular Stroke	√	√
Fatal: Ischemic Cerebrovascular Stroke	√	√
Cerebrovascular Venous Thrombosis	√	
Fatal: Cerebrovascular Venous Thrombosis	√	√
Transient Ischemic Attack	√	
Hemorrhagic Events		
Hemorrhagic Cerebrovascular Stroke‡		√
Fatal: Hemorrhagic Cerebrovascular Stroke‡		√
Fatal: Hemorrhagic deaths of any cause		√

† APTC = Antiplatelet Trialists' Collaboration.
‡ These events are included as investigator-reported events but not confirmed thrombotic events.

4. VIGOR CV data (Rofecoxib versus Naproxen)

The Vioxx GI Outcomes Research Study (VIGOR) was designed to primarily assess the GI safety of rofecoxib versus naproxen. A total of 8076 patients were randomized. Median duration of exposure was 9 months. The mean age of the study cohort was 58.1 years and 79.7% were female. Approximately half reported a cardiovascular risk factor (hypertension, diabetes mellitus, hypercholesterolemia, or smoking) other than one related to age or gender. The most common risk factor was hypertension. Patients were not to use aspirin or other antiplatelet agents in VIGOR to prevent confounding of the primary GI analyses. Patients who were taking aspirin or other antiplatelet agents for vascular protection were to be excluded from enrollment in

the study. Nevertheless, 4% of patients enrolled in the study met criteria for aspirin prophylaxis as outlined in the U.S. product circular for aspirin. These patients accounted for 28% of the cardiovascular events (see Section 3.2).

4.1 Primary Analysis of Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR

A total of 96 patients (64 in the rofecoxib group and 32 in the naproxen group) had 1 or more thrombotic serious adverse experiences which were referred to the adjudication committee (Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences). Of these, 64 patients had one or more events during VIGOR that were adjudicated as thrombotic events by the committees (Confirmed Thrombotic Cardiovascular Serious Adverse Experiences) (Table 2). In keeping with the data analysis section of the Adjudication SOP, Table 2 does not include 3 events that were determined by adjudication to be hemorrhagic cerebrovascular accidents. The overall incidence of confirmed thrombotic cardiovascular serious adverse experiences in VIGOR is presented by treatment group in Table 2. The rate of confirmed thrombotic cardiovascular serious adverse experiences was 0.70 per 100 patient-years for the naproxen group and 1.67 per 100 patient-years for the rofecoxib group. The relative risk, 2.37 for rofecoxib compared to naproxen, was statistically significant (p=0.002) This difference was mostly attributable to a difference in the incidence of myocardial infarction (MI) between the groups.

Table 2

Analysis of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR[†]

Event Category	Treatment Group	N	Patients With Events	PYR[‡]	Rates[‡]	Relative Risk[ϕ] Estimate	95% CI
All thrombotic events	Rofecoxib	4047	45	2697	1.67		
	Naproxen	4029	19	2698	0.70	2.37	(1.39, 4.06)
All cardiac events	Rofecoxib	4047	28	2698	1.04		
	Naproxen	4029	10	2698	0.37	2.80	(1.36, 5.77)
All cerebrovascular events	Rofecoxib	4047	11	2699	0.41		
	Naproxen	4029	8	2699	0.30	1.38	(0.55, 3.43)
All peripheral vascular events	Rofecoxib	4047	6	2699	0.22		
	Naproxen	4029	1	2699	0.04	6.00	(0.73, 276.0)

† In keeping with the data analysis section of the Adjudication SOP, this table does not include events determined by adjudication to be hemorrhagic cerebrovascular accidents.

‡ Per 100 patient-years at risk (PYR).

ϕ Relative risk of rofecoxib with respect to naproxen from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Table 3 presents the incidences of the various thrombotic cardiovascular serious adverse experience adjudication diagnoses. The incidence of confirmed acute myocardial infarction was 0.5% in patients treated with rofecoxib and 0.1% in patients treated with naproxen. Most of these events were judged to have occurred spontaneously (i.e., not as a consequence of a GI bleed, major surgery, or coronary revascularization).

Table 3

Summary of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR[†]

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Any Event	**45**	**(1.1)**	**19**	**(0.5)**
Arterial Event	40	(1.0)	18	(0.4)
Venous Event	5	(0.1)	1	(0.0)
Cardiovascular Death	**5**	**(0.1)**	**5**	**(0.1)**
Fatal Acute Myocardial Infarction	2	(0.0)	0	(0.0)
Fatal Ischemic Cerebrovascular Stroke	0	(0.0)	1	(0.0)
Sudden Cardiac Death	3	(0.1)	4	(0.1)
Cardiac Events (Fatal/Nonfatal)	**28**	**(0.7)**	**10**	**(0.2)**
Acute Myocardial Infarction	20	(0.5)	4	(0.1)
Sudden Cardiac Death	3	(0.1)	4	(0.1)
Unstable Angina Pectoris	5	(0.1)	3	(0.1)
Cerebrovascular Events (Fatal/Nonfatal)	**11**	**(0.3)**	**8**	**(0.2)**
Ischemic Cerebrovascular Stroke	9	(0.2)	8	(0.2)
Transient Ischemic Attack	2	(0.0)	0	(0.0)
Peripheral Vascular Events (Fatal/Nonfatal)	**6**	**(0.1)**	**1**	**(0.0)**
Peripheral Arterial Thrombosis	1	(0.0)	0	(0.0)
Peripheral Venous Thrombosis	5	(0.1)	1	(0.0)

[†] In keeping with the data analysis section of the Adjudication SOP, this table does not include events determined by adjudication to be hemorrhagic cerebrovascular accidents. Patients may be counted in more than one row but are only counted once within a row.

4.2 Subgroup and Sensitivity Analyses of Thrombotic Cardiovascular Events in VIGOR

Thrombotic Cardiovascular Serious Adverse Experiences Analyzed by Baseline Risk Factors

The baseline demographics of the cohort of patients with confirmed thrombotic cardiovascular serious adverse experiences differ from the overall population of patients in the study in that a greater percentage of patients with confirmed thrombotic cardiovascular serious adverse experiences had typical risk factors for atherosclerotic cardiovascular disease (Table 4). Compared with the overall VIGOR cohort, patients who experienced a confirmed thrombotic cardiovascular serious adverse experience were older (64% ≥65 years old for patients who experienced such an event versus 26% for the entire study) and more likely to be male (42% versus 20%) and/or current smokers (34% versus 19%). Patients with a confirmed thrombotic cardiovascular event had a substantially higher incidence of a history of atherosclerotic cardiovascular disease, hypertension, and hypercholesterolemia prior to enrollment than the

general study population and 81% had at least 1 cardiovascular risk factor versus 50% for the entire study population.

Table 4

Baseline Cardiovascular Demographics of all Patients in VIGOR and Patients Who had a Confirmed Thrombotic Cardiovascular Serious Adverse Experience

Demographic	All Patients (N=8076)		Patients With Events (N=64)†	
	n	(%)	n	(%)
Age				
<65 Years Old	6009	(74.4)	23	(35.9)
≥65 Years Old	2067	(25.6)	41	(64.1)
Gender				
Female	6438	(79.7)	37	(57.8)
Male	1638	(20.3)	27	(42.2)
Past Cardiovascular History				
Past History of Atherosclerotic Cardiovascular Disease	454	(5.6)	21	(32.8)
Cardiovascular Risk Factors				
Any Cardiovascular Risk Factors	4035	(50.0)	52	(81.3)
Hypertension	2385	(29.5)	32	(50.0)
Diabetes Mellitus	494	(6.1)	3	(4.7)
Hypercholesterolemia	636	(7.9)	11	(17.2)
Current Smoker	1569	(19.4)	22	(34.4)
Indication for Aspirin Therapy				
Aspirin Therapy Indicated‡	321	(4.0)	18	(28.1)

† Two patients experienced >1 confirmed thrombotic cardiovascular serious adverse experience. AN 10677 (rofecoxib group) experienced 2 ischemic cerebrovascular accidents. AN 00560 (naproxen group) experienced unstable angina and myocardial infarction. Because the analysis of rates of confirmed thrombotic cardiovascular serious adverse experiences counted number of patients with events, these patients are counted once within each adjudication category.

‡ Patients with past medical histories of one of the following cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions.

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients With a Baseline Indication for Vascular-Protective Aspirin Therapy

Patients with symptomatic coronary or cerebrovascular disease are at high risk for the development of recurrent thrombotic cardiovascular events. There is widespread agreement among cardiovascular public health authorities that chronic vascular-protective low-dose aspirin therapy is indicated in these patients for the prevention of recurrent thrombotic events. Of note, despite the proscription on the enrollment of patients in whom low-dose aspirin therapy was indicated, 4% of the patients in VIGOR met accepted criteria for aspirin therapy as outlined in the U.S. product circular for aspirin (Table 4). The incidence of thrombotic cardiovascular serious adverse experiences occurred disproportionately in the population of patients in whom aspirin was indicated but who were not taking aspirin. In patients who received rofecoxib and had a confirmed thrombotic cardiovascular serious adverse experience, 33% had a past medical history of symptomatic coronary or cerebrovascular disease, and therefore a clear indication for chronic aspirin therapy. Although such patients accounted for only 4% of the study population, they experienced 28% of all confirmed thrombotic cardiovascular serious adverse experiences. These data highlight the benefit of adequate antiplatelet activity in such high-risk patients.

There was no treatment-by-subgroup interaction for thrombotic events (p=0.177) in the subgroups of patients with or without an indication for aspirin. Thus, the relative risk comparing rofecoxib to naproxen for having thrombotic cardiovascular serious adverse experiences was statistically similar in the aspirin-indicated and aspirin not-indicated subgroups. However, consistent with the higher overall incidence of events in the aspirin-indicated subgroup, the numeric difference between rofecoxib and naproxen in the incidence of CV events was greater in the patients with an indication for aspirin therapy that in patients without this indication for aspirin.

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients Who Experienced Hypertension Adverse Experiences During the Study

A hypertension adverse experience occurred before the cardiovascular event in only 4 patients on rofecoxib (ANs 1449, 2044, 2214, and 7670). Thus only a minority of patients with a confirmed thrombotic cardiovascular serious adverse experience had developed a hypertension-related adverse experience prior to the event.

Two analyses were performed to determine if the imbalance in cardiovascular outcomes between the treatment groups in the study was related to whether or not a patient had a hypertension-related adverse experience prior to the cardiovascular event. The first analysis sought to determine if thrombotic cardiovascular serious adverse experiences were more common in patients who had an antecedent hypertension-related adverse experience (Table 5). The incidence rates of confirmed thrombotic serious adverse experiences were compared by treatment group in patients with and without an antecedent hypertension-related adverse experience. For the rofecoxib group, 1.0% of the patients who had an antecedent hypertension-related adverse experience had a thrombotic cardiovascular serious adverse experience whereas 1.1% of the patients had a thrombotic cardiovascular serious adverse experience without an antecedent hypertensive adverse experience; For naproxen, the 2 values are 0.0% and 0.5%, respectively.

Table 5

Incidence of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients With and Without Hypertension-Related Adverse Experiences in VIGOR

Subgroup	Treatment Group	N	Patients With a Confirmed Cardiovascular Serious Adverse Experience	
			n	(%)
Incidence of a Confirmed Thrombotic Cardiovascular Serious Adverse Experience				
Patients with a hypertension-related adverse experience before the thrombotic event	Rofecoxib	394	4	(1.0)
Patients without a hypertension-related adverse experience before the thrombotic event	Rofecoxib	3653	41	(1.1)
Patients with a hypertension-related adverse experience before the thrombotic event	Naproxen	221	0	(0.0)
Patients without a hypertension-related adverse experience before the thrombotic event	Naproxen	3808	19	(0.5)

A second approach sought to determine if patients with confirmed thrombotic cardiovascular serious adverse experiences were more likely to have experienced an antecedent hypertension-related adverse experience (Table 6). Overall, only 4 of the 64 patients with confirmed thrombotic cardiovascular serious adverse experiences had also experienced an antecedent hypertension-related adverse experience. The incidence of hypertension-related adverse experiences occurring before a confirmed thrombotic cardiovascular serious adverse experience was comparable to the incidence of hypertension-related adverse experiences in patients without a confirmed thrombotic cardiovascular serious adverse experience.

Table 6

Incidence of Antecedent Hypertension-Related Adverse Experiences in Patients With and Without Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR

Subgroup	Treatment Group	N	Patients With a Hypertension-Related Adverse Experience	
			n	(%)
Incidence of an Antecedent Hypertension-Related Adverse Experience				
Patients with a confirmed thrombotic cardiovascular serious adverse experience	Rofecoxib	45	4	(8.9)
Patients without a confirmed thrombotic cardiovascular serious adverse experience	Rofecoxib	4002	387	(9.7)
Patients with a confirmed thrombotic cardiovascular serious adverse experience	Naproxen	19	0	(0.0)
Patients without a confirmed thrombotic cardiovascular serious adverse experience	Naproxen	4010	220	(5.5)

Blood Pressure Measurements in Patients With and Without Confirmed Thrombotic Cardiovascular Serious Adverse Experiences

Changes in blood pressure measurements were compared in patients with and without confirmed thrombotic cardiovascular serious adverse experiences. As expected, in both treatment groups, mean systolic blood pressure in patients who had confirmed thrombotic events was 6 to 9 mm Hg higher at baseline compared to patients without events. However, mean changes from baseline in systolic and diastolic blood pressure were similar in rofecoxib-treated patients with and without confirmed thrombotic events. In addition, the percent of patients with elevations in blood pressure which exceeded 20 mm Hg in systolic blood pressure or 15 mm Hg in diastolic blood pressure was similar in patients with and without confirmed thrombotic events. Lastly, there was no correlation between the magnitude of change in blood pressure and the risk of sustaining a confirmed thrombotic event. Thus, differential effects on blood pressure do not appear to explain the imbalance in confirmed thrombotic cardiovascular serious adverse experiences in VIGOR.

4.3 Analysis of VIGOR Using the Antiplatelet Trialists' Collaboration Combined Endpoint

The most common and widely accepted method to quantify the overall cardiovascular impact of antithrombotic compounds in cardiovascular clinical trials is by determining the effect of these compounds on the incidence of fatal and irreversible morbid cardiovascular events. The metric used for such an analysis as defined by the Antiplatelet Trialists' Collaboration (APTC) is the incidence of the combined endpoint of cardiovascular, hemorrhagic, and unknown death, myocardial infarction, and cerebrovascular accident (APTC combined endpoint). An analysis of the APTC combined endpoint was performed for the VIGOR population (Table 7). Overall, the relative risk of the APTC combined endpoint for rofecoxib with respect to naproxen was 1.95 (95% CI 1.10, 3.44). Of the individual endpoints, the incidence of death and stroke were the same in the 2 groups. The difference in the event rates between the treatment groups was due primarily to a difference in the rates of MI.

Table 7

Analyses of Confirmed Cardiovascular Events in VIGOR Using the Antiplatelet Trialists' Collaboration (APTC) Combined Endpoint

Event Category	Treatment Group	N	Number of Patients With Events	PYR†	Rates‡	Relative Risk§ Estimate	95% CI
All Patients							
Cardiovascular deaths%, MI, stroke¶	Rofecoxib	4047	35	2698	1.30		
	Naproxen	4029	18	2698	0.67	1.95	(1.10, 3.44)
Cardiovascular deaths%	Rofecoxib	4047	7	2700	0.26		
	Naproxen	4029	7	2699	0.26	1.00	(0.35, 2.85)
Myocardial infarction (MI)	Rofecoxib	4047	20	2699	0.74		
	Naproxen	4029	4	2699	0.15	5.00	(1.71, 14.64)
Stroke¶	Rofecoxib	4047	11	2699	0.41		
	Naproxen	4029	9	2699	0.33	1.23	(0.51, 2.96)

† Patient-years at risk.
‡ Per 100 PYR.
§ Relative risk of rofecoxib with respect to naproxen from unstratified Cox model.
% Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal GI bleeding episode.
¶ Includes fatal or nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes.

4.4 Supportive Analysis: Incidence of Events Judged by Investigators to be Potential Thrombotic Cardiovascular Serious Adverse Experiences

According to the Adjudication SOP, the analysis of the incidences of all reported cardiovascular serious adverse experiences eligible for adjudication was to be considered as a secondary, supportive analysis. Thirty-two and 64 patients who received naproxen and rofecoxib, respectively, experienced these events (Table 8). Thus, patients who received naproxen experienced these events at a rate of 1.19 per 100 patient-years versus 2.37 per 100 patient-years for patients on rofecoxib (relative risk of 2.00, rofecoxib versus naproxen).

A summary of the cardiovascular serious adverse experiences referred for adjudication that occurred in the VIGOR study is provided in Table 9. Of note, several events thought to be cerebrovascular accidents by the site investigators were not confirmed to be thrombotic cerebrovascular events by the expert panel of adjudicators in the VIGOR study. Thus, following the adjudication process, the difference between treatment groups in the incidence of confirmed cerebrovascular accidents was much smaller (9 and 8 ischemic cerebrovascular strokes and 2 and 1 hemorrhagic strokes in the rofecoxib and naproxen groups, respectively).

addition, 158 patients were assigned to rofecoxib 5 mg in Part I of the Phase IIb Dose-Range Finding study. Patients on placebo or rofecoxib 5 mg in Part I of studies were reassigned to rofecoxib 25 mg or naproxen in Part II of the studies. Overall, exposure in all study parts combined was 183 patient-years for placebo, 1643 patient-years for rofecoxib, and 522 patient-years for naproxen. Aspirin use in the RA program was limited; there were only 65 patients who used low-dose aspirin both at baseline and also concomitantly during studies. Demographics of the patient population in the RA Phase IIb/III program were similar to those in VIGOR. Approximately 80% of the patients were female, the mean age was 54 years, 21% of patients had a history of hypertension, 5% had a history of hypercholesterolemia, and 3% had a history of diabetes mellitus.

Rates of serious clinical adverse experiences in the Phase IIb and III RA studies reported by investigators with terms identified as potentially indicative of a thromboembolic cardiovascular episode were determined. Fatal and nonfatal cases from the Phase III RA studies (Protocols 096, 097, and 098/103) were subject to the blinded adjudication process described above. The ongoing adjudication process was enacted after initiation of Protocol 068; hence, for the Phase IIb study, nonfatal events were not subject to adjudication; only fatal adverse experiences (from Protocol 068) were adjudicated in retrospect.

Table 21 gives an analysis of investigator-reported events, confirmed thrombotic, and APTC endpoint events in the RA Phase IIb/III program. The rates of investigator reported events were 2.0 per 100 treatment-years for the 3 rofecoxib treatment groups combined (12.5 mg, 25 mg, and 50 mg) and 2.1 per 100 treatment-years for naproxen. The rates of confirmed thrombotic cardiovascular serious adverse experiences were 1.7 per 100 patient-years for the combined rofecoxib group and 1.2 per 100 patient-years for the naproxen group. The rates of APTC events were 1.0 per 100 patient-years for the combined rofecoxib group and 0.6 per 100 patient-years for the naproxen group. In these analyses, the confirmed and APTC endpoints use investigator-reported events from Protocol 068 as the adjudication process was enacted after the initiation of Protocol 068. Therefore, Table 22 gives an analysis of investigator-reported events and confirmed, APTC endpoint events only for those studies in which adjudication was performed (Protocols 096, 097, and 0-98/103). The results are consistent with those in Table 21.

Table 21
Rates of Thrombotic Cardiovascular Events (by Assigned Treatment) (Protocols 068, 096, 097, and 098/103)

Assigned Therapy	Patient-Years at Risk	Number of Investigator-Reported Events[1]	Rate of Investigator-Reported Adverse Experiences[1] (per 100 Patient-Years at Risk)	Number of Confirmed Events[2]	Rate of Confirmed Events[2] (per 100 Patient-Years at Risk)	APTC Events[2]	Rate of APTC Events (per 100 Patient-Years at Risk)
Placebo	183	2	1.1	1	0.5	1	0.5
Refecoxib 12.5 mg	29	3	10.3	3	10.3	2	6.9
Refecoxib 25 mg	861	13	1.5	10	1.2	4	0.5
Refecoxib 50 mg	753	17	2.3	15	2.0	11	1.5
Refecoxib treatment groups combined	1643	33	2.0	28	1.7	17	1.0
Naproxen 1000 mg	522	11	2.1	6	1.2	3	0.6

[1] Includes events reported by investigators under terms prespecified as potentially thromboembolic.
[2] Ascertainment of Confirmed Events and of Anti-Platelet Trialists Collaboration (APTC) events based on investigator-reported term(s) where adjudication was not performed (Protocol 068) or is pending. Otherwise, events were based on the adjudicated diagnosis.
Note: Protocol 068 was initiated prior to the program-wide cardiovascular-event monitoring.

Table 22
Rates of Thrombotic Cardiovascular Events (by Assigned Treatment) (Protocols 096, 097, and 098/103)

Assigned Therapy	Patient-Years at Risk	Number of Investigator-Reported Events[1]	Rate of Investigator-Reported Adverse Experiences[1] (Per 100 Patient-Years at Risk)	Confirmed Thrombotic Events[1]	Rate of Confirmed Thrombotic Events[1] (Per 100 Patient-Years at Risk)	Confirmed APTC Events[1]	Rate of Confirmed APTC Events[2] (Per 100 Patient-Years at Risk)
Placebo	160	2	1.3	1	0.6	1	0.6
Refecoxib 12.5 mg	29	3	10.3	3	10.3	2	6.9
Refecoxib 25 mg	501	10	2.0	7	1.4	3	0.6
Refecoxib 50 mg	430	11	2.6	9	2.1	5	1.2
Refecoxib treatment groups combined	960	24	2.5	19	2.0	10	1.0
Naproxen 1000 mg	406	6	1.5	1	0.2	1	0.2

[1] Includes events reported by investigators under terms prespecified as potentially thromboembolic.
[2] Combined analysis using only adjudicated confirmed APTC events from Protocols 096, 097, and 098/103.
Note: Protocol 068 was initiated prior to the program-wide cardiovascular-event monitoring, and is not included in this table.

8. ADVANTAGE CV data (Rofecoxib versus Naproxen)

ADVANTAGE was a 12-week study comparing rofecoxib 25 mg to naproxen 1000 mg daily in OA patients (N=5557). Patients taking low-dose aspirin were allowed to enroll in ADVANTAGE and approximately 13% of patients were low-dose aspirin users. An analysis of the 3 thrombotic cardiovascular endpoints described above for the entire cohort of patients in the ADVANTAGE trial is presented in Table 23. A similar number of patients in the rofecoxib and naproxen groups had investigator reported thrombotic cardiovascular serious adverse experiences. More patients in the naproxen group had confirmed thrombotic cardiovascular serious adverse experiences compared with the rofecoxib group. More patients in the rofecoxib group had an APTC combined endpoint event compared with the naproxen group. Despite small differences in the point estimates of the relative risks of the 3 different endpoints, the 95% CI for the relative risks were all similar and none suggested statistically significant differences between the treatment groups. Summaries of events contributing to the confirmed thrombotic cardiovascular serious adverse experience endpoint and to the APTC combined endpoint are provided in Table 24 and Table 25.

Table 23

Summary of Analysis of Thrombotic Cardiovascular Serious Adverse Experiences
ADVANTAGE Study

Subgroup	Treatment	N	Patients With Events	PYR[1]	Rates[2]	Relative Risk[3] Estimate	95% CI
Investigator Reported Thrombotic Cardiovascular Serious Adverse Experiences							
Total Cohort	Rofecoxib	2785	14	639	2.19	1.06	(0.50, 2.26)
	Naproxen	2772	13	629	2.07		
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences							
Total Cohort	Rofecoxib	2785	9	640	1.41	0.74	(0.31, 1.75)
	Naproxen	2772	12	629	1.91		
APTC Combined Endpoint							
Total Cohort	Rofecoxib	2785	10	640	1.56	1.41	(0.54, 3.69)
	Naproxen	2772	7	629	1.11		

† Patient-years at risk.
‡ Per 100 PYR.
¶ Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is the ratio of rates.

Table 24

Summary of Confirmed Thrombotic Cardiovascular
Serious Adverse Experiences in the ADVANTAGE Trial

	Rofecoxib (N=2785)		Naproxen (N=2772)	
Thrombotic Serious Cardiovascular Term	n	(%)	n	(%)
Total number of patients with AE	**9**	**(0.32)**	**12**	**(0.43)**
Cardiac Events	**8**	**(0.29)**	**3**	**(0.11)**
Acute Myocardial Infarction	5	(0.18)	1	(0.04)
Sudden Cardiac Death	2	(0.07)	0	(0.00)
Unstable Angina Pectoris	1	(0.04)	2	(0.07)
Cerebrovascular Events	**1**	**(0.04)**	**7**	**(0.25)**
Ischemic Cerebrovascular Stroke	0	(0.00)	6	(0.22)
Transient Ischemic Attack	1	(0.04)	1	(0.04)
Peripheral Venous Events	**0**	**(0.00)**	**2**	**(0.07)**
Peripheral Venous Thrombosis	0	(0.00)	2	(0.07)

This term was revised from the original APTC term of Hypertensive Heart Disease
Patients may be counted in more than one row but are only counted once within a row.

Table 25

Summary of the APTC Combined Endpoint in the ADVANTAGE Trial

APTC Term	Rofecoxib (N=2785) n	(%)	Naproxen (N=2772) n	(%)
Total number of patients with AE	**10**	**(0.36)**	**7**	**(0.25)**
Cardiac Events	**7**	**(0.25)**	**1**	**(0.04)**
Acute Myocardial Infarction	5	(0.18)	1	(0.04)
Sudden Cardiac Death	2	(0.07)	0	(0.00)
Cerebrovascular Events	**0**	**(0.00)**	**6**	**(0.22)**
Ischemic Cerebrovascular Stroke	0	(0.00)	6	(0.22)
Other Events	**3**	**(0.11)**	**0**	**(0.00)**
Arterial Rupture	1	(0.04)	0	(0.00)
Hemorrhagic Stroke	1	(0.04)	0	(0.00)
Unknown Cause of Death†	1	(0.04)	0	(0.00)

† This term was revised from the original APTC term of Hypertensive Heart Disease.
Note: Patients may be counted in more than one row but are only counted once within a row.

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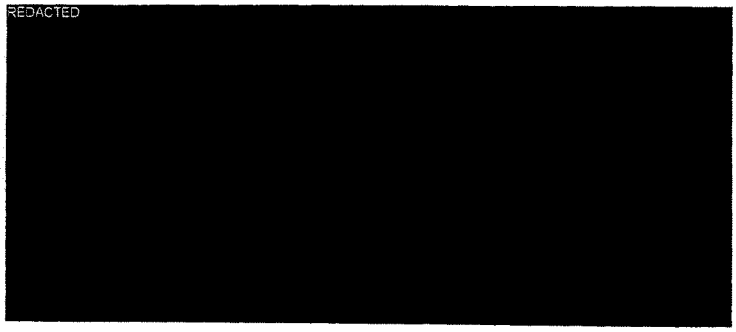

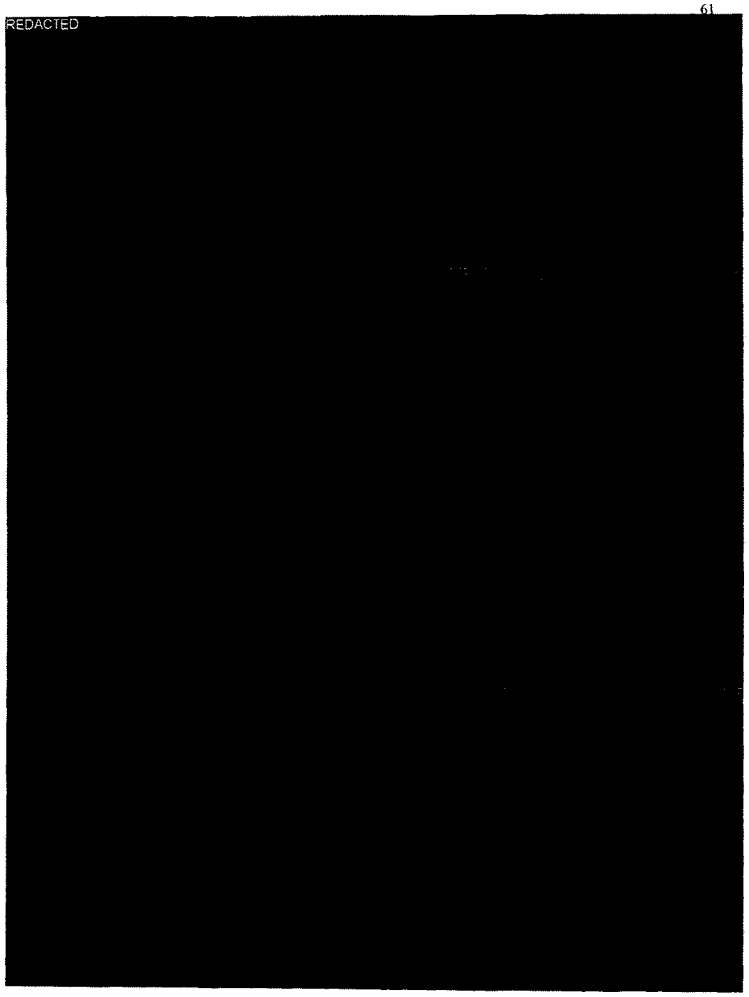
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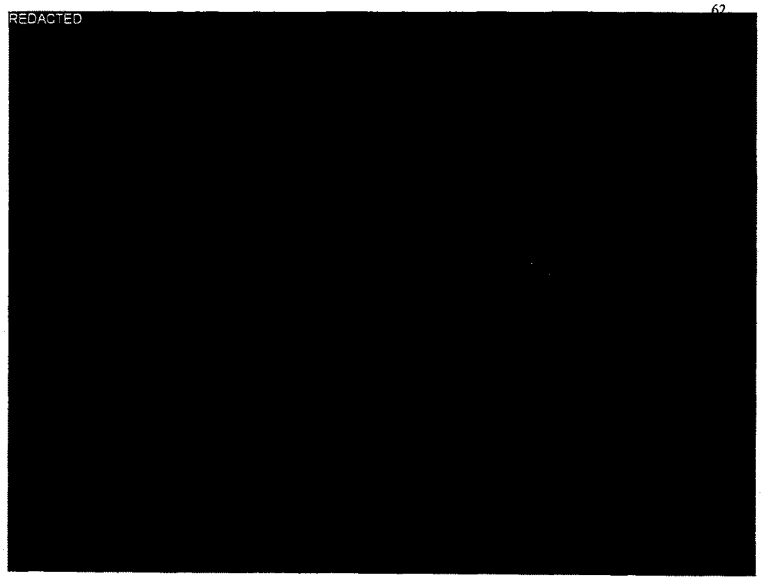
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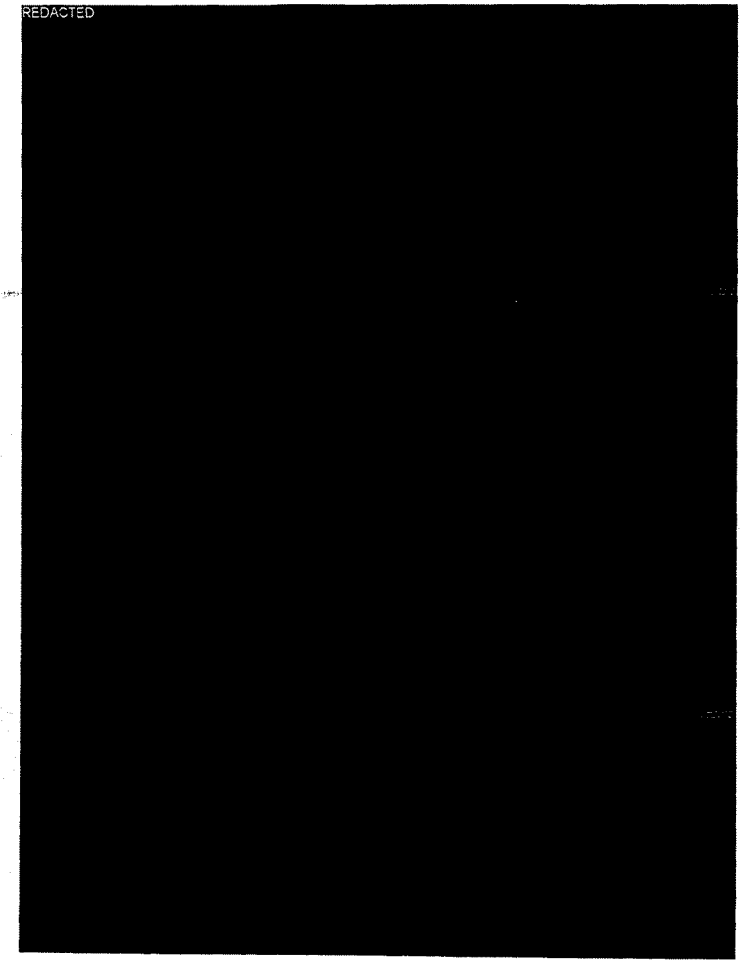
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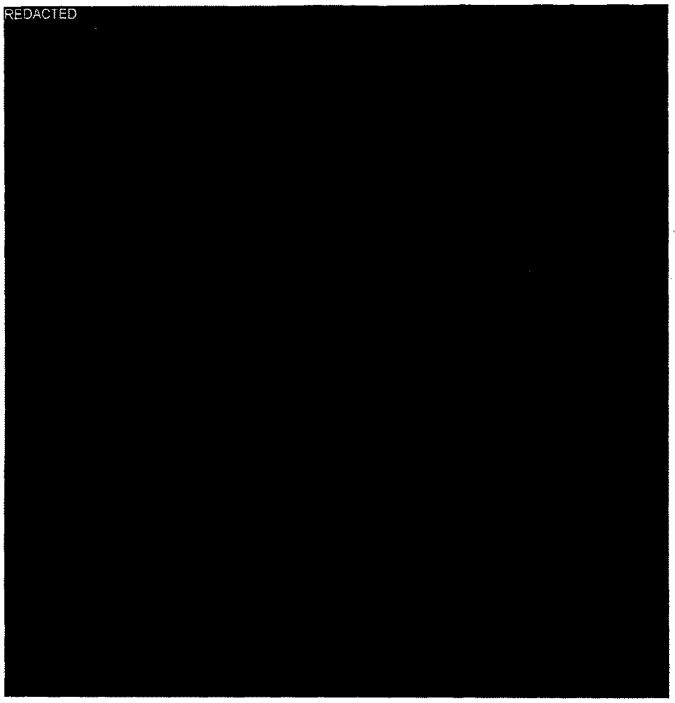

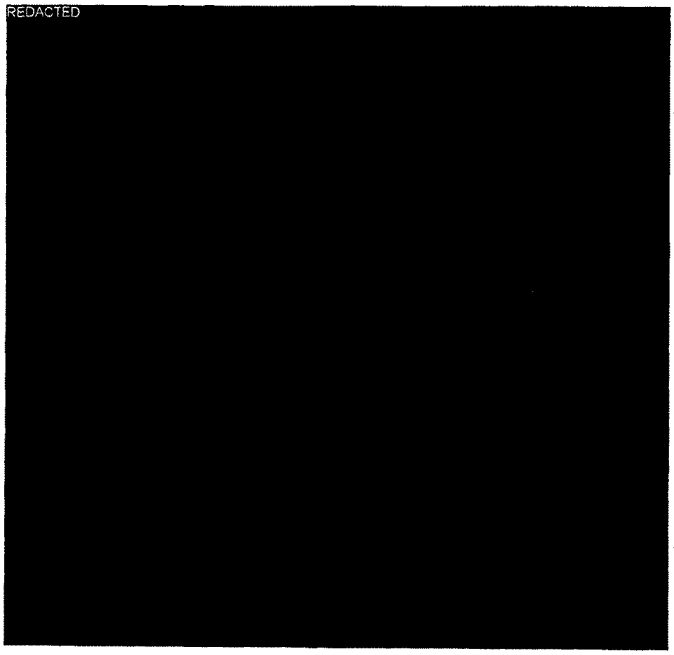

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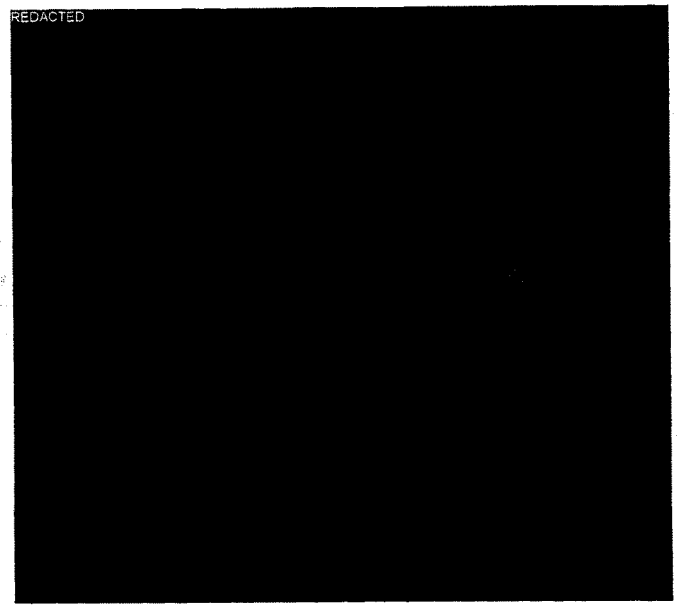

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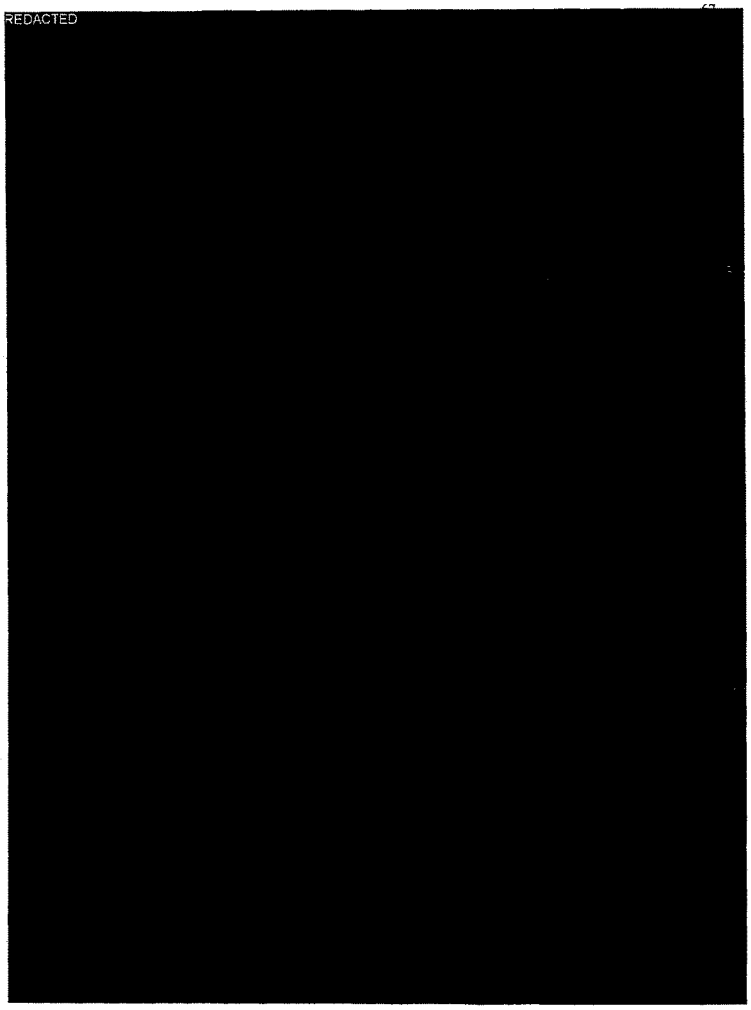
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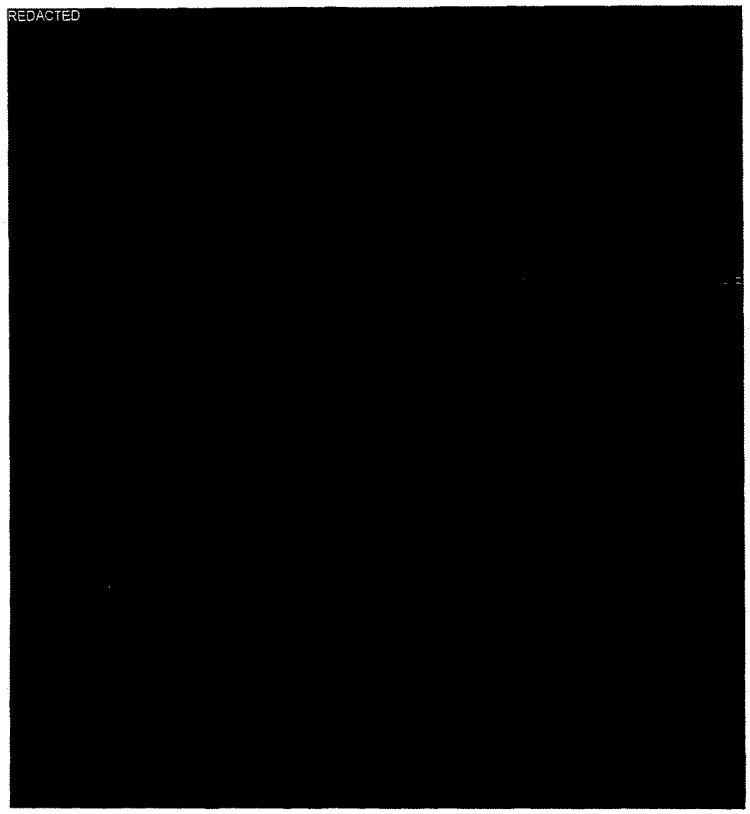
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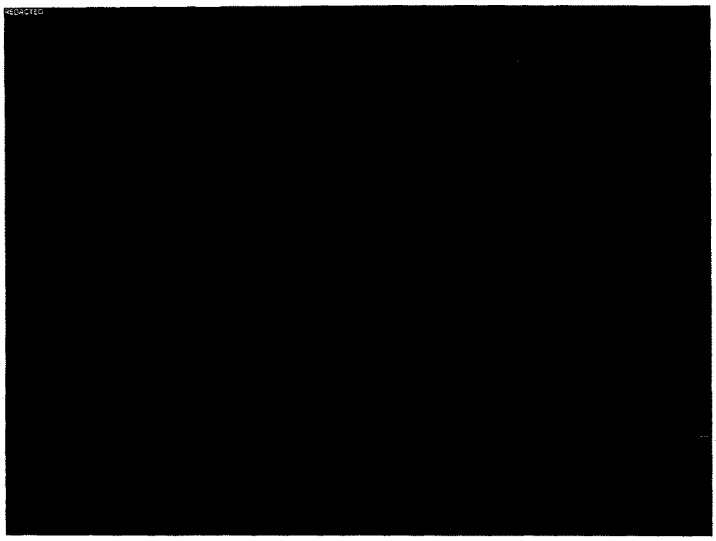
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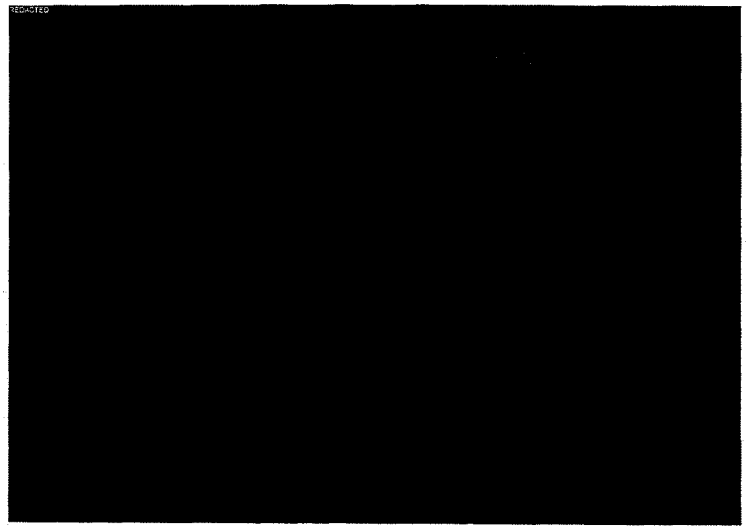
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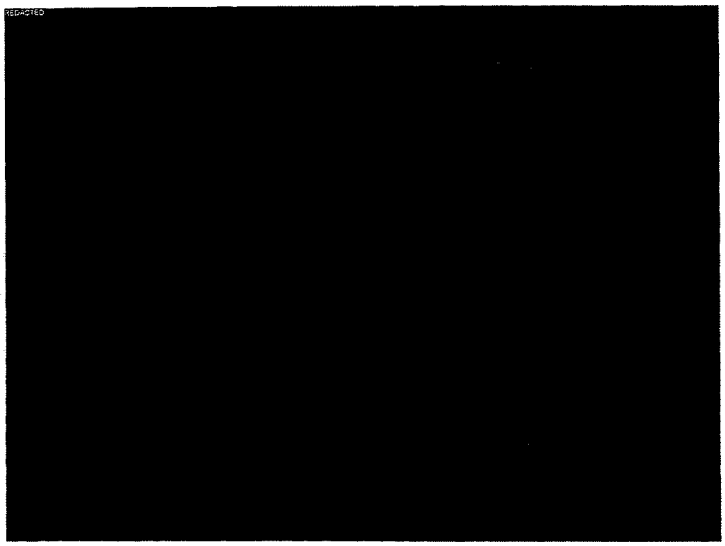
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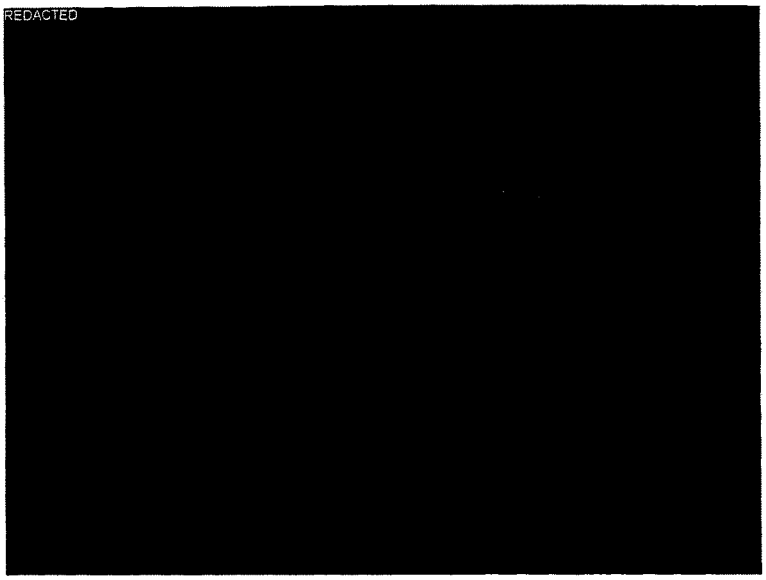


10. Mortality Data in the Rofecoxib and Etoricoxib Programs

Rates of overall mortality and of cardiovascular mortality were generally similar across treatment groups in the rofecoxib program. Although there are examples in individual disease programs (eg: the OA Phase IIb/III program and the Alzheimer's disease program) in which differences between groups reached statistical significance, these low numbers of events should not be over interpreted. In the OA program rates were significantly lower on rofecoxib than comparator NSAIDs; in the Alzheimer's Disease program rates were significantly lower on placebo than rofecoxib. Overall, there were no trends in the numerous assigned causes of mortality to suggest causality. Rates of overall mortality on etoricoxib were not high and were similar to the rates throughout the rofecoxib program. A possible difference in cardiovascular mortality between etoricoxib and naproxen was observed.

10.1 Mortality Data in the Rofecoxib Program

Data on mortality come from the following sources:

- OA Phase IIb/III Program (OA patients; Rofecoxib versus Diclofenac, Ibuprofen, and Nabumetone)
- ADVANTAGE (OA patients; Rofecoxib versus Naproxen)
- VIGOR (RA patients; Rofecoxib versus Naproxen)
- RA Phase IIb/III Program (RA patients; Rofecoxib versus Naproxen)
- Alzheimer's Disease Program (Elderly patients with Alzheimer's Disease or Minimal Cognitive Impairment; Rofecoxib versus Placebo)

Deaths are attributed to one of the treatment groups if the adverse experience leading to death began within 14 days of the patient's discontinuing study therapy.

OA Phase IIb/III Program Mortality Data

There were a total of 13 deaths in the 8 protocols (029, 033, 034, 035, 040, 044, 045, 058): 5 deaths in patients taking rofecoxib (N=3358, patient-years = 2390; rate = 0.22 per 100 patient-years) and 8 in patients taking the non-selective NSAIDs ibuprofen, diclofenac, or nabumetone (N=1565, patient-years = 1032; rate = 0.82 per 100 patient-years). The p-value for the logrank comparison between rofecoxib and non-selective NSAIDs was 0.014.

ADVANTAGE Mortality Data

There were 9 deaths in the ADVANTAGE study: 5 in patients taking rofecoxib (0.78 per 100 patient-years) and 4 (0.64 per 100 patient-years) in patients taking naproxen. Cardiovascular etiologies accounted for 4 deaths in the rofecoxib and none in the naproxen group.

VIGOR Mortality Data

There were a total of 37 deaths in the VIGOR study: 22 in patients taking rofecoxib (0.81 per 100 patient-years) and 15 in patients taking naproxen (0.56 per 100 patient-years). The difference between the groups was not statistically significant. Cardiovascular mortality was similar in the 2 treatment groups.

RA Phase IIb/III Mortality Data

A total of 8 patients died in the RA Phase IIb/III program: 1 on placebo (183 patients-years; rate = 0.55 per 100 patient-years), 5 on rofecoxib (1665 patients-years, rate = 0.30 per 100 patient-years), and 2 on naproxen (512 patient-years; rate = 0.39 per 100 patient-years). There was 1 cardiovascular death in the rofecoxib group and 1 in the naproxen group. There were no significant differences between the treatment groups.

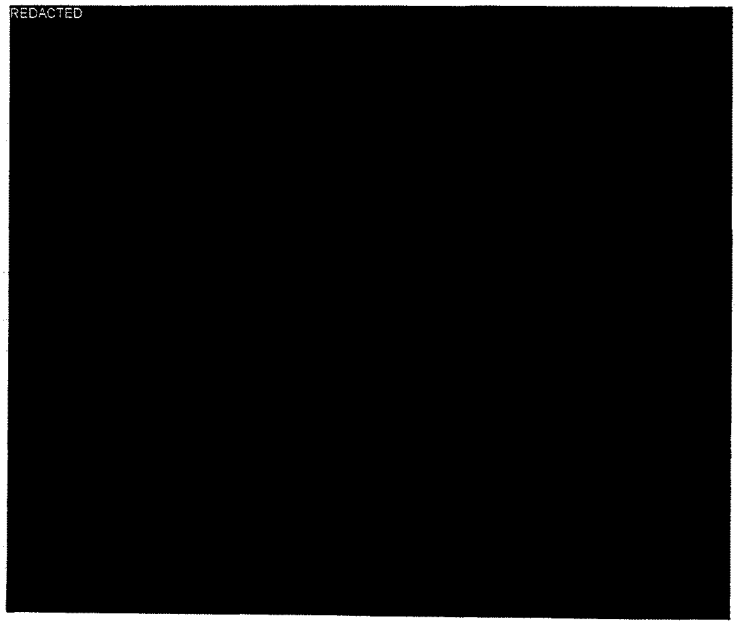
Alzheimer's Disease Program Mortality Data

At the time of data cutoff for the SUR of July-2001, the overall exposure to rofecoxib 25 mg or placebo in 3 Alzheimer's studies (Protocols 078, 091, and 126) was 1461 patient-years in the rofecoxib group (N=1448) and 1634 patient-years in the placebo group (N=1451). There have been a total of 53 deaths in these 3 studies. In final data from Protocols 091 and 126, 18 patients in the rofecoxib group and 11 in the placebo group died; in interim data from Protocol 078, an additional 15 patients in the rofecoxib group and 9 in the placebo group died. Overall, there were 33 deaths in the rofecoxib group (2.2 per 100 patient-years) and 20 deaths in the placebo group (1.2 per 100 patient-years). The p-value for the logrank comparison between rofecoxib and placebo was 0.026.

Although there was a significant difference between rofecoxib and placebo groups in overall mortality based on the total number of deaths in all 3 protocols combined, there were no notable trends in the data. Examination of the most frequent causes of death reveals that 4 and 7 patients in the rofecoxib and placebo groups, respectively, died due to malignancies; 8 and 5 died from infectious causes (some associated with underlying malignancies); 4 and 1 died due to trauma; and 10 and 6 patients in the rofecoxib and placebo groups, respectively, died from a cardiovascular adverse experience. Based on these data, it was concluded that the difference between rofecoxib and placebo in overall mortality does not reflect any increases in particular types of events to suggest causality. As one of the studies is ongoing, these results will be carefully followed.

Overall Conclusions — Rofecoxib Mortality Data

There is no trend for a difference in the rate of mortality with rofecoxib compared with other NSAIDs. Although interim data from the Alzheimer's Disease program suggest a possible increased rate of overall mortality versus placebo, there were no trends for increases in particular types of events to suggest causality.



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11. Epidemiologic data on CV Events in Naproxen Users

Epidemiological studies evaluating the association of use of any NSAID and thromboembolic events have generally found no relationship between the exposure and the outcome {3074, 3079, 3080, 3082, 3077}. In one possible exception, Sajadieh used data from the randomized, double-blind, placebo-controlled Danish Verapamil Infarction Trial (DAVIT) II to study the association of baseline NSAID use with the trial outcome of overall mortality, first re-infarction, and major cardiac event (first re-infarction or death) in patients with recent acute myocardial infarction (MI) {3078}. There was a trend in favor of those with NSAIDs at baseline compared with those with no NSAIDs at baseline, adjusting for age, gender, and hypertension. The adjusted relative risks (95% CI) of mortality, re-infarction, and major event were 0.59 (0.28, 1.25), 0.76 (0.37, 1.55), and 0.67 (0.37, 1.55), respectively, among those with NSAIDs at baseline (n=88) compared with those with no NSAIDs at baseline (n=1687). The authors concluded that the non-significant benefit of NSAIDs observed in the study was worth evaluation in a prospective randomized clinical trial {3078}.

As described below, six studies have looked at the association of naproxen with thromboembolic events; 1 showed no effect of naproxen; 1 identified a trend in favor of naproxen; and 3 demonstrated a relationship between the use of naproxen and reduction in CV outcomes.

In a recent report, Ray et al. examined a group of 50 to 84 year old Tennessee Medicaid enrollees who received a new prescription for a non-aspirin NSAID and compared them to a control group without an NSAID prescription {3077}. The relative rates of hospitalization for acute MI or coronary heart disease death were determined for the overall cohorts and for 2 subgroups: ibuprofen users and naproxen users. They found no association between use of any NSAID, naproxen or ibuprofen and the outcome. Analyses of long term (>60 days) users of these drugs also found no association of the exposure with the endpoint. Although the authors concluded there was no evidence of a cardioprotective effect of naproxen or other non-aspirin NSAIDs in the study, they acknowledged that the lack of a protective effect for naproxen could be due to the manner in which NSAIDs were used by the study population; in the general population NSAIDs are mostly taken for acute pain and osteoarthritis and as a result their use is likely to be intermittent. As detailed in the Clinical Pharmacology section, the intermittent use of naproxen 500 mg would not be expected to be cardioprotective . Such an effect of naproxen would more likely be evident in patients who use naproxen on a consistent basis such as those with RA or patients in a clinical trial.

A subanalyses of individual NSAIDs was also performed by Schlienger *et al.* as part of their large analysis of all NSAIDs mentioned above {3079}. Although underpowered, a trend was identified for a decreased risk of thromboembolic events with naproxen use compared with no NSAID use (odds ratio 0.7). A decreased risk was not evident with other NSAIDs {3079}.

Notably, three recent reports identified a statistically significant decreased risk of thromboembolic events with naproxen {3076, 3081, 3083}. Rahme et al. studied the association of NSAIDs, and naproxen specifically, with hospitalization for first acute MI (AMI) in a

population-based study of 14,163 elderly patients with AMI and 14,160 gender- and age-matched controls in Quebec. The odds ratio (OR) for concurrent chronic exposure to naproxen (at least 2 prescriptions and a total of ≥60 consecutive exposure days in the prior year) and exposure at the index date was 0.65 (95% CI 0.48, 0.87) compared with concurrent chronic users of other NSAIDs, controlling for use in the prior year of anticoagulants, nitrates, antidiabetic agents, antihypertensive agents, lipid lowering agents, and baseline comorbidity. The OR for concurrent users of naproxen versus concurrent users of other NSAIDs was 0.79 (95% CI 0.63, 1.00). The authors concluded that concurrent naproxen prescription had a protective effect against AMI and that this effect seemed only to be present with current use and was strongest in chronic users. {3076}.

Solomon et al. examined the association between NSAID use and 4,425 patients with MI among 22,125 enrollees in the New Jersey Medicare and Medicaid programs. When all NSAID preparations were studied as a group, NSAID users had the same risk of MI as non-users, whether such use was measured on the index date or at any time in the prior 6 months, controlling for demographic and clinical characteristics that might confound the relationship between NSAID use and subsequent MI. However, use of naproxen was associated with a significant reduction in the risk of MI (OR = 0.84; 95% CI 0.72, 0.98; P = 0.027) and this effect was consistent across several subgroups of the population. The authors concluded that use of naproxen specifically appeared to be associated with a reduced rate of MI. {3081}.

Watson et al. studied the risk of first acute thromboembolic events (MI, stroke, and sudden death) with naproxen use among 17,006 patients 40 to 79 years old with RA in the UK population-based General Practice Research Database. Eight hundred seventy three patients with acute thromboembolic events were identified and compared with 2013 gender-, age- and practice-matched controls. Current naproxen use (prescription within 30 days) was more common in controls (6.5%) than cases (3.6%). The OR and (95% CI) for current naproxen (vs. none in the past year) with adjustment for potential confounders including cardiovascular disease risk was 0.58 (0.37, 0.92). Sensitivity analyses supported this finding. The authors concluded that RA patients currently treated with naproxen may have a reduced risk of acute major thromboembolic events relative to those with no naproxen in the past year. {3083}.

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[redacted]

Ref.	First author	Study Design	Number of patients	Outcome Evaluated	Therapy assessed	Relative Risk (95% CI)	Caveats
{3074}	G-Rodriguez	Retrospective cohort, post-menopausal 50-74 yo) UK women	1242 cases 5000 controls	Acute MI	Any NSAID: Current Past	 1.45 (1.18, 1.79) 0.89 ((0.76, 1.05)	Most NSAID therapy for acute indications or OA No OTC drug use data No compliance data Lower CHD risk population Not all CHD risk factors assessed
{3078}	Sajadieh	Clinical trial sub-analysis, patients post-acute MI, treated with verapamil or placebo (<76 yo)	NSAIDs at baseline (N=88) No NSAID at baseline (N=1687)	Endpoints 1. Overall mortality 2. First re-infarction 3. Above combined	Any NSAID at baseline vs. none	For endpoint: 1. 0.59 (0.28, 1.25) 2. 0.76 (0.37, 1.55) 3. 0.67 (0.37, 1.55)	Clinical trial subset analysis Low power to assess NSAID effects
{3080}	Solomon	Case-control, NJ medicare/ medicaid patients (age unknown)	4772 cases 19,148 controls	Acute MI	Any NSAID Current Within 6 months	Unadjusted 1.02 (0.91, 1.15) 1.02 (0.95, 1.09) Similar results on multivariable analyses	No OTC drug use data No compliance data Not all CHD risk factors assessed
{3082}	Valentgas	Retrospective cohort, HMO patients (40-64 yo)	78,822 patients 123 case in 45,883 py of follow-up	Acute MI or CHD death	Current any NSAID	0.97 (0.53, 1.78)	Details unknown

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Ref.	First author	Study Design	Number of patients	Outcome Evaluated	Therapy assessed	Relative Risk (95% CI)	Caveats
{3077}	Ray	Retrospective cohort, Tennessee Medicaid patients (50-84 yo)	181,144 treatment periods and same number of control periods	Acute MI or death from coronary heart disease	Current: Any NSAID Ibuprofen Naproxen	1.03 ((0.92, 1.16) 1.15 (1.02, 1.28) 0.95 (0.82, 1.09)	Most NSAID therapy for acute indications or OA No OTC drug use data No compliance data Not all CHD risk factors assessed
{3079}	Schlienger	Case-control, UK general population (≤75)	3315 cases 13,139 controls	Acute MI	Any NSAID Current Recent Past Naproxen Current	 1.2 (0.9, 1.4) 1.3 (1.0, 1.6) 1.0 (0.9, 1.1) 0.7 (0.4, 1.1)	No OTC drug use data No compliance data Low power to assess individual NSAID effects Not all CHD risk factors assessed
{3076}	Rahme	Case-control, elderly (≥65 yo) Canadians	14,163 case 14,160 controls	Hospitalization for acute MI	Naproxen vs. other NSAID: Chronic current Current	 0.65 (0.48, 0.87) 0.79 (0.63, 1.00)	Most NSAID therapy for acute indications or OA No OTC drug use data No compliance data Not all CHD risk factors assessed
{3081}	Solomon	Case-control, NJ medicare/ medicaid patients (all ages)	4425 cases 17,700 controls	Hospitalization for acute MI	Current: Any NSAID Ibuprofen Naproxen	 1.04 (0.92 - 1.18) 1.00 (unknown) 0.84 (0.72, 0.98)	No OTC drug use data No compliance data Not all CHD risk factors assessed
{3083}	Watson	Case-control, UK general population, patients with RA (40-79)	873 cases 2013 controls	Thromboembolic events (MI, stroke, sudden death)	Current naproxen	0.58 (0.37, 0.92)	RA patient population No OTC drug use data No compliance data Not all CHD risk factors assessed

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Attachment 1 Pooled-Analysis of Cardiovascular Events with Rofecoxib

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Table 19

Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences
Rofecoxib Versus Placebo in Alzheimer's Disease Protocols
Updated Results

Indication for Treatment	Study Group	Rofecoxib N	Rofecoxib Cases/PYR[1] (Rate[2])	Placebo N	Placebo Cases/PYR[1] (Rate[2])	Relative Risk (95% CI)[3]
Rofecoxib Vs. Placebo						
Alzheimer's	Protocol 078	721	32/987 (3.24)	729	42/1080 (3.89)	0.83 (0.51, 1.35)
	Protocol 091	346	12/298 (4.02)	346	15/366 (4.10)	0.98 (0.42, 2.25)
	Protocol 126	381	8/164 (4.86)	376	5/169 (2.95)	1.65 (0.47, 6.40)
Total	All	1448	52/1450 (3.59)	1451	62/1615 (3.84)	0.93 (0.63, 1.37)

[1]Patient-years at risk.
[2]Per 100 PYR.
[3]Relative risk of rofecoxib with respect to comparator is calculated from ratio of rates.

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Table 20

Summary of Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences by Type of Event—Alzheimer's Disease Protocols

	Rofecoxib N=1448		Placebo N=1451	
	n	(%)	n	(%)
Patients with one or more adverse experiences	52	3.59	62	4.27
Patients with no adverse experience	1396	96.41	1389	95.73
Cardiac Events	**28**	**1.93**	**32**	**2.21**
Acute myocardial infarction	3	0.21	3	0.21
Angina pectoris	2	0.14	5	0.34
Cardiac arrest	4	0.28	2	0.14
Coronary artery disease	11	0.76	9	0.62
Coronary artery occlusion	2	0.14	3	0.21
Coronary artery stenosis	0	0	1	0.07
Myocardial infarction	7	0.48	12	0.83
Non-Q-wave myocardial infarction	1	0.07	1	0.07
Unstable angina	3	0.21	3	0.21
Ventricular fibrillation	2	0.14	0	0
Ventricular tachycardia	0	0	4	0.28
Cerebrovascular Events	**21**	**1.45**	**29**	**2.00**
Carotid artery obstruction	2	0.14	8	0.55
Cerebellar hemorrhage	0	0	1	0.07
Cerebral atherosclerosis	1	0.07	0	0
Cerebral infarction	1	0.07	0	0
Cerebrovascular accident	10	0.69	10	0.69
Intracranial hemorrhage	1	0.07	1	0.07
Lacunar infarction	0	0	1	0.07
Transient ischemic attack	9	0.62	8	0.55
Peripheral Events	**3**	**0.21**	**4**	**0.28**
Deep venous thrombosis	0	0	3	0.21
Femoral artery occlusion	0	0	1	0.07
Pulmonary embolism	2	0.14	0	0
Thrombosis	1	0.07	0	0
Vascular graft occlusion	0	0	1	0.07

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

7. RA Phase IIb/III Program CV data (Rofecoxib versus Naproxen)

The RA Phase IIb/III program consisted of 4 studies. Protocol 068 was an 8-week placebo-controlled Phase IIb dose-range finding study with naproxen-controlled extensions; Protocols 096 and 097 were 12-week Phase III, placebo and naproxen-controlled, pivotal efficacy studies with naproxen-controlled extensions, and Protocol 098/103 was a 12-week placebo and naproxen-controlled endoscopy trial. There were 989 patients initially assigned to the placebo group, 1623 assigned to rofecoxib 12.5, 25, or 50 mg, and 516 patients assigned to naproxen. In

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx: Putting Patient Safety First?"

November 18, 2004

Exhibit 43

To: Anstice, David W.
From: Cannell, Thomas R.
Cc Schechter, Adam H
Bcc:
Date: 2002-02-12 12:46:35
Subject: RE: Month #4 VIP Update

Hi David. We expect another ~10% of targeted accounts to enroll – which will bring us to ~75%. Of the remaining 25%, the most common reasons are: (1) concerns about CV issues, and (2) non-restrictive formularies (they don't want to make any product "exclusive"). At our Operations Review next Monday we'll have a slide with account-specific info on the flagship accounts that haven't enrolled.

Regarding your 2nd point, we will definitely come to you before we make a final decision on how to manage hospitals that failed to achieve the 80% threshold. That is a critical issue and there are some key lessons learned from SAVE and FLEX.

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx: Putting Patient Safety First?"

November 18, 2004

Exhibit 44

U.S. Food and Drug Administration

FDA Talk Paper

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T02-18
April 11, 2002

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA Approves New Indication and Label Changes for the Arthritis Drug, Vioxx

FDA has approved a supplemental application for the use of Vioxx (rofecoxib) for rheumatoid arthritis adding the indication to the previously approved indications for osteoarthritis and pain. FDA has also approved new label text and precautions that are based on the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR).

The VIGOR study, a prospective, randomized, double-blind, one year study, evaluated approximately 4000 patients on Vioxx 50 mg a day (twice the highest approved dose for chronic use) and approximately 4000 patients on the standard dose of naproxen (1000 mg a day), a non-steroidal anti-inflammatory drug (NSAID). Patients who were under treatment with low dose aspirin for heart attack prevention were excluded from the study.

The study demonstrated that Vioxx was associated with a lower incidence of serious upper gastrointestinal(GI) adverse events of major bleeding, perforation and obstruction compared to naproxen. The reduction in risk was over 50 percent in cumulative rates for Vioxx (.52%) compared to naproxen (1.22%).

An additional finding in the study, however, was that there was a higher cumulative rate of serious cardiovascular thromboembolic adverse events (such as heart attacks, angina pectoris, and peripheral vascular events) in the Vioxx group (1.8%) compared to the naproxen group (0.6%). Data from two smaller studies comparing placebo and Vioxx 25 mg daily did not show a difference in the rate of serious cardiovascular thromboembolic adverse events. The relationship of the cardiovascular findings in the VIGOR study to use of Vioxx is not known.

After carefully reviewing the results of the VIGOR Study, FDA agreed with the Arthritis Advisory Committee recommendations of February 8, 2001 that the label for Vioxx should include the gastrointestinal and cardiovascular information. The committee advised that the NSAID-class warning regarding GI adverse events should be modified, but not removed from the VIOXX label. This warning advises patients and their doctors about the risks of GI ulcers, bleeding, and perforation.

The committee also advised that the CV findings should be included in the Vioxx label to provide doctors and patients with the available data on the potential risks and benefits of Vioxx compared to naproxen. The new labeling information approved by FDA will advise doctors to use caution in prescribing Vioxx for patients with ischemic heart disease and notes that Vioxx 50 mg is not recommended for chronic use.

In addition, the new label provides information from studies of patients with rheumatoid arthritis at the chronic dose of 25 mg, showing that Vioxx was associated with a higher incidence of hypertension compared to naproxen 1000 mg.

In addition, the geriatric section of the label will reinforce information in the existing standard warning section of all NSAIDs indicating that the elderly are at higher risk of serious GI and renal events such GI bleeding and acute renal failure.

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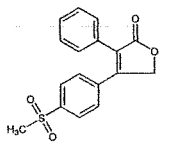
VIOXX®

(rofecoxib tablets and oral suspension)

DESCRIPTION

VIOXX® (rofecoxib) is described chemically as 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone. It has the following chemical structure:



Rofecoxib is a white to off-white to light yellow powder. It is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol, and insoluble in water. The empirical formula for rofecoxib is $C_{17}H_{14}O_4S$, and the molecular weight is 314.36.

Each tablet of VIOXX for oral administration contains either 12.5 mg, 25 mg, or 50 mg of rofecoxib and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide. The 50 mg tablets also contain red ferric oxide.

Each 5 mL of the oral suspension contains either 12.5 or 25 mg of rofecoxib and the following inactive ingredients: citric acid (monohydrate), sodium citrate (dihydrate), sorbitol solution, strawberry flavor, xanthan gum, and purified water. Added as preservatives are sodium methylparaben 0.13% and sodium propylparaben 0.02%.

CLINICAL PHARMACOLOGY

Mechanism of Action

VIOXX is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Pharmacokinetics

Absorption

The mean oral bioavailability of VIOXX at therapeutically recommended doses of 12.5, 25, and 50 mg is approximately 93%. The area under the curve (AUC) and peak plasma level (C_{max}) following a single 25-mg dose were 3286 (±843) ng•hr/mL and 207 (±111) ng/mL, respectively. Both C_{max} and AUC are roughly dose proportional across the clinical dose range. At doses greater than 50 mg, there is a less than proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. The plasma concentration-time profile exhibited multiple peaks. The median time to maximal concentration (T_{max}), as assessed in nine pharmacokinetic studies, is 2 to 3 hours. Individual T_{max} values in these studies ranged between 2 to 5 hours. This may not reflect rate of absorption as T_{max} may occur as a secondary peak in some individuals. With multiple dosing, steady-state conditions are reached by Day 4. The AUC_{24hr} and C_{max} at steady state after multiple doses of 25-mg rofecoxib was 4018 (±1140) ng•hr/mL and 321 (±104) ng/mL, respectively. The accumulation factor based on geometric means was 1.67.

VIOXX Tablets 12.5 mg and 25 mg are bioequivalent to VIOXX Oral Suspension 12.5 mg/5 mL and 25 mg/5 mL, respectively.

Food and Antacid Effects

Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of rofecoxib when VIOXX Tablets were taken with a high fat meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1 to 2 hours. The food effect on the suspension formulation has not been studied. VIOXX tablets can be administered without regard to timing of meals.

There was a 13% and 8% decrease in AUC when VIOXX was administered with calcium carbonate antacid and magnesium/aluminum antacid to elderly subjects, respectively. There was an approximate 20% decrease in C_{max} of rofecoxib with either antacid.

Distribution

Rofecoxib is approximately 87% bound to human plasma protein over the range of concentrations of 0.05 to 25 mcg/mL. The apparent volume of distribution at steady state (V_{ss}) is approximately 91 L following a 12.5-mg dose and 86 L following a 25-mg dose.

Rofecoxib has been shown to cross the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Metabolism of rofecoxib is primarily mediated through reduction by cytosolic enzymes. The principal metabolic products are the *cis*-dihydro and *trans*-dihydro derivatives of rofecoxib, which account for nearly 56% of recovered radioactivity in the urine. An additional 9.8% of the dose was recovered as the glucuronide of the hydroxy derivative, a product of oxidative metabolism. The biotransformation of rofecoxib and this metabolite is reversible in humans to a limited extent (<5%). These metabolites are inactive as COX-1 or COX-2 inhibitors.

Cytochrome P450 plays a minor role in metabolism of rofecoxib. Inhibition of CYP 3A activity by administration of ketoconazole 400 mg daily does not affect rofecoxib disposition. However, induction of general hepatic metabolic activity by administration of the non-specific inducer rifampin 600 mg daily produces a 50% decrease in rofecoxib plasma concentrations. (Also see *Drug Interactions*.)

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Excretion

Rofecoxib is eliminated predominantly by hepatic metabolism with little (<1%) unchanged drug recovered in the urine. Following a single radiolabeled dose of 125 mg, approximately 72% of the dose was excreted into the urine as metabolites and 14% in the feces as unchanged drug.

The plasma clearance after 12.5- and 25-mg doses was approximately 141 and 120 mL/min, respectively. Higher plasma clearance was observed at doses below the therapeutic range, suggesting the presence of a saturable route of metabolism (i.e., non-linear elimination). The effective half-life (based on steady-state levels) was approximately 17 hours.

Special Populations

Gender

The pharmacokinetics of rofecoxib are comparable in men and women.

Geriatric

After a single dose of 75 mg VIOXX in elderly subjects (over 65 years old) a 34% increase in AUC was observed as compared to the young subjects. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

Pediatric

VIOXX has not been investigated in patients below 18 years of age.

Race

Meta-analysis of pharmacokinetic studies has suggested a slightly (10-15%) higher AUC of rofecoxib in Blacks and Hispanics as compared to Caucasians. No dosage adjustment is necessary on the basis of race.

Hepatic Insufficiency

A single dose pharmacokinetic study in mild (Child-Pugh score ≤6) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. [redacted] Patients with severe hepatic insufficiency have not been studied.

Renal Insufficiency

In a study (N=6) of patients with end stage renal disease undergoing dialysis, peak rofecoxib plasma levels and AUC declined 18% and 9%, respectively, when dialysis occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the elimination profile of rofecoxib was unchanged. While renal insufficiency does not influence the pharmacokinetics of rofecoxib, use of VIOXX in advanced renal disease is not recommended. [redacted]

Drug Interactions (Also see PRECAUTIONS, *Drug Interactions*.)

General

In human studies the potential for rofecoxib to inhibit or induce CYP 3A4 activity was investigated in studies using the intravenous erythromycin breath test and the oral midazolam test. No significant difference in erythromycin demethylation was observed with rofecoxib (75 mg daily) compared to placebo, indicating no induction of hepatic CYP 3A4. A 30% reduction of the AUC of midazolam was observed with rofecoxib (25 mg daily). This reduction is most likely due to increased first pass metabolism through induction of intestinal CYP 3A4 by rofecoxib. *In vitro* studies in rat hepatocytes also suggest that rofecoxib might be a mild inducer for CYP 3A4.

Drug interaction studies with [redacted] rofecoxib have identified potentially significant interactions with rifampin, [redacted] and warfarin. Patients receiving these agents with VIOXX should be appropriately monitored. Drug interaction studies do not support the potential for clinically important interactions between antacids or cimetidine with rofecoxib. Similar to experience with other nonsteroidal anti-inflammatory drugs (NSAIDs), studies with rofecoxib suggest the potential for interaction with ACE inhibitors. The effects of rofecoxib on the pharmacokinetics and/or pharmacodynamics of ketoconazole, prednisone/prednisolone, oral contraceptives, and digoxin have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Osteoarthritis (OA)

VIOXX has demonstrated significant reduction in joint pain compared to placebo. VIOXX was evaluated for the treatment of the signs and symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of 6 to 86 weeks duration that enrolled approximately 3000 patients. In patients with OA, treatment with VIOXX 12.5 mg and 25 mg once daily resulted in improvement in patient and physician global assessments and in the WOMAC (Western Ontario and McMaster Universities) osteoarthritis questionnaire, including pain, stiffness, and functional measures of OA. In six studies of pain accompanying OA flare, VIOXX provided a significant reduction in pain at the first determination (after one week in one study, after two weeks in the remaining five studies) that continued for the duration of the studies. In all OA clinical studies, once daily treatment in the morning with VIOXX 12.5 and 25 mg was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg, the effectiveness of VIOXX was shown to be comparable to ibuprofen 800 mg TID and diclofenac 50 mg TID for treatment of the signs and symptoms of OA. The ibuprofen studies were 6-week studies; the diclofenac studies were 12-month studies in which patients could receive additional arthritis medication during the last 6 months.

Rheumatoid Arthritis (RA)

[redacted]

Analgesia, including Dysmenorrhea

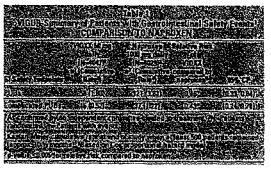
In acute analgesic models of post-operative dental pain, post-orthopedic surgical pain, and primary dysmenorrhea, VIOXX relieved pain that was rated by patients as moderate to severe. The analgesic effect (including onset of action) of a single 50-mg dose of VIOXX was generally similar to 550 mg of naproxen sodium or 400 mg of ibuprofen. In single-dose post-operative dental pain studies, the onset of analgesia with a single 50-mg dose of VIOXX occurred within 45 minutes. In a multiple-dose study of post-orthopedic surgical pain in which patients received VIOXX or placebo for up to 5 days, 50 mg of VIOXX once daily was effective in reducing pain. In this study, patients on VIOXX consumed a significantly smaller amount of additional analgesic medication than patients treated with placebo (1.5 versus 2.5 doses per day of additional analgesic medication for VIOXX and placebo, respectively).

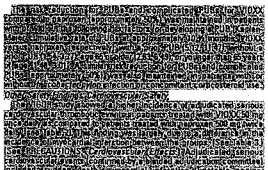
Special Studies

[redacted]

VIOXX Gastrointestinal Outcomes Research (VIGOR Study)

[redacted]





Cardiovascular Thrombotic Events

[redacted]

[redacted]

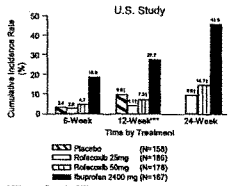
Two identical (U.S. and Multinational) endoscopy studies in a total of 1516 patients were conducted to compare the percentage of patients who developed endoscopically detectable gastroduodenal ulcers with VIOXX 25 mg daily or 50 mg daily, ibuprofen 2400 mg daily, or placebo. Entry criteria for these studies permitted enrollment of patients with active *Helicobacter pylori* infection, baseline gastroduodenal erosions, prior history of an upper gastrointestinal perforation, ulcer, or bleed (PUB), and/or age ≥65 years. However, patients receiving aspirin (including low-dose aspirin for cardiovascular prophylaxis) were not enrolled in these studies. Patients who were 50 years of age and older with osteoarthritis and who had no ulcers at baseline were evaluated by endoscopy after weeks 6, 12, and 24 of treatment. The placebo-treatment group was discontinued at week 16 by design.

Treatment with VIOXX 25 mg daily or 50 mg daily was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. See Figures 1 and 2 for the results of these studies.

Figure 1

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3mm (Intention-to-Treat)**



* p < 0.001 versus Ibuprofen 2400 mg

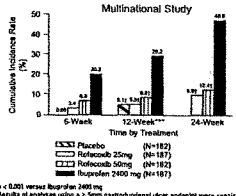
** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.

*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

Figure 2

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3mm (Intention-to-Treat)**



* p < 0.001 versus Ibuprofen 2400 mg

** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.

*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

[redacted]

Serious clinically significant upper GI bleeding has been observed in patients receiving VIOXX in controlled trials, albeit infrequently (see WARNINGS, *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation*).

Assessment of Fecal Occult Blood Loss in Healthy Subjects

Occult fecal blood loss associated with VIOXX 25 mg daily, VIOXX 50 mg daily, ibuprofen 2400 mg per day, and placebo was evaluated in a study utilizing ^{51}Cr-tagged red blood cells in 87 healthy males. After 4 weeks of treatment with VIOXX 25 mg daily or VIOXX 50 mg daily, the increase in the amount of fecal blood loss was not statistically significant compared with placebo-treated subjects. In contrast, ibuprofen 2400 mg per day produced a statistically significant increase in fecal blood loss as compared with placebo-treated subjects and VIOXX-treated subjects. The clinical relevance of this finding is unknown.

Platelets

Multiple doses of VIOXX 12.5, 25, and up to 375 mg administered daily up to 12 days had no effect on bleeding time relative to placebo. There was no inhibition of ex vivo arachidonic acid- or collagen-induced platelet aggregation with 12.5, 25, and 50 mg of VIOXX.

[redacted]

INDICATIONS AND USAGE

VIOXX is indicated:

For relief of the signs and symptoms of osteoarthritis.

For relief of the signs and symptoms of rheumatoid arthritis in adults.

For the management of acute pain in adults.

For the treatment of primary dysmenorrhea.

CONTRAINDICATIONS

VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX.

VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, *Anaphylactoid Reactions* and PRECAUTIONS, *Preexisting Asthma*).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

[redacted]

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

[redacted] studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to VIOXX. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving VIOXX. VIOXX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, *Preexisting Asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

[redacted] with VIOXX is not recommended in patients with advanced renal disease. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, *Renal Effects*).

Pregnancy

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

VIOXX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Cardiovascular Effects

[redacted]

Renal Effects

[redacted]

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs, including VIOXX. In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking rofecoxib (12.5 or 25 mg QD) and 0.1% of patients taking placebo had notable elevations of ALT or AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with VIOXX. Use of VIOXX is not recommended in patients with severe hepatic insufficiency (see *Pharmacokinetics, Special Populations*). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), VIOXX should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving VIOXX. In placebo-controlled trials, there were no significant differences observed

between VIOXX and placebo in clinical reports of anemia. Patients on long-term treatment with VIOXX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. VIOXX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages (see CLINICAL STUDIES, *Special Studies, Platelets*).

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, VIOXX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

[redacted]

VIOXX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up. [redacted] WARNINGS, *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation.* [redacted]

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, edema [redacted] to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

Drug Interactions

ACE Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. In patients with mild to moderate hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mm Hg compared to ACE inhibitor alone. This interaction should be given consideration in patients taking VIOXX concomitantly with ACE inhibitors.

Aspirin: Concomitant administration of low-dose aspirin with VIOXX may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX alone. At steady state, VIOXX 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by *ex vivo* platelet aggregation and serum TXB_2 generation in clotting blood. [redacted] VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. [redacted]

Cimetidine: Co-administration with high doses of cimetidine (800 mg twice daily) increased the C_{max} of rofecoxib by 21%, the $AUC_{0-120hr}$ by 23% and the $t_{1/2}$ by 15%. These small changes are not clinically significant and no dose adjustment is necessary.

Digoxin: Rofecoxib 75 mg once daily for 11 days does not alter the plasma concentration profile or renal elimination of digoxin after a single 0.5 mg oral dose.

Furosemide: Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Ketoconazole: Ketoconazole 400 mg daily did not have any clinically important effect on the pharmacokinetics of rofecoxib.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. In post-marketing experience there have been reports of increases in plasma lithium levels. Thus, when VIOXX and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: [redacted] VIOXX 75 mg administered once daily for 10 days increased plasma concentrations by 23% as measured by AUC_{0-24hr} in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. At 24 hours postdose, a similar proportion of patients treated with methotrexate alone (94%) and subsequently treated with methotrexate co-administered with 75 mg of rofecoxib (88%) had methotrexate plasma concentrations below the measurable limit (5 ng/mL). Standard monitoring of methotrexate-related toxicity should be continued if VIOXX and methotrexate are administered concomitantly.

Oral Contraceptives: Rofecoxib did not have any clinically important effect on the pharmacokinetics of ethinyl estradiol and norethindrone.

Prednisone/prednisolone: Rofecoxib did not have any clinically important effect on the pharmacokinetics of prednisolone or prednisone.

Rifampin: Co-administration of VIOXX with rifampin 600 mg daily, a potent inducer of hepatic metabolism, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, a starting daily dose of 25 mg of VIOXX should be considered for the treatment of osteoarthritis when VIOXX is co-administered with potent inducers of hepatic metabolism.

[redacted]

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing VIOXX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. In single and multiple dose studies in healthy subjects receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rofecoxib was not carcinogenic in mice given oral doses up to 30 mg/kg (male) and 60 mg/kg (female) (approximately 5- and 2-fold the human exposure at 25 and 50 mg daily based on AUC_{0-24}) and in male and female rats given oral doses up to 8 mg/kg (approximately 6- and 2-fold the human exposure at 25 and 50 mg daily based on AUC_{0-24}) for two years.

Rofecoxib was not mutagenic in an Ames test or in a V-79 mammalian cell mutagenesis assay, nor clastogenic in a chromosome aberration assay in Chinese hamster ovary (CHO) cells, in an *in vitro* and an *in vivo* alkaline elution assay, or in an *in vivo* chromosomal aberration test in mouse bone marrow.

Rofecoxib did not impair male fertility in rats at oral doses up to 100 mg/kg (approximately 20- and 7-fold human exposure at 25 and 50 mg daily based on the AUC_{0-24}) and rofecoxib had no effect on fertility in female rats at doses up to 30 mg/kg (approximately 19- and 7-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}).

Pregnancy

Teratogenic effects: Pregnancy Category C.

Rofecoxib was not teratogenic in rats at doses up to 50 mg/kg/day (approximately 28- and 10-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). There was a slight, non-statistically significant increase in the overall incidence of vertebral malformations only in the rabbit at doses of 50 mg/kg/day (approximately 1- or <1-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). There are no studies in pregnant women. VIOXX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects

Rofecoxib produced peri-implantation and post-implantation losses and reduced embryo/fetal survival in rats and rabbits at oral doses ≥10 and ≥75 mg/kg/day, respectively (approximately 9- and 3-fold [rats] and 2- and <1-fold [rabbits] human exposure based on the AUC_{0-24} at 25 and 50 mg daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function. There was an increase in the incidence of postnatal pup mortality in rats at ≥5 mg/kg/day (approximately 5- and 2-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). In studies in pregnant rats administered single doses of rofecoxib, there was a treatment-related decrease in the diameter of the ductus arteriosus at all doses used (3-300 mg/kg: 3 mg/kg is approximately 2- and <1-fold human exposure at 25 or 50 mg daily based on AUC_{0-24}). As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX during the third trimester of pregnancy should be avoided.

Labor and delivery

Rofecoxib produced no evidence of significantly delayed labor or parturition in females at doses 15 mg/kg in rats (approximately 10- and 3-fold human exposure as measured by the AUC_{0-24} at 25 and 50 mg). The effects of VIOXX on labor and delivery in pregnant women are unknown.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to VIOXX while pregnant. Healthcare providers are encouraged to report any prenatal exposure to VIOXX by calling the Pregnancy Registry at (800) 986-8999.

Nursing mothers

Rofecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. There was an increase in pup mortality and a decrease in pup body weight following exposure of pups to milk from dams administered VIOXX during lactation. The dose tested represents an approximate 18- and 6-fold human exposure at 25 and 50 mg based on AUC_{0-24}. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VIOXX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Of the patients who received VIOXX in osteoarthritis clinical trials, 1455 were 65 years of age or older. This included 460 patients who were 75 years or older, and in one of these studies, 174 patients who were 80 years or older. No substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. As with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

ADVERSE REACTIONS

Osteoarthritis

Approximately 3600 patients with osteoarthritis were treated with VIOXX; approximately 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for one year or longer. The following table of adverse experiences lists all adverse events, regardless of causality, occurring in at least 2% of patients receiving VIOXX in nine controlled studies of 6-week to 6-month duration conducted in patients with OA at the therapeutically recommended doses (12.5 and 25 mg), which included a placebo and/or positive control group.

Clinical Adverse Experiences occurring in ≥ 2.0% of Patients Treated with VIOXX in OA Clinical Trials

	Placebo	VIOXX 12.5 or 25 mg daily	Ibuprofen 2400 mg daily	Diclofenac 150 mg daily
	(N = 783)	(N = 2829)	(N = 847)	(N = 498)
Body As A Whole/Site Unspecified				
Abdominal Pain	4.1	3.4	4.6	5.8
Asthenia/Fatigue	1.0	2.2	2.0	2.6
Dizziness	2.2	3.0	2.7	3.4
Influenza-Like Disease	3.1	2.9	1.5	3.2
Lower Extremity Edema	1.1	3.7	3.8	3.4
Upper Respiratory Infection	7.8	8.5	5.8	8.2
Cardiovascular System				
Hypertension	1.3	3.5	3.0	1.6
Digestive System				
Diarrhea	6.8	6.5	7.1	10.6
Dyspepsia	2.7	3.5	4.7	4.0
Epigastric Discomfort	2.8	3.8	9.2	5.4
Heartburn	3.6	4.2	5.2	4.6
Nausea	2.9	5.2	7.1	7.4
Eyes, Ears, Nose, And Throat				
Sinusitis	2.0	2.7	1.8	2.4
Musculoskeletal System				
Back Pain	1.9	2.5	1.4	2.8
Nervous System				
Headache	7.5	4.7	6.1	8.0
Respiratory System				
Bronchitis	0.8	2.0	1.4	3.2
Urogenital System				
Urinary Tract Infection	2.7	2.8	2.5	3.6

In the OA studies, the following spontaneous adverse events occurred in >0.1% to 1.9% of patients treated with VIOXX regardless of causality:

Body as a Whole: abdominal distension, abdominal tenderness, abscess, chest pain, chills, contusion, cyst, diaphragmatic hernia, fever, fluid retention, flushing, fungal infection, infection, laceration, pain, pelvic pain, peripheral edema, postoperative pain, syncope, trauma, upper extremity edema, viral syndrome.

Cardiovascular System: angina pectoris, atrial fibrillation, bradycardia, hematoma, irregular heartbeat, palpitation, premature ventricular contraction, tachycardia, venous insufficiency.

Digestive System: acid reflux, aphthous stomatitis, constipation, dental caries, dental pain, digestive gas symptoms, dry mouth, duodenal disorder, dysgeusia, esophagitis, flatulence, gastric disorder, gastritis, gastroenteritis, hematochezia, hemorrhoids, infectious gastroenteritis, oral infection, oral lesion, oral ulcer, vomiting.

Eyes, Ears, Nose, and Throat: allergic rhinitis, blurred vision, cerumen impaction, conjunctivitis, dry throat, epistaxis, laryngitis, nasal congestion, nasal secretion, ophthalmic injection, otic pain, otitis, otitis media, pharyngitis, tinnitus, tonsillitis.

Immune System: allergy, hypersensitivity, insect bite reaction.

Metabolism and Nutrition: appetite change, hypercholesterolemia, weight gain.

Musculoskeletal System: ankle sprain, arm pain, arthralgia, back strain, bursitis, cartilage trauma, joint swelling, muscular cramp, muscular disorder, muscular weakness, musculoskeletal pain, musculoskeletal stiffness, myalgia, osteoarthritis, tendinitis, traumatic arthropathy, wrist fracture.

Nervous System: hypesthesia, insomnia, median nerve neuropathy, migraine, muscular spasm, paresthesia, sciatica, somnolence, vertigo.

Psychiatric: anxiety, depression, mental acuity decreased.

Respiratory System: asthma, cough, dyspnea, pneumonia, pulmonary congestion, respiratory infection.

Skin and Skin Appendages: abrasion, alopecia, atopic dermatitis, basal cell carcinoma, blister, cellulitis, contact dermatitis, herpes simplex, herpes zoster, nail unit disorder, perspiration, pruritus, rash, skin erythema, urticaria, xerosis.

Urogenital System: breast mass, cystitis, dysuria, menopausal symptoms, menstrual disorder, nocturia, urinary retention, vaginitis.

The following serious adverse events have been reported rarely (estimated <0.1%) in patients taking VIOXX, regardless of causality. Cases reported only in the post-marketing experience are indicated in italics.

Cardiovascular: cerebrovascular accident, congestive heart failure, deep venous thrombosis, myocardial infarction, *pulmonary edema*, pulmonary embolism, transient ischemic attack, unstable angina.

Gastrointestinal: cholecystitis, colitis, colonic malignant neoplasm, *duodenal perforation*, duodenal ulcer, *esophageal ulcer*, *gastric perforation*, *gastric ulcer*, gastrointestinal bleeding, *hepatic failure*, *hepatitis*, intestinal obstruction, *jaundice*, pancreatitis.

Hemic and lymphatic: agranulocytosis, leukopenia, lymphoma, *thrombocytopenia.*

Immune System: anaphylactic/anaphylactoid reaction, angioedema, bronchospasm, hypersensitivity vasculitis.

Metabolism and nutrition: hyponatremia.

Nervous System: aseptic meningitis.

Psychiatric: confusion, hallucinations.

Skin and Skin Appendages: severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Urogenital System: acute renal failure, breast malignant neoplasm, *hyperkalemia, interstitial nephritis,* prostatic malignant neoplasm, urolithiasis, *worsening chronic renal failure.*

In 1-year controlled clinical trials and in extension studies for up to 86 weeks (approximately 900 patients treated with VIOXX for one year or longer), the adverse experience profile was qualitatively similar to that observed in studies of shorter duration.

[redacted]

[redacted]

Approximately one thousand patients were treated with VIOXX in analgesia studies. All patients in post-dental surgery pain studies received only a single dose of study medication. Patients in primary dysmenorrhea studies may have taken up to 3 daily doses of VIOXX, and those in the post-orthopedic surgery pain study were prescribed 5 daily doses of VIOXX.

The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies. The following additional adverse experience, which occurred at an incidence of at least 2% of patients treated with VIOXX, was observed in the post-dental pain surgery studies: post-dental extraction alveolitis (dry socket).

[redacted]

[redacted]

OVERDOSAGE

No overdoses of VIOXX were reported during clinical trials. Administration of single doses of VIOXX 1000 mg to 6 healthy volunteers and multiple doses of 250 mg/day for 14 days to 75 healthy volunteers did not result in serious toxicity.

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

Rofecoxib is not removed by hemodialysis; it is not known whether rofecoxib is removed by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

VIOXX is administered orally. The lowest dose of VIOXX should be sought for each patient.

Osteoarthritis

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

[redacted]

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended dose of VIOXX is 50 mg once daily. [redacted] Use of VIOXX for more than 5 days in management of pain has not been studied. [redacted]

[redacted]

VIOXX Tablets may be taken with or without food.

Oral Suspension

VIOXX Oral Suspension 12.5 mg/5 mL or 25 mg/5 mL may be substituted for VIOXX Tablets 12.5 or 25 mg, respectively, in any of the above indications. Shake before using.

HOW SUPPLIED

No. 3810 — Tablets VIOXX, 12.5 mg, are cream/off-white, round, shallow cup tablets engraved MRK 74 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0074-31 unit of use bottles of 30
NDC 0006-0074-28 unit dose packages of 100
NDC 0006-0074-68 bottles of 100
NDC 0006-0074-82 bottles of 1000
NDC 0006-0074-80 bottles of 8000.

No. 3834 — Tablets VIOXX, 25 mg, are yellow, round tablets engraved MRK 110 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0110-31 unit of use bottles of 30
NDC 0006-0110-28 unit dose packages of 100
NDC 0006-0110-68 bottles of 100
NDC 0006-0110-82 bottles of 1000
NDC 0006-0110-80 bottles of 8000.

No. 3835 — Tablets VIOXX, 50 mg, are orange, round tablets engraved MRK 114 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0114-31 unit of use bottles of 30
NDC 0006-0114-28 unit dose packages of 100
NDC 0006-0114-68 bottles of 100
NDC 0006-0114-74 bottles of 500
NDC 0006-0114-81 bottles of 4000.

No. 3784 — Oral Suspension VIOXX, 12.5 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

[redacted]

VIOXX® (rofecoxib tablets and oral suspension)

NDC 0006-3784-54 unit of use bottles containing 150 mL (12.5 mg/5 mL).

No. 3785 — Oral Suspension VIOXX, 25 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

NDC 0006-3785-54 unit of use bottles containing 150 mL (25 mg/5 mL).

Storage

VIOXX Tablets:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

VIOXX Oral Suspension:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

Rx only

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued [redacted]
Printed in USA 918383(3)

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx: Putting Patient Safety First?"

November 18, 2004

Exhibit 45

To: Dan Rader
From: Santanello, Nancy C.
Cc:
Bcc:
Received Date: 2004-03-01 03:43:00
Subject: Please print out for Carolyn

Hi Dan - please print out for Carolyn

Hi Carolyn,

Hope things are going well and that Caleb is eating and sleeping like a good boy so his mom has some time to herself.

I am communicating Alise's response to your voicemail which I had forwarded to her.

Alise agrees with me that while the hypertension issue in the discussion is the number one issue the idea of putting into the abstract findings that were not statistically significant is important to raise with Dan Solomon. Given that this is an observational study with all of the limitations taking a non-significant finding, even if it approaches significance, is not appropriate.

Alise also said that you had everything else dead on regarding hypertension and diclofenac.

Finally, Alise was concerned about getting something back to Dan Solomon as soon as possible. She doe not trust him to send you the galley proofs and wants to make sure that he sees our position on the hypertension issue and the abstract as soon as possible so that we can make a decision regarding whether or not to continue to keep you on as an author.

Let me know if you have any other questions. I am in meetings all day, but will have my cell phone on - REDACTED

Nancy

>>>>>>>>>>>>>>>>>>
Nancy Santanello, MD, MS
Executive Director, Epidemiology
Merck Research Laboratories
BL 1-7, PO Box 4
West Point, PA 19486
Tel: 484-344-7060
FAX: 484-344-2992
nancy_santanello@merck.com
Administrative Assistant: Dawn Moyer (484-344-2938)

To: Santanello, Nancy C.
From: Harry Guess
Cc:
Bcc:
Received Date: 2004-04-08 16:49:05
Subject: Re: Carolyn Cannuscio and manuscript - question/perspective

---

Hi Nancy,

Cindy was removed from authorship on one manuscript.

I don't recall Rob or Eva having been removed, it is possible but I don't recall it.

I removed myself, Paul Coplan, and all Merck authors from an abstract where there was controversy on the methods.

There may well have been other times.

You are very supportive!!!

I'd be happy to discuss this with you.

I'll be working from home tomorrow because it is a UNC holiday.

You can call me at home REDACTED anytime after about 9:00AM. I'll be in and out of the house.

Otherwise call after 5:30PM today on my cellphone REDACTED

I'm at a student presentation in another building between a few minutes from now and about 5:00PM.

Please always feel free to call on things like this.

Harry

Harry A. Guess, MD, PhD
Professor
Department of Epidemiology
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Chapel Hill, NC 27599-7435
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Phone: 919-966-7415
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Administrative Assistant: Lisa Bradley
Phone : 919-966-7405
e-mail: lisa_bradley@unc.edu

Santanello, Nancy C wrote:

>Hi Harry -
>
[redacted]
[redacted] I feel
>that Dan S. is playing a little with Carolyn because he wants her name
>somewhere on this paper to reduce our being able to criticize the paper.
>
>Carolyn wants me to ask your opinion on her being removed from the paper and
>the limited acknowledgement. I told her that in the past you have removed
>Merck Epi co-authors from papers where we found the paper unbalanced or for
>other reasons. My recollection is that this occurred with studies involving
>Cindy on at least one occasion and Rob and Eva. Is this true?
[redacted]
[redacted] Any perspective on this? Any
>advice?
>
>Thanks, Nancy
>
>
>Nancy Santanello, MD, MS
>Executive Director, Epidemiology
>Merck Research Laboratories
>BL 1-7, PO Box 4
>West Point, PA 19486
>Tel: 484-344-7060
>FAX: 484-344-2992
>nancy_santanello@merck.com
>Administrative Assistant: Dawn Moyer (484-344-2938)
>
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>----------
>Notice: This e-mail message, together with any attachments, contains
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>

Watson, Douglas J.

From: Watson, Douglas J.
Sent: Tuesday, February 10, 2004 11:23 AM
To: Schechter, Adam H; Reicin, Alise S.
Cc: Santanello, Nancy C.; Cannuscio, Carolyn C
Subject: RE: Solomon cox2 and mi manuscript accepted to Circ

This was in the last prior version I know of: → from version Dan sent to Circ w/o talking to us

Several biological pathways could underlie a potential association between selective COX-2 inhibition and coronary events. While non-selective NSAIDs inhibit both COX isoforms, selective inhibition of COX-2 results in decreased prostacyclin, a vasodilator and moderator of platelet activation, without reducing COX-1 dependent thromboxanes, contributors to platelet aggregation and vasoconstriction. (21, 22) Emerging data support a varied role for COX-2 in the vascular bed, with important functions in vascular resistance (23), late pre-conditioning (24), endothelial function (25-6), and atherogenesis (27-28). Data from rat models of hypertension suggest that celecoxib but not rofecoxib may be associated with improvements in endothelial function and reductions in oxidative stress (29), but this finding has not been reported in other studies. Rofecoxib has been found to be associated with elevations in blood pressure, whereas celecoxib was not (31). ← new.

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26 . Cheng Y, Austin SC, Rocca B, Koller BH, Coffman TM, Grosser T, Lawson JA, FitzGerald GA. Role of prostacyclin in the cardiovascular response to thromboxane A2. Science 2002;296:539-41.

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28 . Cipollone F, Prontera C, Pini B, et al. Overexpression of functionally coupled cyclooxygenase-2 and prostaglandin E synthase in symptomatic atherosclerotic plaques as a basis of prostaglandin E(2)-dependent plaque instability. Circulation 2001; 104:921-7.

29 . Hermann M, Camici G, Fratton A, et al. Differential effects of selective cyclooxygenase-2 inhibitors on endothelial dysfunction in salt-induced hypertension. Circulation 2003;108:2308-11.

30 . Title LM, Giddens K, McInerney MM, McQueen MJ, Nassar BA. Effect of cyclooxygenase-2 inhibition with rofecoxib on endothelial dysfunction and inflammatory markers in patients with coronary artery disease. J Am Coll Cardiol 2003;42:1747-53.

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-----Original Message-----
From: Schechter, Adam H
Sent: Tuesday, February 10, 2004 11:09 AM
To: Watson, Douglas J.; Reicin, Alise S.

Confidential - Subject To Protective Order

Cc: Santanello, Nancy C.; Cannuscio, Carolyn C
Subject: FW: Solomon cox2 and mi manuscript accepted to Circ

Did the publication have the data from Whelton in here before (page 16) and state that rofecoxib has been associated with and increase in hypertension and celebrex is not?? Also the data that says celecoxib has a positive effect on endothelial dysfunction and VIOXX does not? I didn't remember that before.
Adam

-----Original Message-----
From: Hayward, Kathryn S.
Sent: Tuesday, February 10, 2004 10:55 AM
To: Strasburger, Matt W; Schechter, Adam H
Cc: Stanton, Michael A
Subject: FW: Solomon cox2 and mi manuscript accepted to Circ

FYI. Circulation has accepted manuscript. No publication date yet.
K

-----Original Message-----
From: Watson, Douglas J.
Sent: Tuesday, February 10, 2004 10:52 AM
To: Reicin, Alise S.; Korn, Scott H.; Lahner, Joanne; Blake, Mary Elizabeth; Stanton, Michael A; Bolognese, James A.; Braunstein, Ned S.; Duong, Phong T.; Hayward, Kathryn S.; Holland, Ken W; Johnson, Patricia A.; Malloy, Tracey; Simpson, Sandra L.; van Adelsberg, Janet
Cc: Santanello, Nancy C.; Cannuscio, Carolyn C
Subject: FW: Solomon cox2 and mi manuscript accepted to Circ

All,
FYI, see message below regarding the manuscript by Dan Solomon, which has been accepted to Circulation.
Doug

-----Original Message-----
From: Solomon, Daniel Hal,M.D.,M.P.H. [mailto:DHSOLOMON@PARTNERS.ORG]
Sent: Tuesday, February 10, 2004 10:35 AM
To: 'douglas_watson@merck.com'; 'Cannuscio, Carolyn C'
Subject: cox2 and mi manuscript

Hi Doug and Carolyn,

We learned late last week that Circulation has accepted the manuscript. I do not yet have a publication date from them.

Here is the version that they accepted. They asked for me to reduce the word count and thus the differences between the version that you have and the attached version.

Regards
Dan

<<cox2 and MI.Circ.Jan152004.pdf>>

Daniel H. Solomon, MD, MPH
Assistant Professor
Division of Pharmacoepidemiology
Division of Rheumatology
Brigham and Women's Hospital
1620 Tremont Street, Suite 3030
Boston MA 02120
T: 617-278-0930 F: 617-232-8602
<< File: cox2 and MI.Circ.Jan152004.pdf >>

2

Restricted Confidential

Draft 11 Feb. 2004

Concerns with the version of the Solomon study paper accepted by Circulation

1. First sentence of the conclusion of the abstract states "In this study, current rofecoxib use was associated with an elevated relative risk of AMI compared with no NSAID use and with celecoxib use." (red text added prior to submission without Merck being aware). The comparison of current rofecoxib with no NSAID use was slight and not statistically significant by the conventional criteria (1.14, 95% CI 1.00 – 1.31, p = 0.054).
2. Notably, in the current study as in many observational studies (Paganini-Hill; Barrett-Connor—see added refs), use of hormone replacement therapy [at baseline] was associated with lower risk of hospitalization for AMI; this finding contrasts with the results of recent randomized controlled trials, which have reported an increased risk of AMI in users of HRT (Hulley; Manson—see added refs).
3. The discussion concerning the effects of rofecoxib on hypertension on page 16 are does not accurately portray the existing literature nor the product labels for the subject drugs on this subject.

   The data from rat models of hypertension in the study by Hermann et al suggest that celecoxib but not rofecoxib ***or diclofenac*** may be associated with improvements in endothelial function and reductions in oxidative stress.[i] The submitted version of the paper omitted the information about diclofenac.

   All NSAIDs, including celecoxib and rofecoxib have been associated with renal effects and hypertension, as noted in the product labels for these medications. In some studies, rofecoxib appears associated with greater elevations in blood pressure than celecoxib [ii]; however, these differences may be dose-related. The points were raised with Dr. Solomon and provide additional information relevant to the discussion but were not included in the paper submitted.

   While some have speculated that these mechanisms may contribute to the apparent differential relationship between selective COX-2 inhibitors and AMI, Title et al. (2003—see added refs at end of biblio) demonstrated no adverse effect of rofecoxib treatment on endothelial function in healthy volunteers.

---

[i]. Hermann M, Camici G, Fratton A, et al. Differential effects of selective cyclooxygenase-2 inhibitors on endothelial dysfunction in salt-induced hypertension. Circulation 2003;108:2308-2311.

[ii]. Whelton A, White WB, Bello AE, Puma JA, Fort JG for the SUCCESS-VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients > or =65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol 2002; 90:959-963.

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Title LM, Giddens K, McInerney MM, McQueen MJ, Nassar BA. Effect of cyclooxygenase-2 inhibition with rofecoxib on endothelial dysfunction and inflammatory markers in patients with coronary artery disease. J Am Coll Cardiol 2003;42:1747–53.

Paganini-Hill A. Hormone replacement therapy and stroke: risk, protection or no effect? Maturitas JID - 7807333 2001; 38:243-261.

Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. Annu Rev Public Health JID - 8006431 1998; 19:55-72.

Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA. 1998; 280:605-613.

Manson J. E., Hsia J., Johnson K. C., Rossouw J. E., Assaf A. R., Lasser N. L., Trevisan M., Black H. R., Heckbert S. R., Detrano R., Strickland O. L., Wong N. D., Crouse J. R., Stein E., Cushman M., the Women's Health Initiative Investigators Estrogen plus Progestin and the Risk of Coronary Heart Disease N Engl J Med 2003; 349:523-534.

J. I. Schwartz et al. Comparison of rofecoxib, celecoxib, and naproxen on renal function in elderly subjects receiving a normal-salt diet. Clin Pharmacol Ther 2002;72:50-61.

Restricted Confidential Sealed access

Draft 13 Feb. 2004

Draft Concerns with the version of the Solomon study paper accepted by Circulation

1. First sentence of the conclusion of the abstract states "In this study, current rofecoxib use was associated with an elevated relative risk of AMI compared with **no NSAID use and** with celecoxib use."

Bolded text added prior to submission without Merck being aware. The comparison of current rofecoxib with no NSAID use was slight and not statistically significant by the conventional criteria (1.14, 95% CI 1.00 – 1.31, p = 0.054).

2. Discussion about study limitations

In this study, as in many observational studies (Paganini-Hill; Barrett-Connor), use of hormone replacement therapy [at baseline] was associated with lower risk of hospitalization for AMI; this finding contrasts with the results of recent randomized controlled trials, which have reported an increased risk of AMI in users of HRT (Hulley; Manson).

3. The discussion on page 16 concerning the effects of rofecoxib on hypertension does not accurately portray all of the existing literature, nor the product labels, for the subject drugs on this subject.

All NSAIDs, including celecoxib and rofecoxib have been associated with renal effects and hypertension, as noted in the product labels for these medications. In some studies, rofecoxib appears associated with greater elevations in blood pressure than celecoxib[i]; however, these differences may be dose-related. The points were raised with Dr. Solomon and additional information relevant to the discussion was provided to Dr. Solomon but was not included in the paper submitted.

The data from Whelton is not in accordance with data on the effects of rofecoxib and celecoxib on blood pressure in the elderly published in Schwartz et al.

The data from rat models of hypertension in the study by Hermann et al suggest that celecoxib but not rofecoxib or diclofenac may be associated with improvements in endothelial function and reductions in oxidative stress.[ii] The submitted version of the paper omitted the bolded information about diclofenac.

While some have speculated that these mechanisms may contribute to the apparent differential relationship between selective COX-2 inhibitors and AMI, Title et al. demonstrated no adverse effect of rofecoxib treatment on endothelial function in healthy volunteers.

References

Barrett-Connor E, Grady D. Hormone replacement therapy, heart disease, and other considerations. Ann Rev Public Health JID - 8006431 1998; 19:55-72.

Restricted Confidential Limited access

Hermann M, Camici G, Fratton A, et al. Differential effects of selective cyclooxygenase-2 inhibitors on endothelial dysfunction in salt-induced hypertension. Circulation 2003;108:2308-2311.

Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA. 1998; 280:605-613.

J. L Schwartz et al. Comparison of rofecoxib, celecoxib, and naproxen on renal function in elderly subjects receiving a normal-salt diet. Clin Pharmacol Ther 2002;72:50-61.

Manson J. E., Hsia J., Johnson K. C., Rossouw J. E., Assaf A. R., Lasser N. L., Trevisan M., Black H. R., Heckbert S. R., Detrano R., Strickland O. L., Wong N. D., Crouse J. R., Stein E., Cushman M., the Women's Health Initiative Investigators Estrogen plus Progestin and the Risk of Coronary Heart Disease N Engl J Med 2003; 349:523-534.

Paganini-Hill A. Hormone replacement therapy and stroke: risk, protection or no effect? Maturitas JID - 7807333 2001; 38:243-261.

Title LM, Giddens K, McInerney MM, McQueen MJ, Nassar BA. Effect of cyclooxygenase-2 inhibition with rofecoxib on endothelial dysfunction and inflammatory markers in patients with coronary artery disease. J Am Coll Cardiol 2003;42:1747–53.

Whelton A, White WB, Bello AE, Puma JA, Fort JG for the SUCCESS-VII Investigators. Effects of celecoxib and rofecoxib on blood pressure and edema in patients > or =65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol 2002; 90:959-963.

Watson, Douglas J.

From: Watson, Douglas J.
Sent: Tuesday, February 10, 2004 11:34 AM
To: Reicin, Alise S.; Schechter, Adam H
Cc: Santanello, Nancy C.; Cannuscio, Carolyn C; Gertz, Barry J.
Subject: RE: Solomon cox2 and mi manuscript accepted to Circ

Carolyn is not reading her e-mail yet as far as I know.

Attached is an e-mail I got from Carolyn in which she stated that Dan submitted his revised paper to Circulation without first talking to us. In it is the version that went to Circulation and it includes the reference to the Whelton paper - it is also the version from which I took the paragraph I just sent to Adam.

FW: thanks for your helpful co..

The versions previous to the above that I have in e-mail, in which Carolyn had incorporated the suggested revisions from Merck reviewers, did not have that reference. So Dan inserted it and re-submitted without our knowledge as best I can determine.

Doug

-----Original Message-----
From: Reicin, Alise S.
Sent: Tuesday, February 10, 2004 11:24 AM
To: Schechter, Adam H; Watson, Douglas J.
Cc: Santanello, Nancy C.; Cannuscio, Carolyn C; Gertz, Barry J.
Subject: RE: Solomon cox2 and mi manuscript accepted to Circ

Carolyn
It appears that be added some sentences including one that says that celebrex does not cause HTN--this is in contrast to their label and other studies. I think we need to give careful consideration to whether a merck author can be on a paper with information that is factually incorrect.
REDACTED
alise

-----Original Message-----
From: Schechter, Adam H
Sent: Tuesday, February 10, 2004 11:09 AM
To: Watson, Douglas J.; Reicin, Alise S.
Cc: Santanello, Nancy C.; Cannuscio, Carolyn C
Subject: FW: Solomon cox2 and mi manuscript accepted to Circ

Did the publication have the data from Whelton in here before (page 16) and state that rofecoxib has been associated with and increase in hypertension and celebrex is not?? Also the data that says celecoxib has a positive effect on endothelial dysfunction and VIOXX does not? I didn't remember that before.
Adam

-----Original Message-----
From: Hayward, Kathryn S.
Sent: Tuesday, February 10, 2004 10:55 AM
To: Strasburger, Matt W; Schechter, Adam H
Cc: Stanton, Michael A
Subject: FW: Solomon cox2 and mi manuscript accepted to Circ

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FYI. Circulation has accepted manuscript. No publication date yet.
K

-----Original Message-----
From: Watson, Douglas J.
Sent: Tuesday, February 10, 2004 10:52 AM
To: Reicin, Alise S.; Kom, Scott H.; Lahner, Joanne; Blake, Mary Elizabeth; Stanton, Michael A; Bolognese, James A.; Braunstein, Ned S.; Duong, Phong T.; Hayward, Kathryn S.; Holland, Ken W; Johnson, Patricia A.; Malloy, Tracey; Simpson, Sandra L.; van Adelsberg, Janet
Cc: Santanello, Nancy C.; Cannuscio, Carolyn C
Subject: FW: Solomon cox2 and mi manuscript accepted to Circ

All,
FYI, see message below regarding the manuscript by Dan Solomon, which has been accepted to Circulation.
Doug

-----Original Message-----
From: Solomon, Daniel Hal,M.D.,M.P.H. [mailto:DHSOLOMON@PARTNERS.ORG]
Sent: Tuesday, February 10, 2004 10:35 AM
To: 'douglas_watson@merck.com'; 'Cannuscio, Carolyn C'
Subject: cox2 and mi manuscript

Hi Doug and Carolyn,

We learned late last week that Circulation has accepted the manuscript. I do not yet have a publication date from them.

Here is the version that they accepted. They asked for me to reduce the word count and thus the differences between the version that you have and the attached version.

Regards
Dan

<<cox2 and MI.Circ.Jan152004.pdf>>

Daniel H. Solomon, MD, MPH
Assistant Professor
Division of Pharmacoepidemiology
Division of Rheumatology
Brigham and Women's Hospital
1620 Tremont Street, Suite 3030
Boston MA 02120
T: 617-278-0930 F: 617-232-8602

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To: Watson, Douglas J.
From: Santanello, Nancy C.
Cc:
Bcc:
Received Date: 2004-03-19 20:09:07
Subject: FW: Manuscript

FYI - Nancy

-----Original Message-----
From: Solomon, Daniel Hal,M.D.,M.P.H. [mailto:DHSOLOMON@PARTNERS.ORG]
Sent: Friday, March 19, 2004 2:08 PM
To: 'Santanello, Nancy C.'
Subject: RE: Manuscript

thanks

look forwarding to speaking next week

dan

-----Original Message-----
From: Santanello, Nancy C. [mailto:nancy_santanello@merck.com]
Sent: Friday, March 19, 2004 1:29 PM
To: Solomon, Daniel Hal,M.D.,M.P.H.
Cc: Santanello, Nancy C.
Subject: Manuscript

Hi Dan,

Carolyn Cannuscio told me she spoke with you yesterday (March 18th) regarding your manuscript and that she let you know I would be contacting you. This is to allow her to spend more time concentrating on her newborn son, Caleb, rather than trying to coordinate issues here at work. She communicated back to me that your preference is to see a proposal in writing first before receiving a phone call. In this spirit, I am sending you our proposed change in the wording for the Conclusion section of the manuscript. I will follow this with a phone call to you next week.

Also, Doug Watson let me know that he faxed you our other suggested changes to the manuscript earlier. We can discuss these as well when I call.

Here is the current wording and our suggested wording:

Current - "In this study, current rofecoxib use was associated with an elevated relative risk of AMI compared with no NSAID use and with celecoxib use."

Suggested - "In this study, current rofecoxib use was associated with an elevated relative risk of AMI compared with celecoxib use. There was also a numerical increase in the risk of AMI among the current rofecoxib use group as compared to no NSAID use, but this result did not reach statistical significance."

Please let me know that you have received this message. If you would like to

talk to me before next week, please feel free to call me today at home - REDACTED

Regards, Nancy
>>>>>>>>>>>>>>>>>>>
Nancy Santanello, MD, MS
Executive Director, Epidemiology
Merck Research Laboratories
BL 1-7, PO Box 4
West Point, PA 19486
Tel: 484-344-7060
FAX: 484-344-2992
nancy_santanello@merck.com
Administrative Assistant: Dawn Moyer (484-344-2938)

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To:	'Solomon, Daniel Hal,M.D.,M.P.H.'
From:	Santanello, Nancy C.
Cc:	Watson, Douglas J.
Bcc:	
Received Date:	2004-04-05 15:13:39
Subject:	RE: Thank you for your time

Hi Dan - I will attempt to contact Carolyn now. It has been difficult reaching her at times. I will keep you updated.

Doug Watson and I were just talking about the galleys. He received them this morning. Doug thought that you might want to consider the following:

Change wording of "other smaller studies in healthy adults suggest similarity between coxibs" to "while a smaller study in healthy elderly adults suggests a similarity between coxibs".

He also thought that you might then want to cite the Schwartz article regarding blood pressure in normal elderly in case the Circulation editors ask for a citation to this statement. It is: Schwartz JI, Vandormael K, Malice MP, et al. Comparison of rofecoxib, celecoxib and naproxen on renal function in elderly subjects receiving a normal-salt diet. Clin Pharmacol Ther 2002;72:50-61.

Additionally, Doug thought that you might want to say "a" large head-to-head randomized controlled trial instead of "several" large head-to-head randomized controlled trials or if you keep it to say "several" consider citing an additional large randomized trial as evidence.

Regards, Nancy

-----Original Message-----
From: Solomon, Daniel Hal,M.D.,M.P.H. [mailto:DHSOLOMON@PARTNERS.ORG]
Sent: Monday, April 05, 2004 10:50 AM
To: 'Santanello, Nancy C.'
Subject: RE: Thank you for your time

Hi Nancy,

I just spoke to the Editorial Offices of Circulation. They will need her statement in writing. If she can fax it to me and then I will need to forward it to them with a revised Title Page. They are expecting the galley proofs today and would like these other items today as well.

Thanks
Dan

-----Original Message-----
From: Santanello, Nancy C. [mailto:nancy_santanello@merck.com]
Sent: Monday, April 05, 2004 10:44 AM
To: Solomon, Daniel Hal,M.D.,M.P.H.
Subject: RE: Thank you for your time

Will do. Nancy

-----Original Message-----
From: Solomon, Daniel Hal,M.D.,M.P.H. [mailto:DHSOLOMON@PARTNERS.ORG]
Sent: Monday, April 05, 2004 10:31 AM
To: 'Santanello, Nancy C.'
Subject: RE: Thank you for your time

Hi Nancy,

Please have Carolyn fax or email a note stating this.

Thanks

Dan

-----Original Message-----
From: Santanello, Nancy C. [mailto:nancy_santanello@merck.com]
Sent: Monday, April 05, 2004 10:26 AM
To: Solomon, Daniel Hal,M.D.,M.P.H.
Subject: RE: Thank you for your time

Dear Dan,

Thank you for sending the galley proofs to me. I appreciate the scientific discussions that you and your team have engaged in and your efforts on this issue. After very careful consideration, I have decided to request that Carolyn remove her name as a co-author.

Please do not hesitate to contact me if you have any questions.

Best regards, Nancy

>>>>>>>>>>>>>>>>>>>
Nancy Santanello, MD, MS
Executive Director, Epidemiology
Merck Research Laboratories
BL 1-7, PO Box 4
West Point, PA 19486
Tel: 484-344-7060
FAX: 484-344-2992
nancy_santanello@merck.com
Administrative Assistant: Dawn Moyer (484-344-2938)

-----Original Message-----
From: Solomon, Daniel Hal,M.D.,M.P.H. [mailto:DHSOLOMON@PARTNERS.ORG]
Sent: Friday, April 02, 2004 4:45 PM
To: 'Santanello, Nancy C.'
Subject: RE: Thank you for your time

Hi Nancy,

We have all spent a lot of time here discussing and re-discussing the issues you raised about our abstract. We have elected to keep the abstract as is but will reverse the order of the comparisons in the Abstract Conclusion:

"In this study, current rofecoxib use was associated with an elevated relative risk of AMI compared with celecoxib use and with no NSAID use."

It is important to note that the Results section of the Abstract clearly states the p-value for the comparison of interest. As well, we state in the

Results section of the text that the adjusted relative risk of AMI was elevated but did not reach statistical significance.

We have just received the galley proofs and I will need to get them back to Circulation by Monday close of business. I am faxing the galley proofs to you now at 484-344-2992 with our edits inserted.

Best regards

Dan

-----Original Message-----
From: Santanello, Nancy C. [mailto:nancy_santanello@merck.com]
Sent: Monday, March 29, 2004 4:44 PM
To: Solomon, Daniel Hal,M.D.,M.P.H.
Cc: Watson, Douglas J.
Subject: Thank you for your time

Dear Dan,

Thank you for your time and for an honest and open discussion. I do appreciate your position.

I just wanted to summarize the two points which we agreed to for follow-up:

1) your decision regarding Discussion section of abstract
2) sending "marked up" galleys to Merck (can send to me or Doug Watson) prior to submitting back to the journal

Please provide me with a date by which I can expect to hear from you on the abstract.

Best regards, Nancy
>>>>>>>>>>>>>>>>>>>
Nancy Santanello, MD, MS
Executive Director, Epidemiology
Merck Research Laboratories
BL 1-7, PO Box 4
West Point, PA 19486
Tel: 484-344-7060
FAX: 484-344-2992
nancy_santanello@merck.com
Administrative Assistant: Dawn Moyer (484-344-2938)

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To: 'Solomon, Daniel Hal,M.D.,M.P.H.'; Santanello, Nancy C.
From: Watson, Douglas J.
Cc:
Bcc:
Received Date: 2004-04-20 20:16:04
Subject: RE: Correction to Manuscript On-Line on Circulation

Thanks Dan. We appreciate it.
Doug

-----Original Message-----
From: Solomon, Daniel Hal,M.D.,M.P.H. [mailto:DHSOLOMON@PARTNERS.ORG]
Sent: Tuesday, April 20, 2004 3:58 PM
To: 'Watson, Douglas J.'
Subject: RE: Correction to Manuscript On-Line on Circulation

Hi Doug,

That was a major oversight.

I will call Circulation and the publisher to make that request.

Thanks for bringing this to our attention.

Regards
Dan

-----Original Message-----
From: Watson, Douglas J. [mailto:douglas_watson@merck.com]
Sent: Tuesday, April 20, 2004 3:49 PM
To: Solomon, Daniel Hal,M.D.,M.P.H.; Santanello, Nancy C.
Subject: Correction to Manuscript On-Line on Circulation
Importance: High

Hi Dan,
I
was sent your paper from the Online Circulation site today. I noticed this statement in the footnotes on the title page:
"Other than Dr Cannuscio, an employee of Merck, no authors have direct personal financial relationships with any pharmaceutical company."

Obviously this statement should not be there as Carolyn is not an author. Nancy has asked that I contact you to request that you contact Circulation to request correction to the online version and deletion on the paper version before it is printed.

Thanks,
Doug Watson

> http://circ.ahajournals.org/cgi/reprint/01.CIR.0000127578.21885.3Ev1?maxto
> show=&HITS=10&hits=10&RESULTFORMAT=&fulltext=solomon&searchid=108246674915
> 0_7286&stored_search=&FIRSTINDEX=0&search_url=http%3A%2F%2Fcirc.ahajournal
> s.org%2Fcgi%2Fsearch&journalcode=circulationaha

>
> <<Solomon.pdf>>
>

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→ pirate version by e-mail

- [outraged]

→ Circulation time frame — for publication
NOT quick.

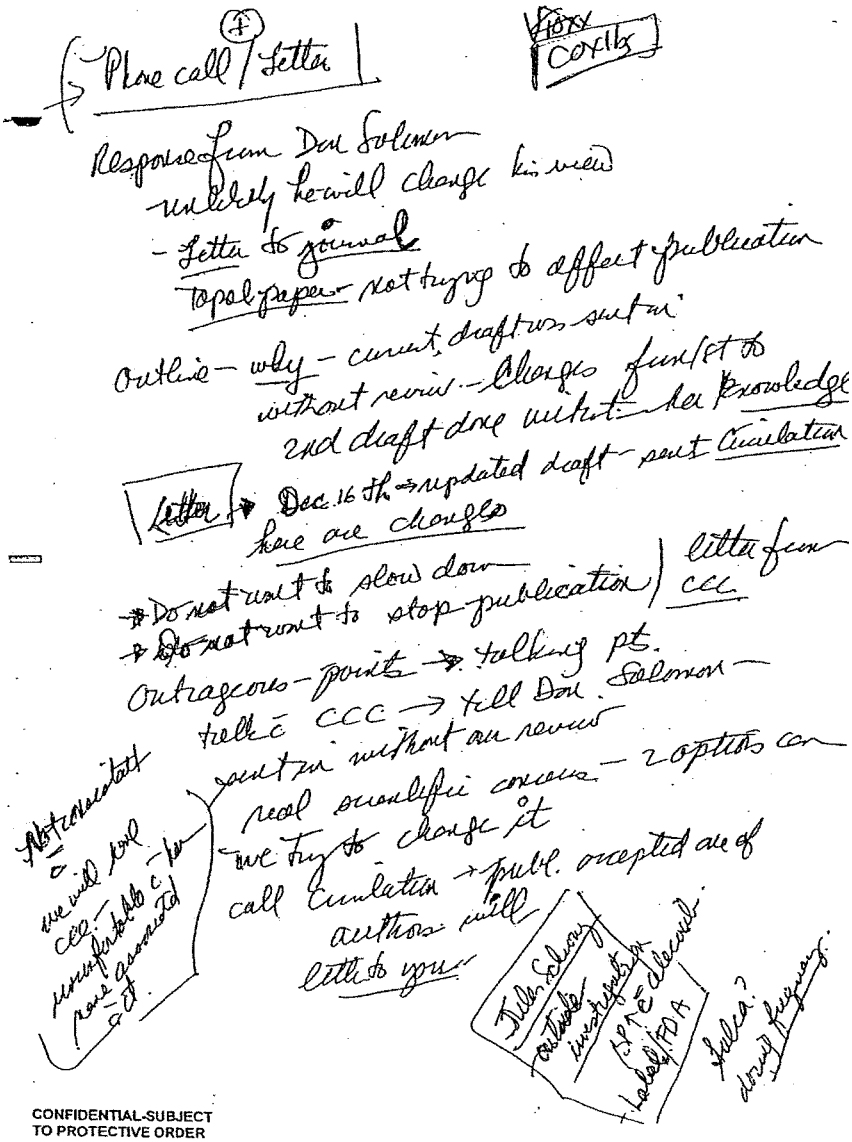
→ draft 16th → Drs. Feldman — latest version
put to us → never answered.

It's been accepted + there it is.

- Editorial & this ?
Letter to Editor ?

→ Addition to abstract — are we comfortable?

CONFIDENTIAL-SUBJECT
TO PROTECTIVE ORDER



CONFIDENTIAL-SUBJECT
TO PROTECTIVE ORDER

Put on Carolyn Cannuscio's letterhead: 2 letters

Address to both Dan H. Solomon and copy to Editor of Circulation

Second letter – address to Editor of Circulation with a copy to Dan Solomon

First letter – address – Dear Dan,

Second letter – address – Dear Dr. Willerson,

James T. Willerson, MD

Editor, Circulation

St Luke's Episcopal Hospital/Texas Heart Institute

6720 Bertner Avenue

Room B524 (MC1-267)

Houston, TX 77030-2697

Phone: 713-794-6585

Fax: 713-794-6810

E-mail: Suzy.Lanier@uth.tmc.edu

Dear Editor,

After careful consideration, I am requesting that my name be removed from the following manuscript: Solomon DH et al. Relationship between selective cyclooxygenase-2 inhibitors an acute myocardial infarction in older adults.

Kind regards,

Carolyn Cannuscio, put in her degree here

TRANSMISSION VERIFICATION REPORT

TIME : 04/12/2004 14:20
NAME :
FAX : 2155738606
TEL :

DATE,TIME	04/12 14:20
FAX NO./NAME	916172328602
DURATION	00:00:17
PAGE(S)	01
RESULT	OK
MODE	STANDARD ECM

Carolyn C. Cannuscio, Sc.D.
Senior Epidemiologist

Merck & Co., Inc.
BL1-7
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2540
Fax 484 344 2992
Email: carolyn_cannuscio@merck.com

April 5, 2004

MERCK
Research Laboratories

Daniel H. Solomon, MD, MPH
Assistant Professor
Division of Pharmacoepidemiology
Division of Rheumatology
Brigham and Women's Hospital
1620 Tremont Street, Ste. 3030
Boston, MA 02120

Dear Dan,

After careful consideration, I am requesting that my name be removed from the following manuscript: Solomon DH et al. "Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults."

Kind regards,

Carolyn C. Cannuscio

Carolyn C. Cannuscio, Sc.D.

Cc: James T. Willerson, M.D.
Nancy C. Santanello, M.D.

Carolyn C. Cannuscio, Sc.D.
Senior Epidemiologist

Merck & Co., Inc.
BL1-7
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2640
Fax 484 344 2992
Email: carolyn_cannuscio@merck.com

April 5, 2004

MERCK
Research Laboratories

Daniel H. Solomon, MD, MPH
Assistant Professor
Division of Pharmacoepidemiology
Division of Rheumatology
Brigham and Women's Hospital
1620 Tremont Street, Ste. 3030
Boston, MA 02120

Dear Dan,

After careful consideration, I am requesting that my name be removed from the following manuscript: Solomon DH et al. "Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults."

Kind regards,

Carolyn C. Cannuscio, Sci.D.

Cc: James T. Willerson, M.D.
Nancy C. Santanello, M.D.

MERCK
Research Laboratories

A MEMO FROM PATRICIA DEVLIN
484-344-2585 Fax 484-344-2992
BL 1-7

Carolyn,
Nancy wants them back so we can make copies w/your signature before we mail them.

FAX NO's:
Dan S. - 617-232-8602
Dr. Willerson - 713-794-6810

617 732 5656
12911

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TRANSMISSION VERIFICATION REPORT

TIME : 04/12/2004 14:21
NAME :
FAX : 2155738605
TEL :

DATE,TIME	04/12 14:21
FAX NO./NAME	917137946810
DURATION	00:00:16
PAGE(S)	01
RESULT	OK
MODE	STANDARD ECM

Carolyn C. Cannuscio, Sc.D.
Senior Epidemiologist

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BL1-7
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2640
Fax 484 344 2932
Email: carolyn_cannuscio@merck.com

April 5, 2004

MERCK
Research Laboratories

James T. Willerson, M.D.
Editor, Circulation
St. Luke's Episcopal Hospital/
Texas Heart Institute
6720 Bertner Avenue
Room B524 (MCH1-267)
Houston, TX 77030-2697

Dear Dr. Willerson:

After careful consideration, I am requesting that my name be removed from the following manuscript: Solomon DH et al. "Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults."

Kind regards,

Carolyn C. Cannuscio

Carolyn C. Cannuscio, Sci.D.

Cc: Daniel H. Solomon, M.D.
Nancy C. Santanello, M.D.

Carolyn C. Cannuscio, Sc.D.
Senior Epidemiologist

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MERCK
Research Laboratories

April 5, 2004

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Texas Heart Institute
6720 Bertner Avenue
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Nancy C. Santanello, M.D.

Santanello, Nancy C.

Cubed file
EPA 7006 CA3.04.25

From: Dan Solomon and Mindy Berman [dhsolomon@comcast.net]
Sent: Monday, April 19, 2004 8:33 AM
To: nancy_santanello@merck.com
Subject: article

my remote work email will not send messages
if responding to this, send emails to dhsolomon@partners.org

hi nancy,
i was traveling on friday and am out of the office today
got your message and had remote email issues

i spoke with the managing editor last week and she assured me that carolyn had been removed as a co-author

no one was quite sure on the publication date because of having to remove her name; it will probably be early may

thanks
dan

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx: Putting Patient Safety First?"

November 18, 2004

Exhibit 46

Diane Louie, MD, MPH
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 2000, RY 32-605
Rahway NJ 07065-0900
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diane_louie@merck.com

October 12, 2004

MERCK
Research Laboratories

Brian E. Harvey, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
HFD-550, Room N314
Office of Drug Evaluation V (CDER)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Serial No. B13

Dear Dr. Harvey:

IND 46,894: VIOXX™ (rofecoxib)

INFORMATION AMENDMENT - CLINICAL

Reference is made to the above subject Investigational New Drug Application submitted by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; to telephone conversations between Dr. Brian Harvey, FDA, and Dr. Dennis M. Erb, MRL, on September 27, 2004; and to a meeting between FDA representatives and MRL representatives on September 28, 2004, during which Merck informed the Agency of results from the APPROVe trial and our decision to voluntarily withdraw VIOXX™ (rofecoxib) from the market. Finally, reference is made to a teleconference between MRL and FDA held at the Agency's request on Thursday, October 7, 2004, to discuss the status of the VIOXX™ withdrawal and the timeline for providing the APPROVe data to the Agency. At the teleconference, MRL informed the Agency of its intention to submit a report by Ingenix Epidemiology.

With this letter, Merck Research Laboratories, a Division of Merck & Co., Inc., is submitting the report mentioned at the teleconference.

A new report prepared by Ingenix Epidemiology (attachment) describes a Merck-sponsored retrospective cohort study of myocardial infarction (MI) and other acute coronary events based on insurance claims records of 424,584 UnitedHealthcare enrollees ages 40-64 who used NSAIDS or COX-2 inhibitors by prescription from 1999-2001. The report was finalized on September 20, 2004. In this retrospective study, the relative risk of the combined endpoint of acute myocardial infarction, acute coronary syndrome, or sudden cardiac death was increased in patients taking rofecoxib compared to a combined reference group of patients taking ibuprofen or diclofenac (RR 1.35, 95% CI 1.09-1.68). There was no apparent association with celecoxib. The data have not yet been presented nor published, although abstracts are planned and a manuscript is being prepared.

Although retrospective analyses such as the one described in the attached report can provide useful information in certain instances, Merck believes that randomized clinical trials are the gold standard by which to judge the safety and efficacy of drugs. That is why Merck conducted large, randomized, prospective placebo-controlled studies with VIOXX™. Merck's decision to withdraw VIOXX™ worldwide from the marketplace was based solely on its evaluation of data from randomized control studies and not from the results of retrospective studies such as described in the attached report.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Diane Louie, M.D., M.P.H. (732-594-7186) or, in my absence, to Ned S. Braunstein, M.D. (732-594-2886).

Sincerely,

Diane Louie, MD, MPH

Diane Louie, M.D., M.P.H.
Director
Regulatory Affairs

Attachment

Federal Express No. 1

Q:\Hill\Vioxx\IND 46894\ingenix.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Merck & Co., Inc.

2. DATE OF SUBMISSION
October 12, 2004

3. ADDRESS (Number, Street, City, State and Zip Code)
P.O. Box 2000, RY 32-605
Rahway, NJ 07065-0900

4. TELEPHONE NUMBER *(Include Area Code)*
(732) 594-7186

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
VIOXX™ (Rofecoxib), L-748731, MK-0966

6. IND NUMBER *(If previously assigned)*
46,894

7. INDICATION(S) *(Covered by this submission)*
Treatment of osteoarthritis, rheumatoid arthritis, acute pain, primary dysmenorrhea

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER (Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR Part 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
813

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☐ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☒ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER (Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ **TREATMENT IND 21 CFR 312.35 (b)** ☐ **TREATMENT PROTOCOL 21 CFR 312.35 (a)** ☐ **CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)**

FOR FDA USE ONLY

CDR/OBIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

FORM FDA 1571 (1/03) PREVIOUS EDITION IS OBSOLETE. Page 1 of 2

MRK-S001505

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- [x] 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- [ ] 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- [ ] 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- [ ] 4. General investigational plan *[21 CFR 312.23(a)(3)]*
- [ ] 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- [ ] 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - [ ] b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [ ] d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- [ ] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - [ ] Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- [ ] 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- [ ] 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- [ ] 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Diane Louie, M.D., M.P.H. **Director, Regulatory Affairs**	Diane Louie MD, MPH	
18. ADDRESS *(Number, Street, City, State and Zip Code)* **P.O. Box 2000, RY 32-605** **Rahway, NJ 07065-0900**	19. TELEPHONE NUMBER *(Include Area Code)* *(732)* 594-7186	20. DATE October 12, 2004

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

FORM FDA 1571 (1/03) PAGE 2 OF 2

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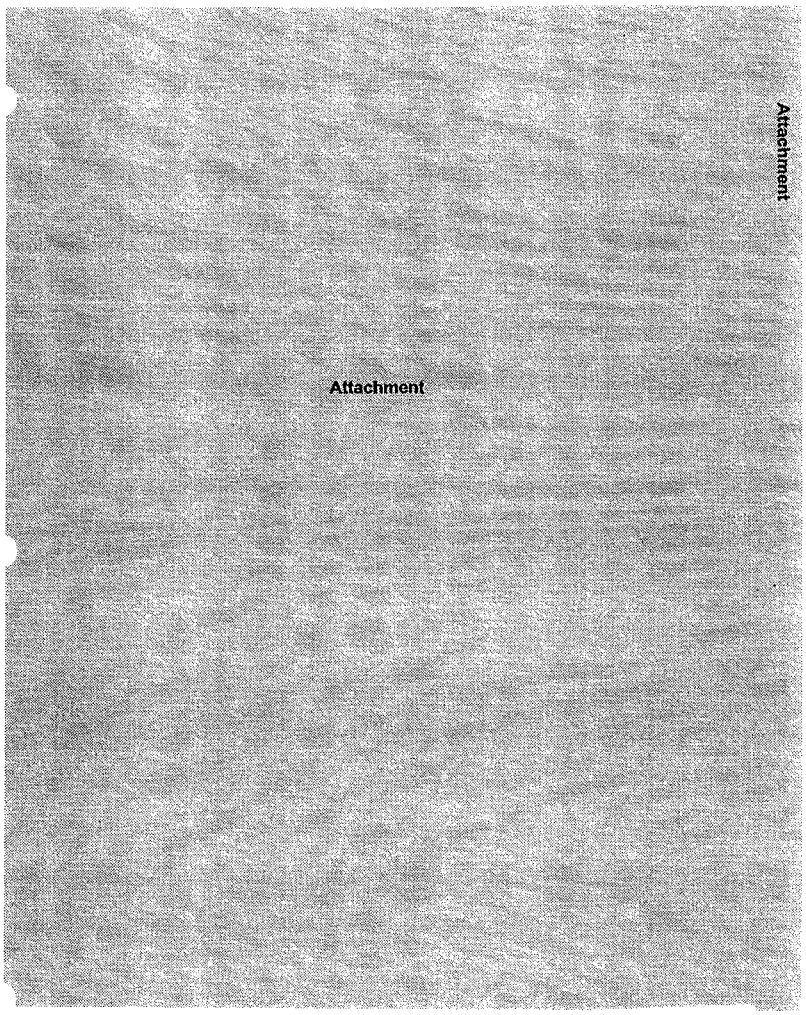
Information and data submitted herein contains trade secrets, privileged or confidential information, the property of Merck & Co. Inc., and government agencies are not authorized to make it public without written permission from Merck.



MRK-S001508

Ingenix Epidemiology

Riverside Center 3-120, 275 Grove Street, Newton, MA 02466
Tel 617 244-1200 Fax 617 244-9669 Internet: www.epidemiology.com

Cardiovascular Risk of COX-2 Inhibitors and Other NANSAIDs

Final Report, Revised

Prepared for Merck and Co., Inc.

Priscilla Velentgas, Ph.D.
William West, Ph.D.
Alexander M. Walker, MD, DrPH

September 20, 2004

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Executive Summary

The cardiovascular safety of the cyclooxygenase (COX)-2 inhibitor non-aspirin, nonsteroidal anti-inflammatory drugs (NANSAIDs), rofecoxib and celecoxib, is a matter of debate and concern, despite their demonstrated gastrointestinal benefits.

Ingenix conducted a retrospective cohort study of myocardial infarction (MI) and other acute coronary events based in insurance claims records of 424,584 UnitedHealthcare enrollees ages 40-64 who used NANSAIDS by prescription from 1999-2001. Using automated medical and pharmacy claims data from the Ingenix Research Database, we computed person-time exposed to rofecoxib, celecoxib, diclofenac, ibuprofen and naproxen and identified hospitalizations for MI and acute coronary syndrome (ACS).

The primary endpoint included MI, ACS and sudden cardiac death, confirmed through hospital medical record documentation or through the National Death Index, and is referred to as "confirmed MI/ACS" throughout this report. The secondary endpoint was comprised of MI or death from coronary heart disease, identified through claims data or through the NDI, and is referred to as "MI claims events" throughout this report. We computed rates of confirmed MI/ACS and MI claims events during periods of current and past NANSAID use, and periods of new, continuous use of NANSAIDs.

Overall, crude and adjusted rates of confirmed MI/ACS were somewhat higher during periods of current rofecoxib use than periods of other NANSAID use (RR vs. ibuprofen or diclofenac 1.35, 95% CI 1.09-1.68). There was not a clear trend with time since onset of use, though risks in the first 30 days of rofecoxib and celecoxib were modestly elevated compared with the first 30 days of ibuprofen or diclofenac (RR for rofecoxib 1.51, 95% CI 0.72-1.42; RR for celecoxib 1.21, 95% CI 0.80-1.84). Dose analyses also did not indicate trends of increasing risk with higher daily dose of rofecoxib (RR for rofecoxib 25 mg 1.54, 95% CI 1.15-2.04; RR for rofecoxib 26-50 mg 0.81, 95% CI 0.41-1.60) or celecoxib (RR for celecoxib 200 mg 0.95, 95% CI 0.72-1.25; RR for celecoxib 201-400 mg 1.14, 95% CI 0.78-1.65) compared with all doses of ibuprofen or diclofenac combined.

This report is the revised final report from this research project incorporating comments from Merck and discussion of these comments between Merck and Ingenix.

Introduction

The cardiovascular safety of the cyclooxygenase (COX)-2 inhibitor non-aspirin, nonsteroidal anti-inflammatory drugs (NANSAIDs), rofecoxib and celecoxib, is a matter of intense debate. Though rofecoxib and celecoxib might be expected to exert a beneficial effect on the atherosclerotic process through inhibiting inflammation, the concern has been raised that they may promote cardiovascular thrombotic events, by adversely affecting the balance between prothrombotic and antithrombotic eicosanoids [1,2].

Concern regarding the cardiovascular safety of the COX-2 inhibitors first arose following reports from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, a clinical trial of gastrointestinal safety of rofecoxib. In that trial, patients assigned to the naproxen arm had a lower risk of myocardial infarction (MI) than patients assigned to take rofecoxib. [3] The authors noted that the excess MIs occurred primarily among a group of high-risk people for whom low-dose aspirin would be indicated, and they hypothesized that naproxen inhibit platelet aggregation as does aspirin. In contrast, the Celecoxib Long-term Arthritis Safety Study (CLASS), which compared celecoxib to ibuprofen or diclofenac, reported no differences in rates of cardiovascular events between celecoxib and the other NANSAIDs. [4] Earlier clinical trials of 7535 patients that compared rofecoxib with placebo and other NANSAIDs (diclofenac, ibuprofen, and nabumetone) also yielded similar MI rates in all groups. One major difference between these trials was that they each used different NANSAIDs as comparators to the COX-2 inhibitors; another difference was that VIGOR included only rheumatoid arthritis patients, among whom elevated MI risk has been documented.

In 2002, Ray and colleagues reported that use of rofecoxib at a dose greater than 25 mg was associated with an increase in risk of serious CHD of 70 percent among all current users (n events=13, adjusted incidence rate ratio or IRR=1.70, 95% confidence interval or CI 0.98-2.95), compared with non-users of NANSAIDs. The risk elevation was 90 percent among those who were new users during the study period (n events=12, adjusted IRR 1.93, 95% CI 1.09-3.43). These results come from a retrospective cohort study of use of COX-2 inhibitors and other NANSAIDs in Medicaid recipients in Tennessee [5]. Use of rofecoxib at doses of 25 mg or less was not associated with any increased risk of CHD in either current users (adjusted IRR 1.03, 95%CI 0.78-1.35) or new users (adjusted IRR 1.02, 95% CI 1.09-3.43). In an abstract presented at the American College of Rheumatology in October 2003, Solomon and colleagues reported small (14-24%) non-statistically significant increased relative risks of acute MI associated with current rofecoxib use of all doses combined, compared with celecoxib use or use of other NSAIDs or no NSAIDs from a matched case control study in a large Medicare enrollee population [6]. Elevations were observed for rofecoxib at a greater than 25 mg dose (OR compared with celecoxib >200 mg 1.70, 95% CI 1.07-2.71; OR compared with no NSAIDs 1.58, 95% CI 1.04-2.40) and in the first 90 days of use (OR rofecoxib 1-30 days compared with celecoxib 1-30 days 1.39, 95% CI 1.10-1.74; OR rofecoxib 31-90 days compared with celecoxib 31-90 days 1.37, 95% CI 1.09-1.71).

When NANSAIDs are considered as a group, there appears to be no association between use of these drugs and cardiovascular risk [7,8]. Results from the retrospective cohort study of Tennessee Medicaid patients found no protective effect of naproxen use at doses greater than or equal to 1000 mg or less than 1000 mg [7], however, the results of several case control studies lend support for the existence of a protective effect for naproxen considered separately from other NANSAIDs. [9-11] Naproxen has been shown to be a stronger inhibitor of COX-1 than diclofenac, ibuprofen, or meloxicam in a randomized pharmacologic study. [12] If naproxen is indeed a stronger inhibitor of COX-1, which mediates platelet aggregation, than other NANSAIDs, it would be expected to inhibit platelet aggregation more strongly as well, which might yield greater protection against thromboembolic cardiovascular events, including MI. Given the complex properties of naproxen and other NANSAIDs, large, population based studies are needed to

MRK-S001514

determine their effects on coronary heart disease, which may also differ with duration of use and with dose.

In summary, the issue of whether individual NANSAIDs, including naproxen, and COX-2 inhibitor NANSAIDs such as rofecoxib and celecoxib raise or lower cardiovascular risk remains an open question. To address this, Ingenix Epidemiology conducted a study of the risk of MI/ACS and sudden cardiac death associated with use of rofecoxib, celecoxib, and specific NANSAIDs (naproxen, diclofenac, and ibuprofen) in the population of enrolled UnitedHealthcare members.

The objective of this study was to estimate the rate of MI/ACS and sudden cardiac death in relation to the use of the COX-2 inhibitor medications, rofecoxib and celecoxib, and other NANSAID drugs, naproxen, diclofenac, and ibuprofen. This study did not test a specific hypothesis; it was an estimation study.

This report is the revised final report from this research project incorporating comments from Merck and discussion of these comments between Merck and Ingenix.

Methods

Source population

Data for this study were based on the administrative records kept by UnitedHealthcare, and supplemented by direct review of patient medical charts. UnitedHealthcare is the largest health care company in the United States, with more than 340,000 physicians contracted to provide health care services to over 10 million members.

We used automated health insurance claims data from the Ingenix Research Database. Ingenix maintains a Research Database of approximately nine million current and former UnitedHealthcare members who have both medical and prescription benefit coverage, and who are not in capitated plans. The Research Database contains records of all claims for medical services and prescription drugs. The records include claims relating to each physician visit, medical procedure, hospitalization, drug dispensing, and test performed. These data have been shown to be valid for research purposes. [13,14]

Each record in the Research Database contains encrypted identifiers for patient and provider, date of service, and all diagnosis and procedure codes corresponding to a given claim. Diagnoses are coded using International Classification of Diseases, Ninth Revision (ICD-9), and procedures are coded using Current Procedural Terminology (CPT) or Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS). Each facility service record contains information on up to nine diagnoses, recorded with the International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes, and up to six procedures recorded with ICD-9 procedure codes, Current Procedural Terminology (CPT) or Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS) codes.

Outpatient visit claims are bundled to correspond to a complete medical encounter. Physician services, tests ordered, and non-physician medical services are recorded in a single record, along with the diagnosis that the physician submitted to justify them. Drugs are identified by chemical entity, brand name, and National Drug Classification (NDC) code. Drug records specify the formulation, dose, and quantity dispensed. Also included in the database are the enrollment start and stop dates for each individual, gender, and date of birth.

Study cohort

The cohort was drawn from 22 health plans located in the Northeast, Southeast, Midwest and Western United States that represent most of the membership within the Ingenix Research Database, excluding Medicare, Medicaid, and capitated plans. Only patients from health plans for which medical record abstraction is permitted were included in the cohort.

We first identified 455,852 patients aged 40-64 years who received at least one dispensing of any of the NANSAIDS rofecoxib, celecoxib, naproxen, ibuprofen, or diclofenac in oral tablet or capsule form during the study period January 1, 1999 through June 30, 2001. For each patient we ascertained date of birth, gender, and dates of UnitedHealthcare membership. Among these patients, we identified all drug dispensings, inpatient services, and outpatient services. We obtained UnitedHealthcare inpatient and outpatient medical claims and pharmacy data for 1998 as well as 1999 through 2001 in order to assess whether there was a history of MI in the year preceding the study observation period, and to identify comorbid conditions. Cohort members were categorized, for secondary analyses, according to duration of continuous enrollment in the Research Database at the time of study entry (< 6 months, 6 months to 1 year, 1+ years).

Patients with a history of MI recorded in their medical claims history in the year prior to first recorded NANSAID use in the study period were excluded from the cohort (n= 6,278). Patients whose dispensing records yielded a computed daily dose of greater than twice the modal dose for

any NANSAID were also excluded from the study cohort (n= 6,679). We also excluded an additional 18,308 enrolled in health plans for which access to medical charts was not possible, as well as three patients whose data from a search of the National Death Index indicated a death date prior to cohort entry. The final study population numbered 424,584.

This study was approved by the New England Internal Review Board and Privacy Board. The study's procedures for maintaining confidentiality of protected health information met criteria for waiver of individual informed consent.

Outcomes

Primary and Secondary Endpoints

The primary study endpoint was the combined endpoint of MI, acute coronary syndrome (ACS) and sudden cardiac death. MI or ACS was identified through screening of patients' inpatient medical claims for ICD-9 codes of 410.xx (myocardial infarction) or 411.1x (intermediate coronary syndrome), and confirmed through review of more detailed information abstracted from patients' hospital medical records. Additionally, we searched the National Death Index (NDI) for evidence of a sudden or cardiac death, which we defined as the presence of an ICD-10 code listed in Appendix 1 as the primary cause of death. The multiple steps in this process are described in more detail below. This endpoint will be referred to as "confirmed MI/ACS" throughout the rest of this report, so as not to be confused with the secondary endpoint described below.

A secondary endpoint was MI or death from coronary heart disease (CHD). This endpoint was included to facilitate comparisons with the results of an earlier published study of risk of serious coronary heart disease associated with COX-2 inhibitor NANSAIDs [5]. It included cases of MI identified from inpatient hospital claims associated with an ICD-9 code for MI, and deaths identified through the NDI with an ICD-10 code consistent with death from ischemic heart disease (Appendix 1). We excluded potential cases of MI identified from hospital claims with less than a three-day length of stay in hospital, as these are unlikely to be true myocardial infarctions, unless the status at discharge was deceased or transferred to another hospital facility. This endpoint did not involve further review of patient medical records as described for the primary endpoint. This endpoint will be referred to as "MI claims events" through the rest of this report, so as not to be confused with the primary endpoint described above.

Table 1 presents complete quantitative detail of the event identification and confirmation process for both the primary and secondary endpoints.

Identification of confirmed MI/ACS from medical claims histories

For the primary endpoint of confirmed MI/ACS, we first screened the medical claims histories of all patients in the NANSAIDs study cohort for the presence of one of the following ICD-9 codes for myocardial infarction or intermediate coronary syndrome in association with an inpatient hospital or provider claim:

410.xx	Myocardial infarction
411.1x	Other acute and subacute forms of ischemic heart disease - intermediate coronary syndrome.

The hospital records from the inpatient stay corresponding to all potential MI/ACS events as identified from medical claims were sought for review.

Medical record abstraction

The medical records of patients with a potential MI/ACS event as identified from medical claims review were sought from inpatient medical facilities. Experienced medical record abstractors received training in use of the abstraction tool, which provided for collection of the following information:

- Verification of hospital admission and discharge dates, or office visit date, and enrollee date of birth
- Admission note(s)
- Discharge note
- Emergency room report
- Autopsy summary
- Cardiologist consult notes
- Critical care consult note(s) (including CCU and MICU attending)
- Surgery report/surgeon's note(s)
- Questions pertaining to the diagnosis of MI/ACS
- Medications administered during hospitalization and prescribed at discharge
- Enrollee's vital status upon discharge

We completed abstraction forms for 1367 of 1798 or 76 percent of target events. Reasons for failure to complete abstractions included unavailable records, refusal by the facility and discrepancies in the dates of the hospitalizations identified from the claims data.

For MI/ACS event adjudication, medical consultants reviewed the forms and photocopies of test results, admission or discharge summaries, physician's notes, and other available material, for each potential case event. Each consultant worked from guidelines for the classification of events as confirmed MI/ACS or not confirmed MI/ACS, which had been developed from commonly used clinical criteria, adapted to information obtained through chart review (Appendix 5). Each reviewer recorded his or her decision (case/non-case/questionable) and comments in a Microsoft Access database, which contained the comments from the earlier review of each patient's claims profile, as well as the patient's full claims history. Each reviewer classified the abstracted event, according to available information, and provided a brief written justification for their decision. Questionable events underwent a further independent review for final adjudication.

A 10 percent sample of records that were identified as potential events were subjected to duplicate chart abstraction and adjudication, carried out using different staff, but with identical forms and training. We calculated the percent of records in which the reviewers agreed with one another, among the records found by at least one reviewer to be a case. This fraction is reported as the "% concordant."

National Death Index Search

We submitted identifying information to the National Death Index (NDI) for 53,495 members of the study cohort whose enrollment with UnitedHealthcare terminated before the end of the study period, with no record of re-enrollment. All records were searched against US death records for the years 1999-2001, depending on the year in which the patient was last enrolled.

The NDI search identified matches of varying degrees using name, social security number, gender, and date of birth. For this study, we accepted as true matches those with status equal to 1, classified by the NDI as having a high likelihood of a true match. The NDI matching algorithm can be found in the documentation provided by the Centers for Disease Control and

Prevention/National Center for Health Statistics in their *National Death Index Plus: Coded Causes of Death, Supplement to the NDI Users Manual* [15].

Deaths were included in the study as confirmed events, with the date of death used as the end of follow-up, if the match was accepted as a true match, and if the date of death preceded the date of disenrollment (with no intervening records of physician medical encounters or inpatient visits identified from the claims records for a given patient), or if the date of death fell within 7 days following the disenrollment date. The NDI Plus service provided us with causes of death along with the fact and date of death. Deaths were included for a given endpoint as specified in Appendix 1, based on the ICD-10 code indicating the primary cause of death.

Table 1, column D shows the numbers of events identified through searching of the National Death Index that were included in computation of the primary and secondary study endpoints, additional to those events identified through the medical claims.

Person-time

The starting date of observation for each individual began on the latest of 1) January 1, 1999, 2) first dispensing of an eligible NANSAID during the study period, 3) the date s/he turned 40. Follow-up for a given patient ended at the earliest of the following dates 1) disenrollment from the health plan, 2) 65th birthday, 3) occurrence of a study event, 4) death, or 5) the end of the study period (June 30, 2001).

Exposure to COX-2s and Other NANSAIDs

We classified exposure to COX-2s and other NANSAIDs using dates of dispensing, days of medication supplied, quantity of drug, and dose in mg from recorded pharmacy dispensings for the COX-2s, rofecoxib and celecoxib, and the other NANSAIDs ibuprofen, naproxen, and diclofenac. Non-oral, non-tablet, and non-capsule formulations were excluded from consideration, as were combination medications of NANSAIDs with narcotics such as hydrocodone.

Periods of current and recent use of NANSAIDs

Exposure classification was done on a person-day basis, and reflects medication use as it changed through time. We distinguished the following periods for COX-2 and comparison NANSAIDs:

> Current use: from the date dispensed through a period that corresponds to the number of days supplied. With each new dispensing, a patient continues or re-initiates on-therapy status, and the start dates for the next two states are reset.
>
> Recent use: from the last date of current use through 60 days following.
>
> Non- use: all person-days more than 60 days following last date of current use of a given NANSAID.

Person-time at risk was aggregated into different time windows according to exposure classification of each individual NANSAID as current use, recent use, and non-use. Periods of non-use of any NANSAID were not included in analysis as comparisons between periods of use of different NANSAIDs were of primary interest.

A small amount of person-time was classified as concurrently exposed to multiple NANSAIDs. These time periods had a mean length of 18 days for an individual patient, less than the typical length of a single medication dispensing, suggesting they reflected primarily switching of medications rather than concurrent use of multiple NANSAIDs. As shown in Tables 5.3 and 5.4, higher rates of study events were observed during multiple use person-time, however the overall

amount of concurrently exposed person time was small. Addition of a separate indicator term for multiple NANSAID exposure to models containing terms for current and recent use of individual NANSAIDs had little impact on comparisons between individual NANSAIDs.

Periods of new, continuous use of NANSAIDs

We also identified periods of new, continuous use of each NANSAID, to permit evaluation of immediate and delayed effects on cardiovascular risk of and to evaluate effects of dose of specific medications used. New, continuous use of an NANSAID was defined as beginning with the first dispensing of a study drug during the study period, with no use of any NANSAID in the 180 days preceding the date of this dispensing. A period of new, continuous NANSAID use ended when a gap in use (as determined from dates of dispensing and days supply) of greater than 30 days occurred, or a new dispensing of a different NANSAID was recorded. Gaps in use of up to 30 days were "bridged" or assumed to comprise a single period of continuous use so as to retain most relevant person-time for this analysis. Each individual patient contributed no more than one period of new, continuous NANSAID use to the total person-time of observation for these analyses.

Computation of daily dose of medication used

We computed the average daily dose of medication used for each medication dispensing during periods of new, continuous use of NANSAIDs, and applied it to the time period of that dispensing in computation of exposed person time. We multiplied the quantity of drug (e.g. 60 pills) by the dose as strength in mg (e.g. rofecoxib 25 mg) and divided by the days supply (e.g. 30 days) to compute the daily dose of medication used over the period of medication dispensing (for the example quantities given, the daily dose would be 50 mg of rofecoxib, applied to the 30 day period of the medication dispensing).

Covariate definition and measurement

In addition to the above classifications of NANSAID exposure, person-time for all cohort members was classified according to covariates computed at baseline. We defined each of the following characteristics for each cohort member, as of the date of cohort entry: age, gender, geographic region of health plan, and months of preceding continuous enrollment with UnitedHealthcare.

History of prior cardiac disease, stroke and of other comorbid conditions in the year prior to study entry was determined for all subjects and was identified by ICD-9 diagnosis code(s) associated with at least one office visit or inpatient hospital stay (Appendix 2). Other comorbid conditions identified were transient ischemic attack, peripheral arterial disease, diabetes mellitus, hypertension, hyperlipidemia/hypercholesterolemia, and rheumatoid arthritis.

Use of cardiovascular and other comedications in the year prior to study entry was determined for all subjects on the basis of a history of dispensings of the selected medications in the pharmacy claims data. Cardiovascular medications are shown in Appendix 3; additionally we classified patients according to use of estrogen replacement therapy and use of oral steroids.

Analysis

Description of characteristics of COX-2 and other NANSAID users

Patients in the study cohort were classified by type of NANSAID(s) used during the study period (rofecoxib, celecoxib, diclofenac, ibuprofen, and naproxen). We calculated the total number of patients using each type of NANSAID at any time during the study period.

Results are presented in tabular form as either numbers and percentages, or mean, and standard deviation for each characteristic. Within the NANSAID cohort, presence of comorbid conditions, use of cardiovascular and other comedications, and patterns of health care utilization are also presented separately according to use of each study medication at any time during the time period of interest (the groups are not mutually exclusive). We calculated days hospitalized and amount paid for medical services for patients with six months of continuous enrollment prior to study entry.

Incidence analysis

Crude and standardized incidence rates of confirmed MI/ACS and sudden death, as well as numbers of study events and person-years were computed for periods of current use of each of the five study drugs. Standardized incidence rates were computed for all five study drugs by weighting exposure-specific person-time according to the proportion of person-years observed in each stratum of age, gender and prior cardiac history, for all current use person time within the overall study population. The STATA statistical package was used to compute exact confidence intervals for the standardized rates using the "dstdize" command.

Multivariate Poisson regression analysis

We used Poisson regression analysis to estimate rates of each endpoint during periods of current and recent use of the NANSAIDs rofecoxib, celecoxib, and naproxen, compared with use of ibuprofen or diclofenac, with adjustment for age, gender, calendar year, comorbidities (Appendix 2) and comedication use (Appendix 3) at time of study entry. The equality of the coefficients for current use of ibuprofen and current use of diclofenac in a multivariate model containing all covariates and terms for current use of other NANSAIDs were tested before creating a combined reference group consisting of current and recent use of these medications. The null hypothesis of equality of the two coefficients was not rejected, p=0.49. Results from Poisson regression models are reported as adjusted rate ratios and 95 percent confidence intervals.

We also used Poisson regression in analyses comparing periods of new, continuous use of rofecoxib, celecoxib, and naproxen with ibuprofen and diclofenac, subcategorized by daily dose of medication used and by duration of use. Rofecoxib use was categorized as <25 mg/day, 25 mg/day (the modal dose), and 26-50 mg/day; celecoxib use was categorized as <200 mg/day, 200 mg/day (the modal dose), and 201-400 mg/day; naproxen use was categorized as <1000 mg/day, 1000 mg/day (the modal dose), and 1001-2000 mg/day and these categories were compared to a referent group of new, continuous use of ibuprofen or diclofenac (of any dosage). Additional comparisons were made between periods of use of specific daily doses of rofecoxib 25 mg/day, rofecoxib 50 mg/day, and celecoxib 400 mg/day each compared with use of ibuprofen or diclofenac of any dosage.

New continuous use of rofecoxib, celecoxib, and naproxen and ibuprofen or diclofenac were categorized as first 30 days of use, next 31-60 days of use, 61-90 days of use, and greater than 90 days of use, with the referent group being periods of the first 30 days of new, continuous use of ibuprofen or diclofenac, adjusted for all covariates.

Additionally, effect modification by age, gender, and prior cardiac history was assessed by testing of interaction terms in Poisson regression analysis. Rheumatoid arthritis was of a priori interest,

however less than 3 percent of the NANSAID cohort had a diagnosis of RA in their medical claims histories. Since some patients' medical claims histories prior to enrollment were less than six months in duration, we also replicated the rates and ratios from Table 6.1, restricting the set for analysis to patients with at least six months of prior history in the claims database. For each potential effect modifier, we tested interaction terms between current use of each study medication and the variable of interest within the model containing all covariates as shown in Table 6.1 for the confirmed MI/ACS endpoint, as well as evaluated whether the effects appeared different to a clinically meaningful degree. None of the interactions tested were significant at $p<0.05$. We noted that interactions of both rofecoxib and celecoxib with age, in the direction of decreasing relative risk of confirmed MI/ACS with age were of borderline significance (<0.10), as was the interaction term for rofecoxib with gender, in the direction of lower relative risk of confirmed MI/ACS for men. Appendix 4 gives exact p-values for these interactions within the multivariate model.

Results

Users of COX-2 inhibitors and NANSAIDs in UnitedHealthcare, 1999 through mid-2001

Numbers of users and dispensings among the study population of each of the five study medications by calendar quarter, gender, and age, for the time period January 1999 through June 2001 are shown in Tables 2.1 through 2.5. Celecoxib was launched in January 1999. Rofecoxib was introduced shortly thereafter in May 1999.

Use of both COX-2 inhibitors grew very rapidly from the times of their respective launches in Q1 and Q2 1999, as can be seen in Figures 1 and 2. Celecoxib attained over 14,000 users per quarter in UnitedHealthcare by Q3 2000, and rofecoxib over 13,000 by Q3 2000. During the same interval, numbers of users of the older NANSAIDs diclofenac, ibuprofen and naproxen either remained steady or fell slightly (while the UnitedHealthcare population was continuing to grow). Of the older NANSAIDs, naproxen experienced the greatest use, with close to 30,000 users most quarters from Q1-1999 until Q1-2001.

The CLASS and VIGOR trials appeared in JAMA and the New England Journal of Medicine, respectively, in the fall of 2000 [3,4]. Both strongly suggested a gastrointestinal safety advantage for the COX-2s over older NANSAIDs. Possibly as a result of these publications, the number of users of both COX-2 inhibitors increased even more rapidly from Q3 2000 through Q2-2001 (the last period for which complete claims data were available to use for analysis). Rofecoxib use surpassed celecoxib use in UnitedHealthcare beginning with Q4 2000, and by Q2 2001 it had edged out all other NANSAIDs, with over 28,000 users during the quarter. These time trends did not differ much by gender or age.

Characteristics of the study population

We identified 424,584 UnitedHealthcare members with at least one dispensing of one of the five study medications, rofecoxib, celecoxib, diclofenac, ibuprofen, or naproxen, and without a history of MI or other exclusions listed above from the Ingenix Research Database. The mean follow-up time while a current or recent user of a study drug contributed by each cohort member during the study period was 5.1 months, for a total of 177,239 person-years of follow-up.

Table 3 compares the subpopulations of the NANSAID cohort with at least one dispensing for each of the five study drugs in regard to demographic characteristics, comorbid conditions and comedication use, and health care utilization in the prior six months at the time of study entry. Since groups of users of each specific NANSAID are defined according to use at any time during the study period, they are not mutually exclusive.

Overall, NANSAID users were 57 percent female, 43 percent male, with the users of the COX-2 medications slightly more likely to be female than users of the predecessor NANSAIDs ibuprofen and naproxen. COX-2 users were notably older than other NANSAID users, with celecoxib users tending to be slightly older than rofecoxib users. Diclofenac users resembled COX-2 users in these respects more closely than users of ibuprofen and naproxen. Given the recent emergence of the COX-2s to the prescription NANSAID market, there was a strong association of more recent study entry with COX-2 medication use.

About seven percent of rofecoxib users and eight percent of celecoxib users had a history of prior cardiac disease in the year prior to first NANSAID dispensing, compared with about five percent of ibuprofen and naproxen users, and 5.8 percent of diclofenac users. Less than one percent of all NANSAID users had a history of stroke or TIA. Prevalence of other comorbid conditions at baseline differed only slightly between groups. Celecoxib users were more likely to have rheumatoid arthritis (3.1%) than rofecoxib or diclofenac users (1.9% for both) and users of other NANSAIDs, likely due to celecoxib's approved indication for use in RA patients.

Celecoxib users had the highest prevalence of cardiovascular and other comedication use at baseline, followed by rofecoxib users, who differed only by 1-2 percent from celecoxib users in any given class. Ibuprofen and naproxen users had the lowest prevalences of cardiovascular medication use, with diclofenac users again intermediate between users of COX-2s and other NANSAIDs.

Rofecoxib and celecoxib users had more physician visits in the preceding six months than did users of other NANSAIDs; about 60 percent of each had one or more visits, and nearly half had two or more visits. There were no substantial differences in frequency of either ER visits or inpatient hospitalizations between users of different NANSAIDs. Among patients with a hospitalization in the past six months (about 3 percent overall), the mean length of stay was highest for celecoxib users (6 days) and rofecoxib users (5.4 days), and somewhat lower for users of other NANSAIDS. Users of COX-2 inhibitors incurred higher total medical care expenditures (exclusive of prescription drugs) in the preceding six months than users of other NANSAIDs ($1,101 for rofecoxib users, $1,137 for celecoxib users compared with less than $800 for all other groups).

Amount and duration of current use of NANSAIDs

Total person-months of current use attributable to each of the study medications during the time period of observation for the cohort are shown in Tables 4.1-4.5. Rofecoxib users contributed a total of about 173,000 person months of current use, compared with about 240,000 person-months of celecoxib use. Naproxen received the most use within the cohort, with about 293,000 person-months of current use.

On average during the study period, patients who used rofecoxib had about two and a half months of current use, compared with somewhat more than three months of use for celecoxib. Naproxen and ibuprofen users had an average of less than two months duration of current use, with diclofenac intermediate at about two and a half months average length of current use.

Incidence of confirmed MI/ACS, MI claims events and use of NANSAIDs

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Tables 5.1 and 5.2 present numbers of confirmed MI/ACS and MI claims events, person-years, and incidence rates of events occurring during current use of each of the five study medications. Both crude incidence rates and rates standardized according to the distribution of age, gender, and prior cardiac history within all current use of NANSAIDs in the study cohort are presented for comparison. The highest adjusted incidence rate of confirmed MI/ACS was observed during periods of rofecoxib use, with an incidence rate (IR) of 8.82 events per 1000 person-years (PY), based on 128 events, while the lowest adjusted incidence of confirmed MI/ACS occurred among periods of ibuprofen use (IR 6.77/1000 PY, based on 91 events) (Table 5.1). Similar patterns were observed for rates of MI claims events (Table 5.2).

Tables 6.1 and 6.2 show adjusted rate ratios from multivariate Poisson regression models for risk of confirmed MI/ACS or MI claims events associated with periods of use of rofecoxib, celecoxib and naproxen in comparison to a combined reference group of current ibuprofen and diclofenac use. Periods of current use of rofecoxib were associated with an approximately 35 percent elevation in risk of confirmed MI/ACS (RR 1.35, 95% CI 1.09-1.68) and 30 percent elevation in risk of MI claims events (RR 1.30, 95% CI 1.00-1.69) compared with ibuprofen or diclofenac use. There was no apparent association of current celecoxib use with risk of confirmed MI/ACS (RR 1.03, 95% CI 0.83-1.27) or MI claims events (RR 1.08, 95% CI 0.85-1.37). The rate ratio for current naproxen use compared with ibuprofen or diclofenac use was 1.14 for confirmed MI/ACS (95% CI 0.93-1.39) and 1.22 for MI claims events (95% CI 0.97-1.52).

We observed the expected associations of increased risk of confirmed MI/ACS (Table 6.1) with increasing age, male gender (RR 2.60, 95% CI 2.24-3.02), comorbid conditions including prior cardiac history (RR 1.78, 95% CI 1.49-2.13), PAD (RR 1.66, 95% CI 1.16-2.37), diabetes (RR 1.92, 95% CI 1.65-2.22), and some cardiovascular medications, particularly beta-blockers (RR 1.38, 95% CI 1.17-1.62) and nitrates (RR 2.39, 95% CI 1.93-2.97). Very similar patterns were observed in regard to predictors of MI claims events (Table 6.2).

We also examined whether time since onset of NANSAID use was related to risk of acute coronary events (Tables 7.1 and 7.2). Among periods of new, continuous use of NANSAIDs, there were not consistent trends of increasing or decreasing risk with time since onset. Though the first 30 days of use of both rofecoxib (RR 1.51, 95% CI 0.98-2.34) and celecoxib (RR 1.21, 95% CI 0.80-1.84) seemed to be associated with somewhat higher rates of confirmed MI/ACS and MI claims events (RR rofecoxib 1.86, 95%CI 1.14-3.04; RR celecoxib 1.43, 95% CI 0.89-2.28), elevations in risk were not confined to that period of exposure nor were there declining risks in subsequent periods of use.

Interactions of current use of each study medication with age (continuous), gender, and prior cardiac history were tested in a multivariate model including all covariates shown in Tables 5-9. None of these interactions were significant at $p<0.05$.

Table 8.1 presents incidence rates of confirmed MI/ACS and rate ratios comparing periods of current and recent NANSAID use similar to those shown in Table 5.1, limited to patients with at least six months of prior enrollment. Results did not differ substantively from those in the study cohort as a whole. Tables 8.2 and 8.3 show the results of subgroup analyses limited to patients with at least six months of prior enrollment reflecting the addition of number of physician visits, ER visits, and hospitalizations in the prior six months as health care utilization indices to the set of covariates included in other multivariate models. Though the crude rates of confirmed MI/ACS and MI claims events were observed to increase with increasing numbers of physician, ER, and hospital visits, the rate ratios for one or two or more visits (compared with none) in the prior six months were all at or below 1, indicating that following adjustment for the constellation of cardiovascular risk factors already included in the models there were not residual associations between these factors.

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Analyses of Dose of NANSAIDs and Incidence of Confirmed MI/ACS and MI Claims Events

Tables 9.1 through 9.4 show the relation of daily dose of NANSAIDs compared with use of any dose of ibuprofen or naproxen during periods of new, continuous use of NANSAIDs. Tables 9.1 and 9.2 present the results of analyses of use of rofecoxib, celecoxib, and naproxen at daily doses equivalent to, less than, and greater than the modal (most commonly prescribed) dose of each medication, for the primary and secondary endpoints. Tables 9.3 and 9.4 present the results of additional dose analyses designed to make specific comparisons between 1) specific doses of rofecoxib (25 mg) and celecoxib (400 mg) at the recommended maximum dose for chronic pain with use of ibuprofen and naproxen (all doses), and 2) the specific dose of rofecoxib (50 mg) recommended for acute pain with use of ibuprofen and naproxen (all doses). During the study period there was no acute pain indication for celecoxib.

Dose analyses did not indicate trends of increasing risk with higher daily dose of rofecoxib (RR of confirmed MI/ACS for rofecoxib 25 mg 1.54, 95% CI 1.15-2.04; RR of confirmed MI/ACS for rofecoxib 26-50 mg 0.81, 95% CI 0.41-1.60), celecoxib (RR of confirmed MI/ACS for celecoxib 200 mg 0.95, 95% CI 0.72-1.25; RR of confirmed MI/ACS for celecoxib 201-400 mg 1.14, 95% CI 0.78-1.65), or naproxen (RR of confirmed MI/ACS for naproxen 1000 mg 0.99, 95% CI 0.78-1.27; RR of confirmed MI/ACS for naproxen 2000 mg 0.67, 95% CI 0.42-1.07), compared with all doses of ibuprofen or diclofenac combined (Table 9.1) There was relatively little use of these medications at doses less than the modal dose, limiting further inference about these relationships. Patterns were similar albeit based on fewer events for the MI claims events endpoint (Table 9.2).

Periods of use of rofecoxib at the recommended maximum chronic pain dose of 25 mg were associated with a relative risk of confirmed MI/ACS of 1.48 (95% CI 1.10-1.99) compared with periods of use of ibuprofen or diclofenac. Periods of use of celecoxib at the recommended maximum chronic pain dose of 400 mg were associated with a relative risk of confirmed MI/ACS of 1.18 (95% CI 0.81-1.73) compared with periods of use of ibuprofen or diclofenac. Use of rofecoxib at the recommended acute pain dose of 50 mg/day was associated with a slightly reduced rate of confirmed MI/ACS, (RR 0.77, 95% CI 0.37-1.58). (Table 9.3) Again, patterns were similar albeit based on fewer events for the secondary MI claims events endpoint (Table 9.4).

In order to provide information regarding the potential for "channeling" of patients with different baseline health status to any specific doses of study drugs being compared, we present in Table 10 the characteristics of users of rofecoxib 25 and 50 mg, celecoxib 400 mg, and users of any dose of ibuprofen or diclofenac. Users of ibuprofen or diclofenac were notably younger than users of other drugs compared, and had lower prevalence of comorbid conditions and use of cardiovascular medications. Users of rofecoxib 25 mg and celecoxib 400 mg (recommended maximum chronic pain doses) were notably older and had similarly higher prevalences of comorbid conditions and use of cardiovascular medications. Users of rofecoxib 50 mg (recommended acute pain dose) were intermediate between the other drug/dose groups in regard to these characteristics.

Validation of Chart Abstracts

We re-abstracted a 10 percent quality assurance sample of potential MI/ACS events. A total of 178 potential MI/ACS events for patients whose charts were successfully abstracted in one round of review were targeted for re-review. Duplicate charts were successfully re-abstracted for a total of 155 patients.

Table 11 summarizes the results of duplicate abstraction and review of medical records. There were 154 records for which at least one reviewer classified the event as a case. Overall 84 percent of records in which at least one reviewer found ACS was so found by both reviewers. The

concordance varied somewhat across drug groups. Concordance was lower among the COX-2 selective inhibitor groups than the NANSAID groups.

Discussion

The COX-2 inhibitors, rofecoxib and celecoxib, which were first marketed in the U.S. in 1999, experienced rapid growth in the numbers of users within the UnitedHealthcare population, as was true for the U.S. as a whole [16], from 1999 through mid-2001. By Q2 2001 there were more users of rofecoxib in the study population than any other NANSAID, including naproxen. NANSAID users were about 60 percent female. Users of COX-2 medications were notably older and also had a slightly higher prevalence of cardiac disease and stroke than users of traditional NANSAIDs.

Overall, crude and adjusted rates of confirmed MI/ACS and MI claims events were somewhat higher during periods of current rofecoxib use than periods of other NANSAID use, including celecoxib, and in this respect the current findings are similar to the results of at least two prior studies [5,6]. There was not a clear trend with time since onset of use, though risks in the first 30 days of rofecoxib and celecoxib were elevated compared with periods of use of ibuprofen or diclofenac. In contrast with results of both the Tennessee Medicaid [5] and Medicare populations from two eastern US states [6], which found that dosages of rofecoxib >25 mg were associated with higher risks of CHD, excess risk of confirmed MI/ACS or MI claims events among rofecoxib users in the present study was limited to users of the 25 mg dose. In this population, users of doses of rofecoxib greater than 25 mg (mostly comprised of the 50 mg dose) had slightly lower rates of confirmed MI/ACS and MI claims events compared with users of other NANSAIDs, raising additional questions of interpretation of any biologic effect of rofecoxib on risk of coronary heart disease.

There are important differences between our study, Ray et al.'s Tennessee Medicaid cohort study, and Solomon et al.'s case-control study within a Medicare population that should be considered when comparing the results. Both the Medicaid and Medicare studies included older patients than this study, which was conducted in a commercially insured population. As the representation of persons over 65 who retain health care coverage through their employer rather than Medicare is disproportionately small, and reflects some unknown characteristics of self-selection, we chose to restrict the age range for this study to patients ages 40-64. To the extent that the relative importance of individual cardiovascular risk factors are known to vary with age, so also may any biological effect of NANSAID use on risk of MI. The present study does not reflect the effects of any of the study drugs in persons older than 65. Additionally, Ray et al. used non-users of NANSAIDs as the reference group for most comparisons. Non-users of NANSAIDs tend to have substantially lower prevalence of treatments for and diagnoses of cardiovascular disease, and lower prevalence of cardiovascular and other comedication use than users of prescription NANSAIDs. Comparisons between periods of use of different NANSAID medications are subject to less confounding by differences in these baseline risk factors than comparisons between periods of use of NANSAIDs with non-use person time; therefore the latter comparisons may also be subject to more residual confounding even after control for measured covariates in multivariate analyses.

Success in obtaining medical record abstracts for this and other Ingenix studies declined in the months leading up to and immediately following implementation of the Health Insurance Portability and Accountability Act (HIPAA) in April 2003. Overall, we obtained a final fraction of 76 percent of the desired medical charts for review, which is below the fraction retrieved in earlier Ingenix studies, which has been 80 percent or more. We believe providers' anxieties about how to apply HIPAA requirements may have led to some of the refusals we encountered. The similarity of results based on the confirmed MI/ACS, primary endpoint and the MI claims events endpoint based on claims data only (which was not subject to incomplete ascertainment) is reassuring. There is no reason to believe that success in obtaining medical records is differential, related to use of rofecoxib or celecoxib, or indeed to NANSAID use in general.

The overall concordance between the results of replicated abstractions and reviews by different study personnel was 84%, with modest variations by study drug (Table 11). These variations in concordance of the chart review process may be reflective of differences in the sensitivity of identification of true cases of MI/ACS, differences in the false identification of true non-cases of MI/ACS as cases, and/or other misclassification; thus, the direction of impact of misclassification of MI/ACS on measures of relative risk is unknown.

The endpoint of acute coronary syndrome, especially on the borderline of medical decision making between patients with angina that is "unstable" and other anginal patterns also reflective of underlying CHD, is by nature subjective in that it relies on interpretation of patients' account of presenting symptoms and patterns of anginal symptoms over time. Data shown in Table 1 indicates that events which were assigned a diagnosis code at the claims data level indicative of MI were confirmed through chart review more than 87 percent of the time, whereas events assigned a diagnosis code of intermediate coronary syndrome but not MI were confirmed only 67 percent of the time at the chart validation step. We also note again the similarity of our results based on either the primary endpoint of confirmed MI/ACS, which relied on chart validation of endpoints for inclusion in analyses or the secondary MI claims events endpoint, which included all events identified at the claims level without regard to chart validation as support of this observation.

Limitations of this study include reliance on computerized pharmacy records to determine periods of NANSAID exposure. Though an unbiased source of exposure information relative to outcome, records of dispensings of NANSAID medications are a proxy for actual use. Use of over the counter NANSAIDs including aspirin, which were not measured in this study, would be unlikely to introduce substantial confounding unless aspirin use differed in regard to NANSAID use. A prior patient survey conducted by Ingenix indicates that aspirin use was unlikely to exert a strong confounding effect on studies of COX-2 inhibitors, other NANSAIDs, and MI [17]. Residual confounding by other unmeasured factors such as smoking, body mass index, diet and exercise may also have affected these results, although the relatively small baseline differences in other measured risk factors might suggest that the magnitude of such confounding is not large.

In conclusion, we observed rates of confirmed MI/ACS and MI claims events during periods of current rofecoxib use that were 35% higher than during periods of current use of ibuprofen or diclofenac, while periods of current use of celecoxib were not associated with higher rates of study events. Our data do not however show support for an increase in risk of acute coronary events with doses of rofecoxib greater than 25 mg; any excess risk of study events appeared to be confined to the rofecoxib 25 mg dose.

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MRK-S001529

Tables

Table 1: Event Ascertainment and Confirmation of Endpoints among NANSAID Users, UnitedHealthcare, 1999-2001

NSAID Exposed patients with ICD-9 codes as identified from medical claims or NDI cause of death	A Id'd from review of claims histories n	B Chart Review Results Obtained n	% of A	C Event Confirmed through Chart review N	% of B	D Additional Events Identified from NDI N	C+D Total Confirmed Events N
MI/ACS and Sudden Cardiac Death [1]	1798	1367	76.0%	1029	75.3%	100	1129
410.xx only	685	515	75.2%	453	87.9%	85	538
411.1x only	1091	833	76.4%	561	67.4%	14	575
Both 410.xx and 411.1x	22	16	72.7%	15	93.8%	1	16
798.xx	110	--	--	--	--	--	--
MI/CHD Death [2]							
410.xx in hospital claims with 3-day stay, transfer or status indicating death	601	--	--	--	--	78	579

[1] Primary endpoint:MI, inclusive of ACS and sudden death, identified from medical claims and confirmed with medical chart abstraction, and through data from the National Death Index.
[2] Secondary endpoint: MI or death from CHD, identified through medical claims and through data from the National Death Index.

MRK-S001530

Table 2.1: Counts of Users and Dispensings of Rofecoxib

Counts of users and dispensings of Rofecoxib by age, gender, and calendar quarter in UnitedHealthcare 1-1-99 through 6-30-01

	AGE											
	40-44		45-49		50-54		55-59		60-64		Total	
	Users	Dispensings	Users	Dispensings	Users	Dispensings	Users	Dispensings	Users	Dispensings	Users	Dispensings
Q1-1999												
Female	0	0	0	0	0	0	0	0	0	0	0	0
Male	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	0	0	0	0	0	0
Q2-1999												
Female	61	67	74	78	90	92	74	78	52	55	351	375
Male	34	36	45	52	30	37	40	44	21	22	170	187
Total	95	103	119	130	120	130	114	120	73	77	521	560
Q3-1999												
Female	344	519	477	664	548	814	495	671	343	575	2,207	3,403
Male	194	258	217	304	254	366	199	462	167	257	1,031	1,578
Total	538	777	694	968	802	1,180	694	1,133	510	833	3,238	4,911
Q4-1999												
Female	568	903	651	1,141	889	1,559	744	1,326	543	965	3,405	5,914
Male	307	480	366	598	390	665	346	627	265	471	1,667	2,812
Total	875	1,383	1,017	1,739	1,279	2,224	1,090	1,953	808	1,436	5,072	8,726
Q1-2000												
Female	897	1,381	1,086	1,803	1,391	2,321	1,123	1,916	770	1,328	5,267	8,749
Male	428	668	530	848	574	954	600	1,081	385	642	2,517	4,193
Total	1,325	2,049	1,616	2,651	1,965	3,275	1,723	2,997	1,155	1,970	7,784	12,942
Q2-2000												
Female	1,107	1,792	1,459	2,404	1,857	3,313	1,520	2,659	1,092	1,681	7,005	13,153
Male	673	1,054	744	1,294	865	1,525	851	1,532	540	948	3,673	6,220
Total	1,780	2,846	2,203	3,698	2,722	4,838	2,371	4,191	1,632	2,629	10,678	18,462
Q3-2000												
Female	1,410	2,327	1,797	3,094	2,278	4,032	1,834	3,348	1,206	2,205	8,525	14,717
Male	924	1,306	1,024	1,678	1,241	2,119	1,130	1,887	757	1,351	5,076	8,543
Total	2,334	3,633	2,821	4,662	3,519	6,151	2,964	5,235	1,963	3,556	13,601	23,260
Q4-2000												
Female	2,425	3,679	2,835	4,510	3,354	5,740	2,668	4,714	1,667	2,912	12,947	21,555
Male	1,899	2,767	2,179	3,386	2,228	3,732	1,998	3,445	1,315	2,273	9,617	15,603
Total	4,324	6,446	5,014	7,896	5,582	9,472	4,662	8,159	2,982	5,185	22,564	37,158
Q1-2001												
Female	3,045	4,421	3,531	5,365	4,132	6,754	3,218	5,449	1,961	3,276	15,887	25,265
Male	2,168	3,052	2,430	3,634	2,498	3,938	2,182	3,545	1,411	2,296	10,689	16,465
Total	5,213	7,473	5,961	8,999	6,630	10,692	5,400	8,994	3,372	5,572	26,576	41,730
Q2-2001												
Female	3,500	5,284	3,841	6,134	4,481	7,384	3,478	6,060	2,064	3,532	17,362	28,595
Male	2,238	3,322	2,412	3,804	2,572	4,311	2,217	2,849	1,375	2,357	10,815	17,643
Total	5,738	8,606	6,253	9,938	7,053	11,695	5,695	8,909	3,439	5,890	28,177	46,238
TOTALS												
1999	1,508	2,263	1,830	2,854	2,201	3,534	1,898	3,198	1,391	2,346	8,821	14,197
2000	8,763	14,976	11,654	16,825	13,768	23,737	11,720	20,582	7,702	13,941	54,607	91,763
2001	10,952	16,079	12,214	16,937	13,683	22,587	11,093	16,903	6,811	11,462	54,753	87,966
Female	13,357	20,272	15,781	25,217	18,000	32,718	15,350	26,644	9,884	16,752	72,968	120,764
Male	8,866	13,048	9,937	15,503	10,650	17,844	9,364	16,420	6,036	10,597	45,256	73,224
Total	22,223	33,320	25,698	40,750	28,672	49,858	24,714	42,061	15,904	27,349	118,211	193,978

Table 2.2: Counts of Users and Dispensings of Celecoxib

Counts of users and dispensings of Celecoxib by age, gender, and calendar quarter in UnitedHealthcare 1-1-99 through 6-30-01

	AGE											
	40-44		45-49		50-54		55-59		60-64		Total	
	Users	Dispensings	Users	Dispensings	Users	Dispensings	Users	Dispensings	Users	Dispensings	Users	Dispensings
Q1-1999												
Female	[illegible]	1,046	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	1,037	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	2,021	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Q2-1999												
Female	1,453	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Q3-1999												
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	1,710	[illegible]	2,314	[illegible]	2,817	[illegible]	[illegible]	[illegible]	1,922	[illegible]	[illegible]	[illegible]
Q4-1999												
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Q1-2000												
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Q2-2000												
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Q3-2000												
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Q4-2000												
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Q1-2001												
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Q2-2001												
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TOTALS												
1999	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2000	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2001	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Female	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

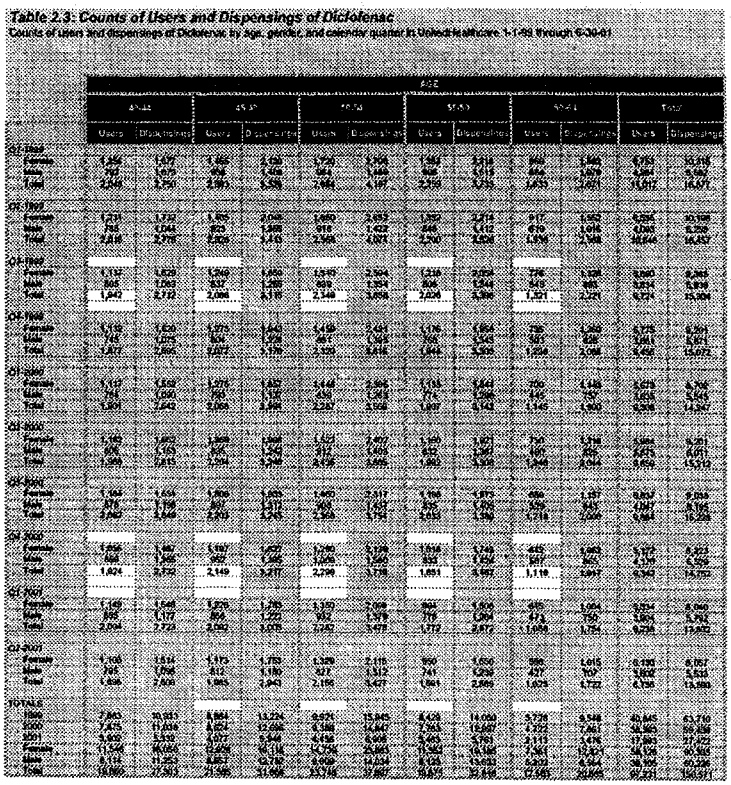

Table 2.3: Counts of Users and Dispensings of Diclofenac

Counts of users and dispensings of Diclofenac by age, gender and calendar quarter in United HealthCare 1-1-98 through 6-30-04

Table 2.4: Counts of Users and Dispensings of Ibuprofen

Counts of users and dispensings of ibuprofen by age, gender, and calendar quarter in UnitedHealthcare 1-1-99 through 6-30-01

	AGE											
	40-44		45-49		50-54		55-59		60-64		Total	
	Users	Dispensings	Users	Dispensings	Users	Dispensings	Users	Dispensings	Users	Dispensings	Users	Dispensings
Q1 1999												
Female	3,738	4,514	3,351	4,182	2,768	3,408	1,818	2,378	1,050	1,817	13,053	16,547
Male	2,835	2,628	2,044	2,544	1,629	2,371	1,290	1,714	760	1,081	8,291	10,536
Total	6,073	7,340	5,395	6,726	4,531	5,799	3,109	4,088	1,840	2,898	20,944	30,083
Q2 1999												
Female	3,653	4,368	3,213	4,062	2,029	3,277	1,775	2,378	1,010	1,386	12,098	15,467
Male	2,222	2,713	1,959	2,514	1,725	2,274	1,274	1,718	845	1,163	8,025	10,188
Total	5,775	7,081	5,162	6,576	4,254	5,356	3,049	4,095	1,864	2,549	20,124	25,455
Q3 1999												
Female	3,583	4,458	3,274	4,117	2,656	3,395	1,711	2,293	1,024	1,355	12,330	15,638
Male	2,898	2,925	1,970	2,405	1,726	2,227	1,256	1,695	799	1,085	8,538	10,418
Total	6,051	7,380	5,244	6,602	4,186	5,622	2,967	3,988	1,820	2,440	20,868	26,032
Q4 1999												
Female	3,845	4,727	3,384	4,300	2,728	3,536	1,847	2,468	1,056	1,430	12,850	16,479
Male	2,469	3,010	2,113	2,681	1,768	2,377	1,339	1,612	782	1,080	8,521	10,940
Total	6,314	7,737	5,497	6,981	4,516	5,914	3,186	4,080	1,847	2,510	21,380	27,419
Q1 2000												
Female	3,958	4,797	3,430	4,240	2,217	3,462	1,783	2,598	1,013	1,336	12,891	16,137
Male	2,587	3,091	2,137	2,640	1,792	2,310	1,259	1,718	725	932	8,538	10,709
Total	6,505	7,888	5,567	6,880	4,009	5,772	3,062	4,008	1,736	2,268	21,429	26,836
Q2 2000												
Female	3,874	4,761	3,403	4,280	2,739	3,504	1,808	2,414	981	1,322	12,903	16,281
Male	2,620	3,027	2,056	2,566	1,856	2,438	1,406	1,869	770	1,032	8,610	10,932
Total	6,494	7,788	5,459	6,846	4,595	5,942	3,214	4,283	1,751	2,354	21,513	27,213
Q3 2000												
Female	4,170	5,088	3,570	4,481	2,828	3,872	1,672	2,450	996	1,318	13,436	16,880
Male	2,866	3,591	2,421	3,053	2,080	2,425	1,505	1,995	796	1,054	9,770	12,370
Total	7,536	8,680	5,991	7,540	4,908	6,297	3,277	4,445	1,789	2,372	23,276	29,399
Q4 2000												
Female	4,120	5,036	3,373	4,299	2,640	3,431	1,655	2,184	899	1,213	12,689	16,175
Male	3,308	3,998	2,783	3,446	2,159	2,821	1,558	2,065	851	1,132	10,657	13,452
Total	7,428	9,034	6,156	7,745	4,799	6,252	3,213	4,249	1,750	2,345	23,346	29,625
Q1 2001												
Female	4,545	5,501	3,606	4,454	2,625	3,597	1,772	2,512	866	1,140	13,615	16,954
Male	3,018	3,584	2,488	3,004	2,040	2,535	1,412	1,617	775	1,017	9,734	11,857
Total	7,564	9,085	6,094	7,458	4,665	6,132	3,184	4,129	1,641	2,157	23,349	28,941
Q2 2001												
Female	4,306	5,155	3,429	4,267	2,760	3,564	1,686	2,234	891	1,176	12,972	16,416
Male	2,522	3,144	2,106	2,612	1,801	2,337	1,217	1,603	685	920	8,433	10,616
Total	6,828	8,299	5,535	6,880	4,561	5,901	2,903	3,837	1,576	2,098	21,405	27,034
TOTALS												
1999	24,212	29,538	21,318	26,816	17,687	22,690	12,309	16,467	7,371	9,986	82,896	105,296
2000	27,813	33,400	23,173	29,017	18,509	24,213	13,666	16,965	7,033	9,359	89,464	113,074
2001	14,392	17,384	11,639	14,337	9,427	12,033	6,087	7,966	3,217	4,256	44,752	55,976
Female	39,773	48,476	34,055	42,690	27,175	35,790	17,798	23,633	9,748	13,065	128,857	162,392
Male	26,438	31,908	22,085	27,547	18,798	24,370	13,558	17,995	7,825	10,905	88,705	112,328
Total	66,211	80,422	56,139	70,229	45,923	60,130	31,395	41,418	17,621	23,600	217,142	274,716

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Table 2.5: Counts of Users and Dispensings of Naproxen

Counts of users and dispensings of Naproxen by age, gender, and calendar quarter in UnitedHealthcare 1-1-99 through 6-30-01.

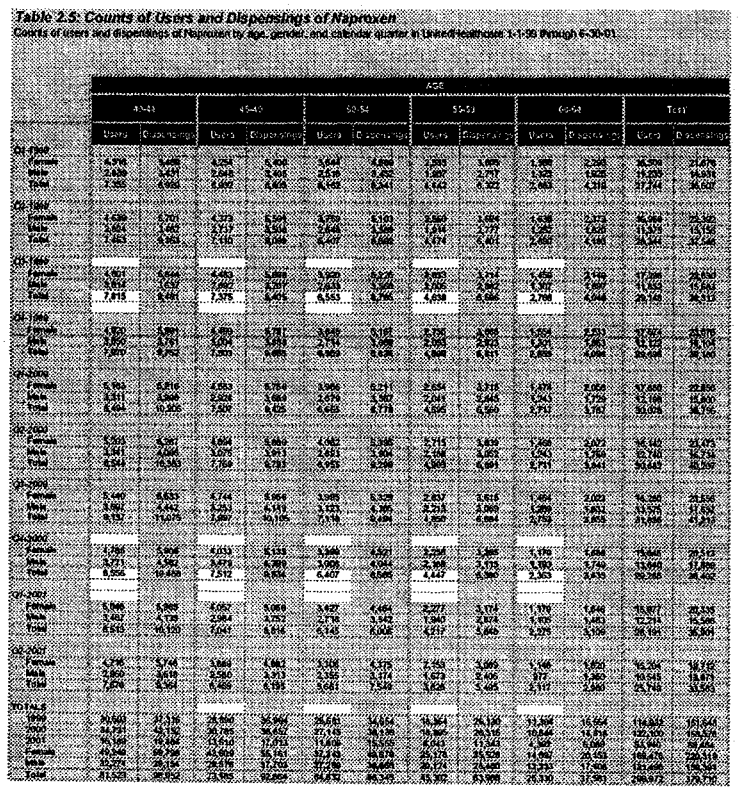

Table 3: Characteristics of COX-2 and Other NANSAID Users in UnitedHealthcare

Gender										
Female	40,667	59.9%	45,817	60.5%	30,483	58.5%	76,716	57.8%	105,808	57.0%
Male	27,212	40.1%	29,886	39.5%	21,597	41.5%	56,785	42.4%	79,716	43.0%
Age When Entered Cohort										
40-44	14,884	21.9%	14,195	18.8%	12,470	23.9%	44,762	33.7%	56,298	30.3%
45-49	15,178	22.4%	14,450	19.1%	12,448	23.9%	36,088	26.9%	47,496	25.6%
50-54	16,396	24.2%	18,475	24.4%	12,112	23.3%	28,466	20.8%	40,058	21.6%
55-59	12,858	18.9%	15,603	20.6%	9,160	17.6%	18,855	13.5%	25,116	14.1%
60-64	8,463	12.5%	10,980	14.5%	5,861	11.3%	10,541	7.6%	15,956	8.2%
Health Plan (region)										
Midwest	28,793	42.5%	32,289	42.7%	19,715	37.9%	60,028	43.3%	76,859	41.3%
Northeast	1,907	2.9%	3,047	4.0%	1,288	2.5%	10,010	7.2%	10,488	5.7%
Southeast	27,365	40.4%	30,010	39.6%	22,814	43.8%	44,666	32.2%	69,746	37.8%
West	5,060	7.5%	5,825	7.4%	4,146	8.0%	19,245	11.7%	15,884	8.6%
After Enrollment Before 1st NSAID										
< 6 months	20,955	30.9%	23,800	31.2%	14,353	27.6%	34,385	24.8%	44,548	24.0%
6 - 11 months	9,994	14.7%	11,724	15.5%	8,035	15.4%	22,241	16.1%	29,506	15.9%
12 + months	36,850	54.4%	40,369	53.3%	29,652	56.9%	81,878	59.1%	111,470	60.1%
Calendar Year of Study Entry										
1999	17,280	25.5%	33,404	44.1%	29,129	55.9%	66,046	47.7%	90,449	48.8%
2000	29,328	43.3%	25,967	34.3%	16,607	31.9%	50,644	36.6%	68,729	37.0%
2001	21,183	31.2%	16,312	21.5%	6,344	12.2%	21,841	15.8%	26,346	14.2%
Presence of Comorbid Condition										
Cardiac History	5,054	7.4%	5,855	7.7%	2,955	5.8%	6,825	5.0%	9,747	5.3%
Stroke	393	0.9%	407	0.6%	276	0.5%	436	0.3%	606	0.3%
Transient Ischemic Attack	341	0.5%	381	0.5%	184	0.4%	441	0.3%	616	0.3%
Peripheral Artery Disease	566	0.8%	716	0.9%	340	0.7%	755	0.5%	1,094	0.6%
Diabetes	5,882	8.7%	7,062	9.3%	4,351	8.4%	10,586	7.8%	13,682	7.4%
Hypertension	17,888	26.2%	20,002	26.4%	12,057	23.2%	29,539	21.3%	40,422	21.8%
Hyperlipidemia	13,565	20.1%	14,888	19.7%	9,843	17.0%	21,347	15.4%	30,277	16.3%
Rheumatoid Arthritis	1,296	1.9%	2,361	3.1%	1,002	1.9%	1,061	0.8%	1,515	0.8%
Cardiovascular Comedication Use										
Anticoagulants	1,105	1.6%	1,393	1.8%	418	0.8%	925	0.7%	1,165	0.6%
Other Anti-hyperlipidemics	10,391	15.3%	11,778	15.6%	6,727	12.9%	14,886	10.7%	20,947	11.3%
Oral Diuretics	9,307	13.7%	11,365	15.1%	6,629	12.7%	15,416	11.1%	20,696	11.2%
ACE Inhibitors	8,254	12.2%	9,947	13.1%	6,234	12.0%	14,991	10.8%	20,089	10.8%
Antiarrhythmics	300	0.4%	366	0.5%	162	0.3%	330	0.2%	428	0.2%
Antiplatelet drugs	465	0.7%	615	0.8%	240	0.5%	509	0.4%	676	0.4%
Beta blockers	6,850	10.1%	7,866	10.4%	4,645	8.9%	10,833	7.8%	14,953	8.1%
Calcium Channel Blockers	7,034	10.4%	8,611	11.4%	5,120	9.8%	11,973	8.6%	16,186	8.7%
Statins	9,440	13.9%	10,750	14.2%	6,106	11.7%	13,555	9.8%	18,427	10.3%
Nitrates	1,363	2.0%	1,668	2.2%	881	1.7%	2,020	1.5%	2,741	1.5%
Estrogens	16,630	24.5%	19,403	25.6%	11,527	22.1%	25,006	18.1%	34,206	18.4%
Angiotensin Receptor Antagonist	2,306	3.4%	2,435	3.2%	1,142	2.2%	2,443	1.8%	3,528	1.9%
Digoxin	644	0.9%	778	1.0%	358	0.7%	770	0.6%	1,027	0.6%
Oral steroids	11,852	17.5%	12,940	17.1%	7,790	15.0%	17,442	12.6%	25,308	13.6%
Health care utilization in preceding six months										
Physician visits										
0	5,784	8.5%	6,124	8.1%	6,166	11.8%	23,323	16.8%	28,706	15.4%
1	9,301	13.7%	8,690	11.5%	7,581	14.6%	22,349	16.1%	31,348	16.9%
2+	52,794	48.1%	37,289	49.3%	23,840	46.0%	58,477	42.2%	80,818	43.6%
ER Visits										
0	42,054	62.0%	46,889	61.9%	34,275	65.8%	92,306	66.6%	127,377	68.7%
1	3,858	5.7%	4,203	5.6%	2,816	5.4%	9,725	7.0%	11,258	6.1%
2+	925	1.4%	1,011	1.3%	596	1.1%	2,088	1.5%	2,340	1.3%
Hospitalizations										
0	44,451	65.5%	49,463	65.3%	36,480	70.0%	96,677	71.2%	136,704	73.7%
1	2,078	3.1%	2,287	3.0%	1,079	2.1%	5,040	3.6%	3,864	2.1%
2+	315	0.5%	353	0.5%	126	0.2%	402	0.3%	407	0.2%
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Number of Hospitalizations	1.17	0.53	1.16	0.52	1.14	0.42	1.10	0.39	1.13	0.47
Length of Stay	5.4	13.54	6.02	14.23	4.84	10.82	4.08	7.72	4.45	10.20
Hospital Cost	6451.99	12293.14	6981.58	17619.5	4837.36	7670.26	4871.40	8052.34	4802.64	7416.47
Total claims for outpatient/ inpatient medical care 6 months prior to first NSAID (not including cost of medication)	1101.33	4461.16	1137.28	5329.50	710.32	2459.86	784.60	3067.94	615.36	2382.18

Table 4.1: Rofecoxib Use in UnitedHealthcare

Rofecoxib use in UnitedHealthcare, January 1, 1999 through June 30, 2001, by age and gender*

	Rofecoxib Users					
	N	Person Months	Mean Months of Current Use per Person	S.D. for Mean Months of Current Use per Person	Minimum Months	Maximum Months
Gender						
Female	40,007	108,611	2.68	3.21	0.03	24.17
Male	27,212	64,269	2.16	2.91	0.03	24.03
Age When Entered Cohort						
40-44	14,564	27,840	1.82	2.43	0.03	23.40
45-49	15,479	35,290	2.28	2.81	0.03	24.17
50-54	16,386	44,768	2.73	3.21	0.03	23.83
55-59	12,656	39,436	3.06	3.54	0.03	24.83
60-64	8,463	25,436	3.01	3.40	0.03	24.83
Total	67,748	172,880	2.65	3.09	0.03	24.83

*Includes patients with any rofecoxib use during the study period

Table 4.2: Celecoxib Use in UnitedHealthcare
Celecoxib use in UnitedHealthcare, January 1, 1999 through June 30, 2001, by age and gender[1]

	Celecoxib Users					
	N	Person Months	Mean Months of Current Use per Person	S.D. for Mean Months of Current Use per Person	Minimum Months	Maximum Months
Gender						
Female	45817	150834.9	3.29	4.13	0.03	29.30
Male	29886	89532.3	3.00	3.91	0.03	29.30
Age When Entered Cohort						
40-44	14195	33362.83	2.35	3.16	0.03	28.30
45-49	16450	47646.17	2.90	3.86	0.03	29.30
50-54	18475	61423.6	3.32	4.16	0.03	28.07
55-59	15003	58517.47	3.75	4.54	0.03	28.30
60-64	10980	39417.13	3.59	4.24	0.03	27.83
Total	75,703	240,367	3.17	4.04	0.03	29.30

[1] Includes patients with any celecoxib use during the study period.

Table 4.3: Diclofenac Use in UnitedHealthcare

Diclofenac use in UnitedHealthcare, January 1, 1999 through June 30, 2001, by age and gender*

	Diclofenac Users					
	N	Person Months	Mean Months of Current Use per Person	S.D. for Mean Months of Current Use per Person	Minimum Months	Maximum Months
Gender						
Female	30,453	80,427	2.64	4.11	0.03	30.33
Male	21,597	52,448	2.43	3.89	0.03	30.03
Age When Entered Cohort						
40-44	12,470	21,846	1.75	2.98	0.03	29.33
45-49	12,445	26,970	2.17	3.47	0.03	29.80
50-54	12,112	33,731	2.78	4.33	0.03	29.77
55-59	9,192	30,628	3.33	4.85	0.03	30.33
60-64	5,861	19,700	3.36	4.50	0.03	30.03
Total	52,080	132,874	2.55	4.01	0.03	30.33

*Includes patients with any diclofenac use during the study period.

Table 4.4: Ibuprofen Use in UnitedHealthcare

Ibuprofen use in UnitedHealthcare, January 1, 1999 through June 30, 2001, by age and gender*

	Ibuprofen Users					
	N	Person-Months	Mean Months of Current Use per Person	S.D. for Mean Months of Current Use per Person	Minimum Months	Maximum Months
Gender						
Female	79,719	105,185	1.32	2.34	0.03	29.93
Male	58,785	72,760	1.24	2.27	0.03	29.77
Age When Entered Cohort						
19-44	44,752	56,689	1.04	1.82	0.03	29.63
45-49	35,099	45,042	1.22	2.20	0.03	29.47
50-54	29,466	40,169	1.41	2.51	0.03	29.70
55-59	18,650	25,749	1.50	2.64	0.03	29.80
60-64	10,541	17,446	1.66	2.75	0.03	29.30
Total	138,504	177,945	1.29	2.30	0.03	29.93

*Includes patients with any ibuprofen use during the study period.

Table 4.5: Naproxen Use in UnitedHealthcare

Naproxen use in UnitedHealthcare, January 1, 1999 through June 30, 2001, by age and gender[1]

	Naproxen Users					
	N	Person Months	Mean Months of Current Use per Person	S.D. for Mean Months of Current Use per Person	Minimum Months	Maximum Months
Gender						
Female	105,806	165,624	1.90	3.61	0.03	29.67
Male	79,718	121,637	1.55	3.54	0.03	29.80
Age When Entered Cohort						
40-44	58,259	88,800	1.22	1.86	0.03	29.17
45-49	47,839	80,267	1.45	2.70	0.03	29.17
50-54	40,059	68,861	1.72	2.78	0.03	29.80
55-59	26,110	53,814	2.06	3.33	0.03	29.50
60-64	15,158	32,099	2.16	3.35	0.03	29.27
Total	185,524	283,160	1.53	2.67	0.03	29.80

[1]Includes patients with any naproxen use during the study period.

Table 5.1: Rates of Confirmed MI/ACS [1] During Current Use of COX-2s and Other NANSAIDs
United Healthcare, 1999-2001

	Events	PY	IR [2]	Adjusted IR [3]	Lower 95% CL [4]	Upper 95% CL [4]
Rofecoxib	129	14,116	9.07	8.82	7.29	10.34
Celecoxib	145	19,635	7.39	6.85	5.71	7.99
Diclofenac	89	10,835	8.21	7.84	6.23	9.47
Ibuprofen	91	14,530	6.26	6.77	5.37	8.16
Naproxen	170	23,897	7.46	7.69	6.56	8.81
Ibu or Dicio	176	25,315	6.95	7.14	6.12	8.23

[1] Primary endpoint composed of MI, acute coronary syndrome and sudden cardiac death, confirmed through hospital medical record documentation or National Death Index.
[2] IR = Incidence rate per 1,000 person - years
[3] Standardized according to age, sex, and prior history of a vascular event
[4] CL = Confidence Limit

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Table 5.2: Rates of MI Claims Events [2] During Current Use of COX-2s and Other NANSAIDs
United Healthcare, 1999-2001

	Events	PY	IR [3]	Adjusted IR [5]	Lower 95% CL [4]	Upper 95% CL [4]
Rofecoxib	74	14,142	5.23	5.04	3.89	6.19
Celecoxib	92	19,668	4.68	4.31	3.42	5.21
Diclofenac	57	10,383	5.28	5.00	3.76	6.31
Ibuprofen	64	14,549	4.40	4.81	3.62	6.00
Naproxen	114	24,015	4.75	4.86	3.97	5.75
Ibu or Diclo	117	25,441	4.62	4.77	3.91	5.63

[1] Secondary endpoint comprised of MI or death from coronary heart disease, identified through claims data or National Death Index.
[3] IR = Incidence rate per 1,000 person - years
[5] Standardized according to age, sex, and prior history of a vascular event
[4] CL = Confidence Limit

Table 5.3: Rates of MIACS [1] During Current Use of COX-2s and Other NANSAIDs
Includes Overlap Periods of Multiple NSAID Use
United Healthcare, 1999-2001

	Events	PY	IR [2]	Adjusted IR [3]	Lower 95% CL [4]	Upper 95% CL [4]
Rofecoxib	124	13,653	9.08	8.90	7.24	10.36
Celecoxib	139	19,064	7.29	6.74	5.61	7.87
Diclofenac	81	10,509	7.71	7.39	5.78	8.99
Ibuprofen	85	14,060	6.04	6.51	5.12	7.91
Naproxen	175	23,407	7.48	7.66	6.55	8.82
Other Diclo	170	25,306	6.96	7.17	6.12	8.23
Multiple NANSAIDs	14	1,110	12.61	12.31	6.08	18.54

[1] Primary endpoint comprised of MI, acute coronary syndrome and sudden cardiac death, confirmed through hospital medical record documentation or National Death Index
[2] IR = Incidence rate per 1,000 person - years
[3] Standardized according to age, sex, and prior history of a vascular event
[4] CL = Confidence Limit

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Table 5.4: Rates of MI Claims Events [1] During Current Use of COX-2s and Other NANSAIDs
Includes Overlap Periods of Multiple NSAID Use
United Healthcare, 1999-2001

	Events	PY	IR [2]	Adjusted IR [3]	Lower 95% CL [4]	Upper 95% CL [4]
Rofecoxib	69	13,715	5.03	4.85	3.76	6.00
Celecoxib	87	19,129	4.55	4.19	3.30	5.09
Diclofenac	49	10,526	4.66	4.44	3.19	5.68
Ibuprofen	58	14,068	4.12	4.49	3.32	5.66
Naproxen	110	23,477	4.69	4.80	3.90	5.70
Ibu or Diclo	117	25,531	4.62	4.77	3.91	5.63
Multiple NANSAIDs	14	1,110	12.61	12.16	6.09	18.23

[1] Secondary endpoint comprised of MI or death from coronary heart disease, identified through claims data or National Death Index.
IR = Incidence rate per 1,000 person - years
[3] Standardized according to age, sex, and prior history of a vascular event
[4] CL = Confidence Limit

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Table 6.1: Rates and Relative Risk of Confirmed MI/ACS [1] associated with NANSAID Use
United Healthcare, 1999-2001

	Events	Person-Years	Crude Rate per 1000 PY	Adjusted Rate Ratio	Lower 95% CL	Upper 95% CL
Ibuprofen/Diclofenac						
Current [2]	176	25,315	6.95	1.00 (REF)		
Recent	227	40,377	5.62	1.00	0.83	1.20
Rofecoxib						
Current	128	14,118	9.07	1.35	1.09	1.68
Recent	73	10,307	7.08	1.15	0.88	1.50
Celecoxib						
Current	145	19,635	7.38	1.03	0.83	1.27
Recent	82	13,574	6.04	0.91	0.70	1.17
Naproxen						
Current	179	23,997	7.46	1.14	0.93	1.39
Recent	182	38,118	4.78	0.86	0.70	1.04
Age						
40-44	100	42,105	2.38	0.43	0.34	0.55
45-49	171	41,853	4.09	0.68	0.56	0.82
50-54	282	41,361	6.82	1.00 (REF)		
55-59	318	42,293	7.52	1.24	1.06	1.46
60+	260	19,913	13.06	1.46	1.22	1.72
Gender						
Male	763	71,356	10.71	2.60	2.24	3.02
Female	362	105,989	3.42	1.00 (REF)		
Calendar Year						
1999	648	100,227	6.47	1.02	0.89	1.18
2000	384	90,825	4.41	1.00 (REF)		
2001	93	17,073	5.45	0.87	0.70	1.10
Presence of Comorbid Conditions						
Prior cardiac history	259	10,852	23.87	1.78	1.49	2.13
Stroke	11	711	15.48	1.05	0.56	1.97
TIA	9	708	12.70	0.83	0.42	1.65
PAD	34	1,224	27.79	1.66	1.16	2.37
Diabetes	270	15,448	17.48	1.92	1.65	2.22
Hypertension	475	43,677	10.88	1.20	1.04	1.40
Hyperlipidemia	319	31,373	10.17	1.27	1.08	1.49
Rheumatoid Arthritis	36	4,212	8.55	1.39	0.99	1.94
Cardiovascular Comedications						
Anticoagulants (inc. Heparin)	27	2,018	13.38	0.84	0.56	1.26
Antihyperlipidemics (inc. statins)	330	24,259	13.60	0.85	0.73	1.00
Diuretics (total)	207	25,154	8.23	0.88	0.74	1.05
ACE-inhibitors	277	22,587	12.27	1.15	0.98	1.34
Antiarrhythmics	12	609	19.71	1.06	0.58	1.93
Antiplatelet drugs	30	932	32.20	1.23	0.83	1.81
Beta-blockers	236	16,888	14.06	1.38	1.17	1.62
Calcium channel blockers	256	18,837	13.59	1.27	1.09	1.48
Nitrates	140	3,196	43.86	2.30	1.93	2.97
Estrogens	172	40,408	4.26	0.87	0.72	1.05
Angiotensin receptor antagonist	47	4,232	11.11	0.98	0.73	1.32
Digoxin	30	1,376	21.80	0.95	0.64	1.41
Oral steroids	171	20,283	8.51	1.00	0.85	1.18

All variables shown in table included in multivariate Poisson regression model.
[1] Primary endpoint comprised of MI, acute coronary syndrome and sudden cardiac death, confirmed through hospital medical record documentation or National Death Index.
[2] Reference group for all categories of current and recent rofecoxib, celecoxib and naproxen use, and recent ibuprofen or diclofenac use.

MRK-S001546

Table 6.2: **Rates and Relative Risk of MI Claims Events [1] associated with NANSAID use**
United Healthcare, 1999-2001

	Events	Person-Years	Crude Rate per 1,000 PY	Adjusted Rate Ratio	Lower 95% CL	Upper 95% CL
Ibuprofen/Diclofenac						
Current [2]	117	25,341	4.62	1.00 [REF]	–	–
Recent	128	40,406	3.17	0.87	0.68	1.10
Rofecoxib						
Current	74	14,142.00	5.23	1.30	1.00	1.69
Recent	45	10,322.00	4.36	1.17	0.85	1.62
Celecoxib						
Current	92	19,668	4.68	1.08	0.85	1.37
Recent	43	13,584	3.18	0.79	0.57	1.09
Naproxen						
Current	114	24,014	4.75	1.22	0.97	1.52
Recent	107	38,137	2.81	0.84	0.67	1.06
Age						
40-44	69	42,110	1.64	0.49	0.36	0.62
45-49	95	41,880	2.27	0.73	0.58	0.93
50-54	164	41,305	3.98	1.00 [REF]	–	–
55-59	168	33,347	5.04	1.35	1.09	1.53
60 +	162	19,656	8.24	1.37	1.11	1.70
Gender						
Male	440	71,306	6.16	2.58	2.14	3.11
Female	239	108,007	2.25	1.00 [REF]	–	–
Calendar Year						
1,999.00	399	100,342	3.97	1.14	0.97	1.35
2,000.00	218	59,973	3.63	1.00 [REF]	–	–
2,001.00	63	17,977	3.50	0.87	0.64	1.18
Presence of Comorbid Conditions						
Prior cardiac history	123	10,915	11.27	1.96	1.60	2.40
Stroke	10	710	14.09	1.03	0.51	2.05
TIA	6	710	8.45	0.72	0.33	1.57
PAD	22	1,228	17.92	1.53	1.02	2.29
Diabetes	154	15,503	9.93	1.96	1.64	2.33
Hypertension	283	43,948	6.44	1.45	1.21	1.73
Hyperlipidemia	168	31,437	5.34	1.18	0.97	1.44
Rheumatoid Arthritis	20	4,219	4.74	1.54	1.06	2.23
Cardiovascular Comedications						
Anticoagulants (inc. heparin)	20	2,023	9.89	0.94	0.60	1.48
Antihyperlipidemics (inc. statins)	8	811	9.82	0.98	0.79	1.23
Diuretics (oral)	141	25,193	5.60	0.88	0.73	1.07
ACE-inhibitors	195	22,610	8.56	1.10	0.92	1.33
Antiarrhythmics	8	841	9.82	1.27	0.68	2.40
Antiplatelet drugs	15	943	15.91	1.36	0.88	2.10
Beta-blockers	132	16,932	7.80	1.29	1.15	1.67
Calcium channel blockers	142	18,865	7.52	1.16	0.96	1.39
Nitrates	60	3,228	18.59	2.27	1.77	2.90
Estrogens	106	40,435	2.62	0.94	0.75	1.18
Angiotensin receptor antagonist	37	4,240	8.73	1.07	0.73	1.44
Digoxin	25	1,379	18.13	0.78	0.48	1.26
Oral steroids	108	26,298	4.11	1.04	0.86	1.25

All variables shown in table included in multivariate Poisson regression model.
[1] Secondary endpoint comprised of MI or death from coronary heart disease, identified through claims data or National Death Index.
[2] Reference group for all categories of current and recent rofecoxib, celecoxib and naproxen use, and recent ibuprofen or diclofenac use.

MRK-S001547

Table 7.1: Rates and Rate Ratios of Confirmed MI/ACS [1] associated with Days of Medication Use During Periods of New, Continuous Use of COX-2s and Other NANSAIDs
United Healthcare, 1999-2001

	Events	Person-Years	Rate per 1,000 PY	Adjusted Rate Ratio [2]	Lower 95% CL	Upper 95% CL
Ibuprofen/Diclofenac						
0-30 [3]	60	11,565	5.71	1.00 [REF]	-	-
31-60	35	7,781	4.51	0.76	0.51	1.17
61-90	15	3,319	4.52	0.74	0.42	1.32
91+	90	5,906	6.10	0.89	0.59	1.34
Rofecoxib						
0-30	31	1,374	9.19	1.51	0.98	2.34
31-60	17	2,734	6.24	1.01	0.58	1.73
61-90	14	1,407	8.42	1.44	0.80	2.57
91+	50	6,875	7.74	1.06	0.69	1.65
Celecoxib						
0-30	35	4,156	6.42	1.21	0.80	1.84
31-60	14	2,903	6.05	0.94	0.52	1.67
61-90	13	2,711	5.47	0.90	0.44	1.45
91+	45	7,582	5.54	0.73	0.49	1.06
Naproxen						
0-30	69	12,124	5.69	1.01	0.72	1.42
31-60	32	6,995	4.96	0.82	0.49	0.94
61-90	14	3,628	3.86	0.62	0.35	1.11
91+	34	5,870	6.21	0.83	0.54	1.26

[1] Primary, outpatient computed of MI, acute coronary syndrome and sudden cardiac death, confirmed through hospital medical record documentation or National Death Index.
[2] Compared with use of ibuprofen or diclofenac (0-30 days), and adjusted for other NANSAID use as shown in table, age, gender, calendar year, comorbid conditions and CV comorbidities use.
[3] Reference group for all categories of days of rofecoxib, celecoxib and naproxen use, and ibuprofen or diclofenac use of 31 days or more.

MRK-S001548

Table 7.2: Rates and Rate Ratios of MI Claims Events [1] associated with Days of Medication Use During Periods of New, Continuous Use of COX-2s and Other NANSAIDs
United Healthcare, 1999-2001

	Events	Person-Years	Rate per 1,000 PY	Adjusted RR Point [2]	Lower 95% CL	Upper 95% CL
Ibuprofen/Diclofenac						
0-30 [3]	43	11566	3.72	1.00 [REF]		
31-60	22	7763	2.83	0.74	0.44	1.24
61-90	5	3320	1.51	0.38	0.15	0.95
91+	21	5918	3.55	0.79	0.47	1.34
Rofecoxib						
0-30	21	3,374	6.22	1.56	1.14	2.04
31-60	11	2,726	4.04	1.20	0.63	2.26
61-90	10	1,498	6.72	1.90	0.98	3.69
91+	16	3,662	4.12	1.10	0.64	1.88
Celecoxib						
0-30	22	4,159	5.29	1.43	0.89	2.28
31-60	10	3,604	2.77	0.74	0.38	1.44
61-90	15	2,215	6.77	1.77	1.02	3.06
91+	31	7,491	4.19	1.05	0.69	1.59
Naproxen						
0-30	39	12,126	3.22	1.06	0.74	1.57
31-60	22	8,886	2.43	0.91	0.61	1.38
61-90	5	3,629	1.38	0.43	0.17	1.05
91+	27	7,476	4.93	1.29	0.94	1.99

[1] Secondary ascribed outpatient MI or death from coronary heart disease, identified through claims data or National Death Index.
[2] Compared with use of ibuprofen or diclofenac 0-30 days/d, but adjusted for other NANSAID use as shown in table, age, gender, calendar year, comorbid conditions and CV co-medication use.
[3] Reference group for all categories of days of ibuprofen, diclofenac and naproxen use, and ibuprofen or diclofenac use of 31 days or more.

MRK-S001549

Table 6.1: Rates and Relative Risk of Confirmed MI/ACS [1] associated with NAINSAID use
Restricted to patients with at least 6 months of continuous baseline enrollment [2]

	Events	Person-Years	Crude Rate per 1,000 PY	Adjusted Rate Ratio	Lower 95% CL	Upper 95% CL
Non-Use/Use/Recent						
Current [3]	112	17,794	6.55	1.00 (REF)		
Recent	161	26,638	5.61	0.96	0.77	1.21
Ibuprofen						
Current	34	5,447	6.65	1.39	1.06	1.83
Recent	31	7,890	3.42	0.95	0.67	1.35
Celecoxib						
Current	91	13,749	6.47	0.97	0.75	1.26
Recent	57	9,426	5.96	0.87	0.64	1.19
Naproxen						
Current	131	17,495	7.43	1.22	0.96	1.54
Recent	130	29,887	4.48	0.88	0.69	1.11
Age						
40-44	65	36,675	2.13	0.46	0.35	0.62
45-49	117	30,275	3.96	0.73	0.58	0.93
50-54	186	28,829	6.21	1	1	1
55-59	215	23,098	9.34	1.25	1.03	1.53
60+	179	14,854	12.05	1.37	1.11	1.7
Gender						
Male	510	57,713	8.75	2.58	2.14	3.11
Female	343	75,468	3.21	1	1	1
Calendar Time						
1,998.00	478	76,980	6.21	1.14	0.97	1.35
2,000.00	244	36,021	6.56	1	1.00	1.00
2,001.50	51	10,912	4.67	0.87	0.64	1.18
Presence of Comorbid Conditions						
Prior cardiac history	215	9,607	22.38	1.96	1.6	2.4
Stroke	8	844	13.86	1.03	0.51	2.05
TIA	7	654	10.71	0.72	0.33	1.57
PAD	20	1,095	23.74	1.53	1.02	2.29
Diabetes	197	11,944	16.65	1.96	1.64	2.33
Hypertension	461	27,702	16.62	1.45	1.21	1.73
Hyperlipidemia	277	27,934	9.82	0.96	0.81	1.15
Rheumatoid Arthritis	30	3,364	8.92	1.54	1.06	2.23
Cardiovascular Comedications						
Anticoagulants (ex. Heparin)	22	1,664	13.25	0.94	0.6	1.48
Antihyperlipidemics (ex. s	341	18,005	12.68	1.18	0.97	1.44
Diuretics (oral)	197	20,188	7.91	0.88	0.73	1.07
ACE-Inhibitors	326	17,674	14.72	1.1	0.92	1.33
Amiodarone	11	664	24.82	1.27	0.68	2.4
Antiplatelet drugs	24	964	37.46	1.36	0.88	2.1
Beta-blockers	582	13,362	13.74	1.39	1.15	1.67
Calcium channel blockers	186	14,736	12.62	1.16	0.96	1.39
Nitrates	403	3,606	40.05	2.27	1.77	2.9
Estrogens	131	31,734	4.13	0.94	0.75	1.18
Angiotensin receptor antag	27	3,795	14.53	0.92	0.73	1.44
Digoxin	20	1,073	18.63	0.78	0.48	1.26
Oral steroids	943	23,519	6.95	1.04	0.86	1.25

All variables shown in table included in multivariate Poisson regression model.
[1] Primary endpoint composed of MI, acute coronary syndrome and sudden cardiac death, confirmed through hospital medical record abstraction or National Death Index.
[2] 941,377 patients of a total study cohort of 452,584 had at least 6 months prior enrollment in UnitedHealthcare.
[3] Reference group for all categories of current and recent rofecoxib, celecoxib and naproxen use, and acetaminophen or diclofenac use.

MRK-S001550

Table 8.2 **Rates and Relative Risk of Confirmed MI/ACS [1] associated with NANSAID use**
Restricted to patients with at least 6 months of continuous baseline enrollment [2]
Includes health care utilization variables

	Events	Person-Years	Crude Rate per 1,000 PY	Adjusted Rate Ratio	Lower 95% CL	Upper 95% CL
NANSAID Dispensed						
Current [3]	117	17,794	6.58	1.00 [REF]	-	-
Recent	151	30,836	5.01	0.86	0.70	1.06
Diltiazem						
Current	64	9,447	8.86	1.41	1.07	1.84
Recent	39	7,190	5.42	0.95	0.67	1.36
Celecoxib						
Current	94	13,344	6.87	0.96	0.75	1.27
Recent	53	9,475	5.59	0.87	0.64	1.20
Naproxen						
Current	131	17,495	7.43	1.21	0.95	1.54
Recent	136	28,947	4.69	0.87	0.68	1.11
Age						
40-44	65	30,575	2.13	0.48	0.34	0.61
45-49	117	30,278	3.86	0.73	0.58	0.92
50-54	186	29,929	6.21	1.00 [REF]	-	-
55-59	215	23,096	9.32	1.26	1.03	1.53
60 +	170	14,154	12.01	1.38	1.12	1.71
Gender						
Male	510	82,313	9.75	2.56	2.12	3.08
Female	243	75,669	3.21	1.00 [REF]	-	-
Calendar Year						
1999	478	76,569	6.24	1.15	0.96	1.36
2000	214	36,621	5.84	1.00 [REF]	-	-
2001	61	10,912	4.67	0.87	0.64	1.18
Presence of Comorbid Conditions						
Prior cardiac history						
Stroke	215	9,507	22.38	1.97	1.61	2.42
TIA	5	644	13.96	1.01	0.50	2.01
PAD	7	654	10.71	0.72	0.33	1.56
Diabetes	26	1,095	23.74	1.53	1.03	2.31
Hypertension	197	11,844	16.63	1.87	1.65	2.35
Hyperlipidemia	401	37,752	10.62	1.47	1.23	1.77
Rheumatoid Arthritis	277	27,934	9.92	1.18	0.97	1.44
	36	3,364	8.92	1.58	1.06	2.29
Cardiovascular Comedications						
Antihypertensive (inc. hospital)	22	1,660	13.26	0.95	0.60	1.49
Antihyperlipidemics (inc. statins)	241	19,006	12.68	0.99	0.82	1.20
Diuretics (oral)	160	20,186	7.93	0.86	0.73	1.07
ACE Inhibitors	206	17,574	11.72	1.10	0.92	1.33
Antiarrhythmics	11	504	21.82	1.28	0.68	2.41
Antiplatelet drugs	34	764	31.40	1.36	0.89	2.13
Beta blockers	182	13,263	13.72	1.30	1.15	1.67
Calcium channel blockers	186	14,736	12.62	1.15	0.96	1.38
Nitrates	108	2,696	40.05	2.26	1.75	2.89

Table 8.2, continued **Rates and Relative Risk of ACS [1] associated with NANSAID use**

Restricted to patients with at least 6 months of continous baseline enrollment [2]
Includes health care utilization variables

	Events	Person-Years	Crude Rate per 1,000 PY	Adjusted Rate Ratio	Lower 95% CI.	Upper 95% CL
Cardiovascular Comedications, cont						
Estrogens	131	31,734	4.13	0.94	0.75	1.18
Angiotensin receptor antagonist	37	3,265	11.33	1.03	0.73	1.44
Digoxin	20	1,073	18.63	0.78	0.48	1.27
Oral steroids	143	23,515	6.08	1.04	0.86	1.25
Dr Visits						
1 One	132	24937	5.29	0.9	0.64	1.25
2 Two +	521	82555	6.31	0.87	0.66	1.16
3 None	100	20510	4.88	1.00 [REF]	-	-
ER Visits						
1 One	71	9903	7.17	1	0.71	1.42
2 Two +	17	2063	8.24	1.03	0.51	2.1
3 None	665	116036	5.73	1.00 [REF]	-	-
Hospital Stays						
1 One	40	4715	8.48	0.98	0.64	1.51
2 Two +	5	517	9.66	0.82	0.26	2.59
3 None	706	122770	5.77	1.00 [REF]	-	-

All variables shown in table included in multivariate Poisson regression model.

[1] Primary endpoint comprised of MI, acute coronary syndrome and sudden cardiac death, confirmed through hospital medical record documentation or National Death Index.

[2] 311,377 patients of a total study cohort of 452,584 had at least 6 months prior enrollment in UnitedHealthcare.

[3] Reference group for all categories of current and recent rofecoxib, celecoxib and naproxen use, and recent ibuprofen or diclofenac use.

MRK-S001552

Table 6.3 **Rates and Relative Risk of MI Claims Events [1] associated with NANSAID use**
Restricted to patients with at least 6 months of continuous baseline enrollment [2]
Includes health care utilization variables

	Events	Person-Years	Crude Rate per 1000 PY	Adjusted Rate Ratio	Lower 95% CL	Upper 95% CL
Aspirin Exposure						
Current [3]	78	17,567	4.44	1.00 [REF]	-	-
Recent	98	39,154	2.62	0.87	0.65	1.16
Antacid						
Current	45	9,462	5.07	1.27	0.89	1.8
Recent	25	7,200	3.47	0.96	0.62	1.5
Diuretic						
Current	63	13,264	4.75	1.08	0.77	1.48
Recent	24	8,461	2.83	0.62	0.4	0.96
Hormone						
Current	83	17,508	4.74	1.21	0.89	1.63
Recent	79	28,902	2.73	0.83	0.61	1.12
Age						
40-44	44	30,577	1.44	0.48	0.34	0.69
45-49	64	30,294	2.11	0.83	0.46	0.86
50-54	114	29,949	5.81	1.00 [REF]	-	-
55-59	151	23,099	5.67	1.28	0.99	1.65
60+	108	14,183	7.81	1.48	1.13	1.94
Gender						
Male	361	52,588	5.75	2.45	1.94	3.09
Female	160	75,715	2.11	1.00 [REF]	-	-
Calendar Year						
1999	306	78,645	3.82	1.29	1.04	1.61
2000	115	38,545	3.09	1.00 [REF]	-	-
2001	34	10,915	3.12	1.05	0.72	1.54
Presence of Comorbid Conditions						
Prior cardiac history	103	9,060	10.86		1.00	1.86
Stroke	9	643	14.01	1.85	0.91	3.77
TIA	4	855	4.13	0.62	0.22	1.75
PAD	17	1,897	15.5	1.69	1.14	3.14
Diabetes	117	11,880	9.85	1.95	1.56	2.45
Hypertension	234	37,818	6.19	1.26	1	1.6
Hyperlipidemia	150	27,985	5.36	0.98	0.75	1.22
Rheumatoid Arthritis				1.36	0.84	2.26
Cardiovascular Comedications						
Antihypertensive (Non-Diuretic)	16	1,665	9.62	1.09	0.63	1.88
Antihyperlipidemics (inc. statins)	124	19,657	6.31	1.02	0.78	1.32
Digoxin (inc)	114	20,217	5.64	1.11	0.87	1.4
ACE-inhibitor	121	17,612	6.87	1.08	0.86	1.37
Antiarrhythmic	5	807	6.96	0.8	0.31	2.05
Antiplatelet drugs	12	773	15.52	1.7	0.95	2.73
Beta-blockers	104	13,295	7.82	1.44	1.15	1.84
Calcium channel blockers	113	14,770	7.65	1.24	0.98	1.57
Nitrates	46	2,721	17.64	1.81	1.27	2.57

MRK-S001553

Table 8.3, continued **Rates and Relative Risk of MI Claims Events [1] associated with NANSAID Use**
Restricted to patients with at least 6 months of continous baseline enrollment [2]
Includes health care utilization variables

	Events	Person-Years	Crude Rate per 1,000 PY	Adjusted Rate Ratio	Lower 95% CL	Upper 95% CL
Cardiovascular Comorbidities (CVC)						
Ischemia	84	31,752	2.65	0.91	0.68	1.21
Postmenopausal hospital assessment	34	3,270	10.40	1.87	1.16	2.4
Diabetes	17	1,075	15.81	1.33	0.76	2.29
Total Model	88	23,534	3.74	1.05	0.83	1.33
Physician visits						
One	79	24,954	3.17	0.90	0.64	1.25
Two +	317	82,851	3.84	0.87	0.66	1.16
None	65	20,519	3.17	1.00 [REF]	-	-
ER visits						
One	35	9,912	3.53	1.00	0.71	1.42
Two +	8	2,006	3.87	1.09	0.53	2.19
None	418	116,126	3.60	1.00 [REF]	-	-
Hospital days						
One	23	4,721	4.87	0.98	0.64	1.51
Two +	3	516	5.80	0.82	0.26	2.56
None	435	122,864	3.54	1.00 [REF]	-	-

All variables shown in table included in multivariate Poisson regression model.
[1] Secondary acquired component of MI or death from coronary heart disease, identified through claims data or National Death Index.
[2] 211,377 patients of a total study cohort of 452,584 had at least 6 months prior enrollment in UnitedHealthcare.
[3] Reference group for all categories of current and recent rofecoxib, celecoxib and naproxen use, and recent ibuprofen or diclofenac use.

MRK-S001554

Table 9.1: Rates and Rate Ratios of Confirmed MVACS [1] associated with Daily Dose of Medication Use During Periods of New, Continuous Use of COX-2s and Other NANSAIDs United Healthcare, 1999-2001

	Events	Person-Years	Rate per 1,000 PY	Adjusted Rate Ratio [2]	Lower 95% CL	Upper 95% CL
Ibuprofen/Diclofenac (all doses)	152	28561	5.32	1.00 [REF]	-	-
Celecoxib						
Less than 25 mg/day	6	945	6.35	1.03	0.45	2.34
25 mg/day	77	8466	9.10	1.54	1.15	2.04
26-50 mg/day	9	2049	4.39	0.81	0.41	1.60
Celecoxib						
Less than 200 mg/day	2	415	4.82	0.76	0.19	3.03
200 mg/day	75	12036	6.23	0.95	0.72	1.25
201-400 mg/day	35	4913	7.12	1.14	0.78	1.66
Naproxen						
Less than 1000 mg/day	14	3381	4.14	0.75	0.44	1.30
1000 mg/day	113	20452	5.53	0.99	0.78	1.27
1001-2000 mg/day	20	6352	3.13	0.67	0.42	1.07

[1] Primary endpoint confirmed MI, acute coronary syndrome and sudden cardiac death, confirmed through hospital medical record documentation or National Death Index.

[2] Compared with use of ibuprofen or diclofenac (all doses), and adjusted for other NANSAID use, age, gender, calendar year, comorbid conditions and OV contact/utilization rate.

Table 9.2: Rates and Rate Ratios of MI Claims Events [1] associated with Daily Dose of Medication Use During Periods of New, Continuous Use of COX-2s and Other NANSAIDs
United Healthcare, 1999-2001

	Events	Person-Years	Rate per 1,000 PY	Adjusted Rate Ratio [2]	Lower 95% CL	Upper 95% CL
Ibuprofen/Diclofenac (all doses)	91	28,566	3.19	1.00 [REF]	-	-
Rofecoxib						
Less than 25 mg/day	6	944	6.34	1.89	0.71	3.85
25 mg/day	46	8,476	5.43	1.63	1.06	2.51
26-50 mg/day	6	2,050	2.93	0.86	0.37	1.90
Celecoxib						
Less than 200 mg/day	2	415	4.82	1.21	0.30	4.91
200 mg/day	57	12,045	4.73	1.21	0.87	1.69
201-400 mg/day	19	4,920	3.86	1.06	0.63	1.79
Naproxen						
Less than 1000 mg/day	14	3,361	4.14	1.27	0.73	2.24
1000 mg/day	67	20,490	3.27	0.99	0.73	1.36
1001-2000 mg/day	12	6,305	1.90	0.58	0.31	1.09

[1] Secondary ambulatory occurrence of MI or death from coronary heart disease, identified through claims data or Retrieval Chart Study.
[2] Compared with use of ibuprofen or diclofenac (all doses), and adjusted for other NANSAID use, age, gender, calendar year, comorbid conditions and CV medication use.

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Table 9.3: Rates and Rate Ratios of Confirmed MI/ACS [1] associated with Specific Doses of Medication Use During Periods of New, Continuous Use of COX-2s and Other NANSAIDs United Healthcare, 1999-2001

	Events	Person-Years	Rate per 1,000 PY	Adjusted Rate Ratio [2]	Lower 95% CL	Upper 95% CL
Ibuprofen/Diclofenac (all doses)	152	28480	5.34	1.00 [REF]	-	-
Rofecoxib						
25 mg/day [3]	77	8,371	9.20	1.48	1.10	1.99
50 mg/day [4]	8 [5]	1,823	4.39	0.77	0.37	1.58
Celecoxib						
400 mg/day [3]	36	4,726	7.61	1.18	0.81	1.73

[1] Primary endpoint (confirmed AMI, acute coronary syndrome and sudden cardiac death), confirmed through hospital medical record documentation or National Death Index and CV medication use.

[2] Compared with use of ibuprofen or diclofenac (all doses), and adjusted for other NANSAID use as shown in table, age, gender, calendar year, comorbid conditions

[3] Recommended maximum daily chronic dose.

[4] Recommended acute pain dose.

[5] Of eight patients taking rofecoxib 50 mg, date lapse from beginning of new rofecoxib use to event were as follows: 7, 15, 36, 51, 64, 90, 116, and 351 days to event. The patient with 116 days from beginning of rofecoxib use to event began on 25 mg, but switched to 50 mg rofecoxib prior to the event.

Table 9.4: Rates and Rate Ratios of MI Claims Events [1] associated with Specific Doses of Medication Use During Periods of New, Continuous Use of COX-2s and Other NANSAIDs
United Healthcare, 1999-2001

	Events	Person-Years	Rate per 1,000 PY	Adjusted Rate Ratio [2]	Lower 95% CL	Upper 95% CL
Ibuprofen/Diclofenac (all doses)	91	28,495	3.19	1.00 [REF]	-	-
Rofecoxib						
25 mg/day [3]	46	8,381	5.49	1.44	0.96	2.11
50 mg/day [4]	4	1,825	2.19	0.60	0.22	1.65
Celecoxib						
400 mg/day [5]	19	4,735	4.01	1.03	0.62	1.72

[1] Secondary endpoint, confirmed MI or death from coronary heart disease, identified through claims data or National Death Index.
[2] Compared with use of ibuprofen or diclofenac (all doses), and adjusted for other NANSAID use as shown in table, age, gender, calendar year, comorbid conditions and CV medication use. Note that covariates for ethnic, socioeconomic modalities, and digoxin were removed from model due to small numbers where exists.
[3] Recommended maximum daily chronic dose.
[4] Recommended acute pain dose.

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Table 10: **Characteristics of Users of COX-2 and Other NANSAIDs by Dose UnitedHealthcare, 1999-2001**

	Rofecoxib 25 mg		Rofecoxib 50 mg		Celecoxib 4[illegible] mg		Any Ibuprofen/Diclofenac	
	N = 31,429		N = 9,722		N = 14,384		N = 146,971	
	N	%	N	%	N	%	N	%
Gender								
Female	18,337	58.3%	5,203	53.5%	8,475	58.9%	63,080	56.5%
Male	13,092	41.7%	4,519	46.5%	5,909	41.1%	63,891	43.5%
Age When Entered Cohort								
40-44	6,543	20.8%	2,658	27.3%	2,787	19.4%	46,114	31.4%
45-49	6,977	22.2%	2,402	24.7%	3,198	22.2%	37,834	25.7%
50-54	7,635	24.3%	2,120	21.8%	3,487	24.2%	30,667	20.9%
55-59	6,009	19.1%	1,573	16.2%	2,915	20.3%	20,419	13.9%
60-64	4,265	13.6%	969	10.0%	1,997	13.9%	11,937	8.1%
Health Plan (region)								
Midwest	12,999	41.4%	3,911	40.2%	6,155	42.8%	59,951	40.8%
Northeast	839	2.7%	265	2.6%	551	3.8%	8,925	6.1%
Southeast	12,806	40.8%	4,145	42.6%	5,670	39.4%	52,284	35.6%
West	2,643	8.1%	831	8.5%	1,099	7.6%	16,877	11.5%
Prior Enrollment Before 1st NSAID								
< 6 months	10,662	33.9%	3,078	31.7%	5,327	37.0%	39,975	27.2%
6 - 11 months	4,576	14.6%	1,483	15.3%	2,206	15.4%	23,748	16.2%
12 + months	16,191	51.5%	5,161	53.1%	6,849	47.6%	83,248	56.6%
Calendar Year of Study Entry								
1999	2,426	7.7%	431	4.4%	4,302	29.9%	62,300	42.4%
2000	15,410	49.0%	4,227	43.5%	5,768	40.1%	58,156	39.6%
2001	13,593	43.2%	5,064	52.1%	4,317	30.0%	26,515	18.0%
Presence of Comorbid Condition								
Cardiac History	2417	7.7%	671	6.9%	1,081	7.5%	7,269	4.9%
Stroke	178	0.6%	49	0.5%	99	0.7%	456	0.3%
Transient Ischemic Attack	170	0.5%	45	0.5%	85	0.6%	466	0.3%
Peripheral Artery Disease	256	0.8%	89	0.9%	154	1.1%	791	0.5%
Diabetes	2795	8.9%	795	8.2%	1,375	9.6%	11,014	7.5%
Hypertension	7854	25.0%	2,258	23.2%	3,668	25.5%	30,124	20.5%
Hyperlipidemia	6610	21.0%	1,855	19.1%	2,708	18.8%	22,397	15.2%
Rheumatoid Arthritis	575	1.8%	122	1.3%	1,023	7.1%	1,071	0.7%
Cardiovascular Comedication Use								
Anticoagulants	600	1.9%	155	1.6%	288	2.0%	934	0.6%
Statins and Other Anti-hyperlipidemics	5147	16.4%	1,350	13.9%	2,198	15.3%	15,777	10.7%
Oral Diuretics	4108	13.1%	1,157	11.9%	2,161	15.0%	15,280	10.4%
ACE Inhibitors	3817	12.1%	1,051	10.8%	1,873	13.0%	15,135	10.3%
Antiarrhythmics	164	0.5%	30	0.4%	73	0.5%	368	0.3%
Antiplatelet drugs	233	0.7%	70	0.7%	139	1.0%	562	0.4%
Beta blockers	3194	10.2%	864	8.9%	1,481	10.3%	11,253	7.7%
Calcium Channel Blockers	3136	10.0%	874	9.0%	1,599	11.1%	12,166	8.3%
Nitrates	646	2.1%	160	1.6%	312	2.2%	2,066	1.4%
Estrogens	7446	23.7%	1,833	18.9%	3,365	23.4%	26,104	17.8%
Angiotensin Receptor Antagonist	1196	3.8%	336	3.5%	497	3.5%	2,664	1.8%
Digoxin	320	1.0%	81	0.8%	136	0.9%	834	0.6%
Oral steroids	5302	16.9%	1,742	17.9%	2,797	19.4%	18,236	12.4%

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Table 11: Concordance Between Repeated Medical Chart Reviews of Potential Cases of ACS Identified from Medical Claims Histories

NANSAID	Classified as ACS case: Both reviews	One review	% Concordant
Ibuprofen/Diclofenac	50	6	89
Rofecoxib	21	5	81
Celecoxib	26	9	74
Naproxen	36	5	88
Any of the Above	130	24	84

Total number of multiple reviews =155. One review classfied by both reviews as a non-case is not shown in the above table.
Numbers for individual agents do not sum to the "Any of the Above" because of overlapping exposure.

Figures

Figure 1: COX-2 and NANSAID Users

UnitedHealthcare, 1999-2001

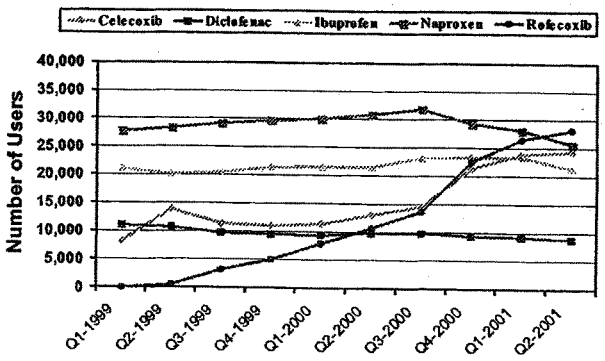
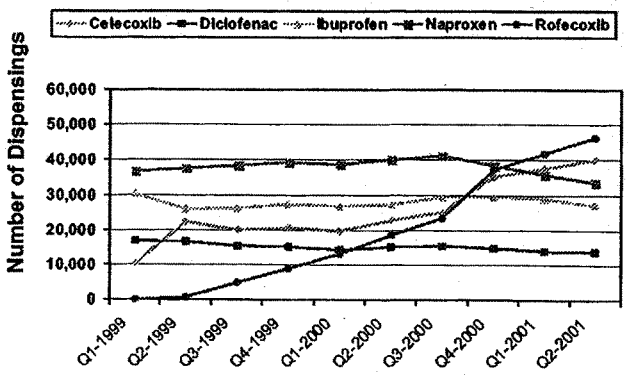


Figure 2: COX-2 and NANSAID Dispensings

UnitedHealthcare, 1999-2001



Appendices

Appendix 1: Primary and Secondary Endpoints

I. The primary endpoint consists of MI and ACS identified through claims and confirmed through review of patient medical charts. Fatal MI and sudden cardiac death will be additionally identified through a search of the National Death Index.

MI and Acute Coronary Syndrome

Non-fatal MIs and ACS will be identified from inpatient medical claims data. Fatal MIs will be additionally identified through the NDI search if MI is the primary cause of death listed on the death certificate.

ICD-9 codes:

410.xx	Myocardial infarction
411.1x	Other acute and subacute forms of ischemic heart disease - intermediate coronary syndrome

Sudden or Cardiac Death

Death as identified through the NDI search with any of the causes below listed as the primary cause of death on the death certificate. A code for sudden death, as listed in the medical claims data, only if NDI search results are consistent with a cardiovascular death.

ICD-10 codes:

I21.x	Acute myocardial infarction, of specific sites or site unspecified
I22.x	Subsequent myocardial infarction
I24.x	Other acute ischemic heart disease
I25.x	Chronic ischemic heart disease
I44.x	Atrioventricular and left bundle-branch block
I45.x	Other conduction disorders
I46.x	Cardiac arrest
I47.x	Paroxysmal tachycardia
I48.x	Atrial fibrillation and flutter
I49.x	Other cardiac arrhythmias
R96.x	Other sudden death, cause unknown (does not include SIDS)
R98	Unattended death

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Appendix 1: Primary and Secondary Endpoints, continued

II. The secondary endpoint consists of MI identified through claims, in conjunction with a three-day hospital stay, or an indication of discharge with a vital status of deceased. Fatal MI and other CHD death will be additionally identified through a search of the National Death Index.

Acute MI

MIs will be identified from inpatient medical claims data.

ICD-9 codes:

410.xx	Myocardial infarction

CHD Death

Death as identified through the NDI search with any of the causes below listed as the primary cause of death on the death certificate.

ICD-10 codes:

I21.x	Acute myocardial infarction, of specific sites or site unspecified
I22.x	Subsequent myocardial infarction
I24.x	Other acute ischemic heart disease
I25.x	Chronic ischemic heart disease

Appendix 2: Comorbid conditions

Prior cardiac history

411.xx	Other acute and subacute forms of ischemic heart disease
413.xx	Angina pectoris
414.xx	Other forms of chronic ischemic heart disease
420.xx	Pericarditis
421.xx	Endocarditis
422.xx	Myocarditis
423.xx	Other diseases of pericardium or endocardium
425.xx	Cardiomyopathy
427.xx	Conduction disorders or arrhythmias
428.xx	Heart Failure
429.xx	Ill-defined complications of heart disease

Stroke

430.xx	Subarachnoid hemorrhage
431.xx	Intracerebral hemorrhage
432.xx	Other and unspecified intracranial hemorrhage
433.xx	Occlusion and stenosis of precerebral arteries
434.xx	Occlusion of cerebral arteries
436.xx	Acute but ill-defined cardiovascular disease (includes "stroke")

Transient ischemic attack (TIA)

435.xx	Transient cerebral ischemia

Peripheral artery disease

440.2	Atherosclerosis of native arteries of the extremities
440.3	Atherosclerosis of bypass graft of extremities
443.8	Other specified peripheral vascular disease
443.9	Peripheral vascular disease, unspecified
38.18	Endarterectomy - lower limb arteries
38.48	Resection of vessel with replacement - lower limb arteries
39.25	Aorto-iliac-femoral bypass
39.29	Other (peripheral) vascular shunt or bypass
39.59	Other repair of vessel - site unspecified
01270	Anesthesia for procedures involving arteries of upper leg, including bypass graft, NOS
01272	Femoral artery ligation
01274	Femoral artery embolectomy

Appendix 2: Comorbid conditions, continued

Peripheral artery disease

01440	Popliteal thromboendarterectomy
01444	Popliteal excision and graft or repair for occlusion or aneurysm
01550	Anesthesia for procedures on arteries of lower leg, including bypass graft NOS
01502	Embolectomy, direct or with catheter
01520	Anesthesia for procedures on veins of lower leg, NOS
01522	Venous thrombectomy, direct or with catheter
34201-34203	Embolectomies of lower leg
35226	Repair blood vessel with or without angioplasty, direct, lower extremity
35256	Repair blood vessel with or without angioplasty, with vein graft, lower extremity
35351	Thromboendarterectomy - iliac
35355	Thromboendarterectomy - iliofemoral
35361	Thromboendarterectomy - combined aortoiliac
35363	Thromboendarterectomy - combined aortoiliofemoral
35371	Thromboendarterectomy - common femoral
35372	Thromboendarterectomy - deep (profunda) femoral
35381	Thromboendarterectomy - femoral
35400	Angioscopy (non-coronary vessels)
35450	Transluminal balloon angioplasty, open, renal or other visceral artery
35454	Angioplasty - iliac
35456	Angioplasty - femoral-popliteal
35458	Angioplasty - brachiocephalic trunk or branches, each vessel
35459	Angioplasty - tibioperoneal trunk and branches
35460	Angioplasty - venous
35470	Transluminal balloon angioplasty, percutaneous; tibioperoneal trunk or branches, each vessel
35471	Angioplasty - renal or visceral artery
35473	Angioplasty – iliac
35474	Angioplasty - femoral-popliteal
35480	Transluminal peripheral atherectomy, open; renal or other visceral artery
35482	Atherectomy - iliac
35483	Atherectomy - femoral-popliteal
35484	Atherectomy - brachiocephalic trunk or branches
35485	Atherectomy - tibioperoneal trunk and branches
35490	Transluminal peripheral atherectomy, percutaneous; renal or other visceral artery
35492	Atherectomy - iliac
35493	Atherectomy - femoral-popliteal
35494	Atherectomy - brachiocephalic trunk or branches

Appendix 2: Comorbid conditions, continued

Peripheral artery disease

35495	Atherectomy - tibioperoneal trunk and branches
35516	Subclavian-axillary bypass
35518	Axilliary-axillary bypass
35521	Axillary-femoral bypass
35533	Axillary-femoral-femoral bypass
35541	Aortoiliac bypass
35546	Aortofemoral or bifemoral bypass
35548	Aortoiliofemoral, unilateral bypass
35549	Aortoiliofemoral, bilateral bypass
35551	Aortofemoral-popliteal bypass
35556	Femoral-popliteal bypass
35558	Femoral-femoral bypass
35563	Ilioiliac bypass
35565	Iliofemoral bypass
35566	Femoral-anterior tibial, posterior tibial, or peroneal artery bypass
35571	Popliteal-tibial or -peroneal bypass
35582	In-situ vein bypass; aortofemoral-popliteal
35583	Femoral-popliteal bypass
35585	Femoral-anterior tibial, posterior tibial, or peroneal artery bypass
35587	Popliteal-tibial or -peroneal bypass
35616	Subclavian-axillary bypass
35621	Axillary-femoral bypass
35641	Aortoiliac bypass
35646	Aortofemoral or bifemoral bypass
35650	Axillary-axillary bypass
35651	Aortofemoral-popliteal bypass
35654	Axillary-femoral-femoral bypass
35656	Femoral-popliteal bypass
35661	Femoral-femoral bypass
35663	Ilioiliac bypass
35665	Iliofemoral bypass
35666	Femoral-anterior tibial, posterior tibial, or peroneal artery bypass
35671	Popliteal-tibial or -peroneal bypass
37205	Transcatheter placement of an intravascular stent (s), (non-coronary vessel), percutaneous; initial vessel
37206	Transcatheter placement of an intravascular stent (s), (non-coronary vessel), percutaneous; each additional vessel
37207	Transcatheter placement of an intravascular stent (s), (non-coronary vessel), open; initial vessel
37208	Transcatheter placement of an intravascular stent (s), (non-coronary vessel), open; each additional vessel

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Appendix 2: Comorbid conditions, continued

Diabetes mellitus

250.xx Diabetes mellitus

and/or prescription drug claims for:

AHFS category 68:20 Antidiabetic agents

Hypertension

401.xx Essential hypertension
402.xx Hypertensive heart disease
403.xx Hypertensive renal disease
404.xx Hypertensive heart and renal disease
405.xx Secondary hypertension

Hyperlipidemia/hypercholesterolemia

272.0 Pure hypercholesterolemia
272.1 Pure hyperglyceridemia
272.2 Mixed hyperlipidemia
272.3 Hyperchylomicronemia
272.4 Other and unspecified hyperlipidemia

Rheumatoid arthritis

714.0 Rheumatoid arthritis

Appendix 3: Medications

Drug Class	How Defined	Medications
ACE Inhibitors	1st databank: A4D	Benazepril Enalapril Fosinopril Captopril Lisinopril Quinapril Ramipril Trandolapril Moexipril
Angiotensin Receptor Antagonists	1st databank: A4F	Losartan Candesartan Irbesartan Valsartan Telmisartan
Antiarrhythmics	1st databank: A2A (add Sotalol by name)	Sotalol Propafenone Quinidine Mexilitine Amiodarone Flecainide Tocainide Dofetilide Disopyramide Procainamide Moricizine
Anticoagulants	AHFS: 20:12.04 (anticoagulants)	Warfarin
Antiplatelet Drugs	1st databank: M9P	Aspirin/Dipyridamole Ticlopidine Cilostazol Clopidogrel Dipyridamole

Appendix 3: Medications, continued

Drug Class	How Defined	Medications
Beta-adrenergic Blockers	1st databank: J7C (Excluding Sotalol) J7A	Acebutolol Atenolol Betaxolol Bisoprolol Carteolol Carvedilol Labetolol Metoprolol Nadolol Penbutolol Pindolol Propranolol Timolol
Calcium Channel Blockers	1st databank: A9A	Nifedipine Verapamil Diltiazem Amlodipine Felodipine Bepridil Isradipine Nicardipine Nisoldipine Nimodipine
Digoxin	1st databank: A1A	Digoxin Digitoxin

Appendix 3: Medications, continued

Drug Class	How Defined	Medications
Diuretics (oral)	AHFS: 40:28 (exclude 1st Databank: R1K) with route="ORAL"	Chlorothiazide Hydrochlorothiazide HCTZ/triamterene HCTZ/bisoprolol Furosemide Bumetanide Indapamide Ethacrynic acid Metolazone Chlorthalidone Bendroflumethiazide Hydroflumethiazide Methyclothiazide Benzthiazide Torsemide Amiloride Spironolactone Triamterene Quinethazone Polythiazide Trichlormethiazide
Estrogen replacement therapy	1st Databank: G1A, (exclude chlorotrainisene, diethylstilbestrol)	Estrogens- conjugated Estradiol Estropipate

Appendix 3: Medications, continued

Drug Class	How Defined	Medications
Heparin	1st databank: M9K	Heparin Enoxaparin Dalteparin Tinzeparin Ardeparin Danaparoid
Nitrates	1st databank: A7B (exclude sodium nitrite& amyl nitrite)	Nitroglycerine Isosorbide Mononitrate Isosorbide Dinitrate
Other anti-hyperlipidemics	AHFS: 24:06 (excluding each statin by name)	Gemfibrozil Bezafibrate Niacin Clofibrate Colestipol Cholestyramine Probucol Fenofibrate
Statins	Identify each by name	Lovastatin Pravastatin Fluvastatin Simvastatin Atorvastatin Cerivastatin
Steroids (oral)	AHFS: 68:04 (adrenals) with route="ORAL"	Prednisone Prednisolone Methylprednisolone Dexamethasone Betamethasone Cortisone Hydrocortisone Triamcinolone

Appendix 4: P-Values from Interactions between Current NANSAID Use and Gender, Age, Prior Cardiac History from Multivariate Poisson Regression Model (LR Statistics)

	Gender	Age group	Prior Cardiac History
Rofecoxib	0.0694	0.1271	0.3247
Celecoxib	0.8342	0.1070	0.7087
Naproxen	0.3236	0.5354	0.7257

Appendix 5: Definitions of Acute Coronary Syndrome Events

I. Background

Discussion:

Constellation of symptoms manifesting as a result of acute myocardial ischemia. Includes unstable angina, non-Q wave MI (or non-ST elevation MI), and ST-elevation MI. Acute coronary syndrome is a pathophysiologically defined rather than clinically- or lab-defined entity.

Thus, ACS is an inclusive term that represents a broad spectrum of conditions. Essentially, we can use our definition of unstable angina to define one end of the spectrum and of myocardial infarction (completed or aborted by interventions) to define the other end.

The diagnostically unclear area lies between the two extremes (leaklet MI; elevation of troponin without elevation of CPK; ischemic EKG changes without CPK/troponin elevation).

For our purposes, however, we only need to define the border between ACS and non-ACS, which in practice is simply the border between unstable angina and no unstable angina. Outcomes fitting our definitions of EITHER MI, or unstable angina, as given below should be confirmed as ACS, with no need to parse outcomes as MI or UA (though reviewer comments can reference the specific diagnosis when it is clear from the record).

Clinical trial definitions of MI:

Definition from clinical trials: new pathologic q waves in 2 related leads, or any 2 of 3 criteria: typical CP >15 mins, doubling or more of CPK levels, evolutionary ST-T wave changes

Enzyme definitions of MI used by major clinical trials: creatine kinase (CK) or CK-MB greater than the upper limit of normal (ULN) in PURSUIT; CK or CK-MB >2× ULN in PRISM, PRISM-PLUS, PARAGON A, and PARAGON B; and CK-MB >3× ULN in GUSTO IV.

Clinical definition of unstable angina:

Braunwald classification of unstable angina: angina while at rest (within 24 hrs of presentation for acute, within 1 month for subacute), new angina, or progressively increasing angina; can be with or without EKG changes; also characterized as post-MI, and with or without other conditions (anemia, fever, hypoxia, tachycardia, or thyrotoxicosis).

Clinical trial definition of unstable angina:

Eligible patients were those who had their most recent episode of chest pain at rest or accelerating chest pain within 24 hours of randomization. Coronary artery disease had to be manifested by one of the following three sets of signs: (1) electrocardiographic evidence of myocardial ischemia in two contiguous leads during an episode of chest pain with new, persistent, or transient ST-segment depression of 0.1 mV or more (0.08 second after the J point); new, persistent, or transient T-wave inversion; or transient ST-segment elevation (lasting less than 20 minutes) of 0.1 mV or more; (2) elevated cardiac-enzyme levels consistent with the occurrence of non–Q-wave myocardial infarction; or (3) a history of myocardial infarction, percutaneous revascularization more than six months earlier,

coronary surgery more than one month earlier, a positive exercise stress test or dipyridamole (or adenosine) nuclear stress test, or narrowing of at least 50 percent of the luminal diameter of a major coronary artery on a previous arteriogram. PRISM, NEJM, 1998

II. Study Definitions

Clinical reviewers were instructed that study events meeting EITHER the definition of myocardial infarction or unstable angina below should be classified as an ACS endpoint for this study.

a) Myocardial Infarction

Criteria to include case:

1. Likely clinical scenario or ECG changes typical for ischemia followed by or during hospitalization and evidence for elevated MB-fraction CPKs or elevated troponin levels; or sudden death.
2. Cardiologist, Emergency Room or other Physician consult note stating that MI occurred prior to or during this hospitalization
3. Likely clinical scenario or ECG changes typical for ischemia followed by immediate coronary revascularization or thrombolysis sufficient to abort MI.

Criteria to exclude case:

No thrombolysis or coronary revascularization procedure, and any of the following:

1. Less than 24 hour hospitalization (excluding transfers, deaths, and patient leaving against medical advice)
2. Normal stress test during or shortly (within 1 month) after hospitalization
3. Cardiologist or appropriate other consult note stating that MI did not occur during this hospitalization or attributes injury and symptoms to a cause other than MI.
4. Trauma case with elevated total CPKs (from muscle injury) but not elevated CPK-MB (from cardiac injury).
5. Myocardial infarctions occurring during cardiac surgery (bypass or valve surgery, coronary catheterization).
6. MI occurs as the terminal event of other, non-cardiovascular, life-threatening morbidity.

Individual lab values for Normal/Elevated levels of enzymes will be used as present in medical record, or statement in record of "elevation" in absence of such values.

b) Unstable angina

Criteria to include case:

1. Admission to hospital from emergency room or clinic with chest pain at rest or accelerating, not primarily attributed to causes other than cardiac (e.g. trauma, GI distress, cholescystitis or pancreatitis, pneumonia, pneumothorax, aortic dissection)

2. Cardiologist, Emergency Room, or other Physician consult note stating that unstable angina occurred prior to or during this hospitalization. Diagnoses of "acute coronary syndrome" or "non-Q-wave MI" will be included unless the event meets our study definition for myocardial infarction.

Strong corroborating evidence includes: initial ischemic changes on EKG that resolve (particularly with nitrate or beta-blocker therapy), positive stress test in patient that did not have an MI, history of stable angina

Supporting evidence includes: use of IIb/IIIa inhibitor (abciximab/reopro, eptifibatide/integrilin or intrifiban, tirofiban/aggrastat, lamifiban), intravenous beta-blocker (esmolol, metoprolol), or heparin

1. *Note*: normal EKG, negative stress test, normal CK-MB or troponin ***do not*** exclude unstable angina

Criteria to exclude case:

1. Diagnosis of non-cardiac origin of chest symptoms at time of discharge
2. Diagnosis of chronic stable angina in patient admitted for other reasons

Individual lab values for Normal/Elevated levels of enzymes will be used as present in medical record, or statement in record of "elevation" in absence of such values.

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Acute Coronary Syndromes
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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx: Putting Patient Safety First?"

November 18, 2004

Exhibit 47

Risk of cardiovascular events and rofecoxib: cumulative meta-analysis

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Published online November 5, 2004
http://image.thelancet.com/extras/04art10237web.pdf

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Summary

Background The cyclo-oxygenase 2 inhibitor rofecoxib was recently withdrawn because of cardiovascular adverse effects. An increased risk of myocardial infarction had been observed in 2000 in the Vioxx Gastrointestinal Outcomes Research study (VIGOR), but was attributed to cardioprotection of naproxen rather than a cardiotoxic effect of rofecoxib. We used standard and cumulative random-effects meta-analyses of randomised controlled trials and observational studies to establish whether robust evidence on the adverse effects of rofecoxib was available before September, 2004.

Methods We searched bibliographic databases and relevant files of the US Food and Drug Administration. We included all randomised controlled trials in patients with chronic musculoskeletal disorders that compared rofecoxib with other non-steroidal anti-inflammatory drugs (NSAIDs) or placebo, and cohort and case-control studies of cardiovascular risk and naproxen. Myocardial infarction was the primary endpoint.

Findings We identified 18 randomised controlled trials and 11 observational studies. By the end of 2000 (52 myocardial infarctions, 20 742 patients) the relative risk from randomised controlled trials was 2·30 (95% CI 1·22–4·33, p=0·010), and 1 year later (64 events, 21 432 patients) it was 2·24 (1·24–4·02, p=0·007). There was little evidence that the relative risk differed depending on the control group (placebo, non-naproxen NSAID, or naproxen; p=0·41) or trial duration (p=0·82). In observational studies, the cardioprotective effect of naproxen was small (combined estimate 0·86 [95% CI 0·75–0·99]) and could not have explained the findings of the VIGOR trial.

Interpretation Our findings indicate that rofecoxib should have been withdrawn several years earlier. The reasons why manufacturer and drug licensing authorities did not continuously monitor and summarise the accumulating evidence need to be clarified.

Introduction

On Sept 30, 2004, a press release from Merck announced the withdrawal of rofecoxib (Vioxx) because of an increased cardiovascular risk in patients taking the drug for more than 18 months.[1] The decision was based on the 3-year results of the unpublished Adenomatous Polyp Prevention on Vioxx (APPROVe) study, a placebo-controlled trial of rofecoxib for the prevention of recurrence of colorectal polyps in patients with a history of colorectal adenomas. By the time it was withdrawn, rofecoxib had been taken by an estimated 80 million people and sales had reached US$2·5 billion in 2003.[1]

Rofecoxib is a non-steroidal anti-inflammatory drug (NSAID) that selectively inhibits cyclo-oxygenase 2 (COX2). The COX enzyme is crucial to the formation of prostaglandins and exists in two isoforms, a constitutive isoform (COX1) and an inducible isoform that is expressed at sites of inflammation (COX2). The idea that anti-inflammatory effects are mediated through inhibition of COX2, whereas adverse gastrointestinal effects are attributable to inhibition of COX1, whose prostaglandins protect the gastric mucosa, led to the development of selective COX2 inhibitors.[2] Approved by the US Food and Drug Administration (FDA) in 1999, COX2 inhibitors soon dominated the prescription-drug market for NSAIDs.

The safety profile of rofecoxib has been questioned since the Vioxx Gastrointestinal Outcomes Research trial (VIGOR),[3] which noted a five-fold higher incidence of myocardial infarction in the rofecoxib group compared with the naproxen group.[3,4] Naproxen inhibits the production of thromboxane and platelet aggregation, and the difference in cardiovascular risk was attributed to a cardioprotective effect of naproxen, rather than a cardiotoxic effect of rofecoxib.[4] This interpretation was reiterated in a 2001 meta-analysis of randomised trials of rofecoxib[5] and three case-control studies of naproxen and myocardial infarction published in 2002.[6–10]

We report the results of a cumulative meta-analysis to establish whether robust evidence on the adverse effects of rofecoxib was available before September, 2004.

Methods

Literature search and inclusion criteria

We aimed to identify all randomised clinical trials that compared rofecoxib with another NSAID or placebo. We searched the Cochrane Controlled Trials Register (issue 3, 2004), and MEDLINE, EMBASE, and CINAHL (from inception to September, 2004). We combined a search for articles relating to rofecoxib with the Cochrane search strategy for randomised trials. We examined citations of key papers in the Science Citation Index, searched conference proceedings, screened

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reference lists of relevant papers, contacted experts, and scrutinised the proceedings of the relevant FDA advisory panels. No large placebo-controlled randomised trials addressing the cardioprotective potential of naproxen are available.[11] We therefore identified observational studies combining drug-specific search terms with terms related to cardiovascular disease.

We included all randomised controlled trials in adult patients with chronic musculoskeletal disorders that compared rofecoxib 12·5–50 mg daily with other NSAIDs or placebo. Data for trial arms using other doses of rofecoxib were excluded. We included cohort and case-control studies that examined the association between naproxen use and cardiovascular risk. Two reviewers (PJ, SR) independently evaluated studies for eligibility.

Data collection and outcome measures

Two reviewers (LN, RS) extracted data for publication status, trial design, patients' characteristics, treatment regimens, outcomes, funding, year of publication, year of first presentation at a major conference, and year of submission of data to the FDA, using a standardised form. Completed data forms were checked by two different reviewers (PJ, SR). We assessed two components of trial quality: concealment of allocation of patients to treatment groups, and external review of serious cardiovascular events.

For rofecoxib trials, fatal or non-fatal acute myocardial infarction was the primary endpoint. The following cardiovascular outcomes were regarded as secondary endpoints: fatal or non-fatal strokes (thrombotic or haemorrhagic); cardiovascular mortality (including deaths of unknown cause); and the composite outcome of serious cardiovascular events previously used in a Merck-sponsored meta-analysis[7]—non-fatal myocardial infarction, non-fatal ischaemic or haemorrhagic stroke, death from a vascular cause, or any death from an unknown cause. In case of discrepancies in the number of cardiovascular events between published reports and FDA files, data from the FDA were used. Finally, we extracted all data for the risk of myocardial infarction and naproxen use from eligible observational studies.

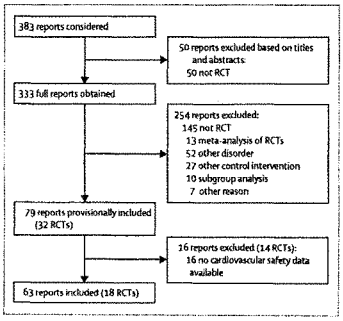

Figure 1: Identification of eligible randomised controlled trials (RCTs)

Statistical analysis

We analysed results from randomised trials using standard and cumulative random-effects meta-analysis. In cumulative meta-analysis, cardiovascular safety data were included the year they first became available—ie, the earliest of: submission of data to the FDA, presentation at a major conference, or publication in a journal. Random-effects meta-regression models were used to examine whether estimates of relative risk were affected by the dose, type of control group (naproxen, other NSAIDs, or placebo), trial duration, adequacy of concealment of allocation, and external review of cardiovascular events. For trials with more than two arms, and for extensions of trials, we used appropriate weighting to avoid duplication of data. Comparisons with no events in either group were excluded; comparisons with events only in one group were analysed by adding 0·5 to all cells.

Risk ratios and odds ratios from observational studies were pooled using random-effects meta-analyses. For the primary analysis we followed the authors' choice of reference group. Comparison of naproxen users with users of other NSAIDs, rather than with non-users, might reduce possible confounding by indication. We therefore also analysed the results from comparisons with non-naproxen NSAIDs. We used meta-regression to establish the effect of study design (case-control or cohort), source of funding (Merck *vs* other), and whether or not analyses had been adjusted for aspirin use.

For all meta-analyses, we calculated the I^2 statistic,[12] which describes the percentage of total variation across studies that is attributable to heterogeneity rather than chance, and did standard tests of heterogeneity. All analyses were undertaken in STATA 8.2 (Stata, College Station, TX, USA).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 summarises the process of identifying eligible clinical trials. 18 randomised controlled trials met inclusion criteria.[4,13–28] We also identified 126 reports of observational studies on naproxen and cardiovascular risk. We excluded 62 articles on the basis of their

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	Protocol number	Submitted to FDA (year)	Treated disorder (number of patients)	Intervention (number of patients)		Duration (weeks)
				Rofecoxib	Control	
Ehrich et al (1999)[14]	019	1998	Osteoarthritis (n=145)	Rofecoxib 25 mg (n=73)	Placebo (n=72)	6
Laine et al (1999)[16]	044	1998	Osteoarthritis (n=742)	Rofecoxib 25 mg (n=195) Rofecoxib 50 mg (n=186)	Placebo (n=177) Ibuprofen 2400 mg (n=184)	24
Schnitzer et al (1999)[15]	068	2001	Rheumatoid arthritis (n=500)	Rofecoxib 25 mg (n=171) Rofecoxib 50 mg (n=163)	Placebo (n=168)	8
Extension of Schnitzer et al (1999)[74]	068-P2	2001	Rheumatoid arthritis (n=544)	Rofecoxib 25 mg (n=235) Rofecoxib 50 mg (n=223)	Naproxen 1000 mg (n=86)	44
Bombardier et al (2000)[9]	088c	2000	Rheumatoid arthritis (n=8076)	Rofecoxib 50 mg (n=4047)	Naproxen 1000 mg (n=4029)	Up to 56
Cannon et al (2000)[24]	035	1998	Osteoarthritis (n=784)	Rofecoxib 12·5 mg (n=259) Rofecoxib 25 mg (n=257)	Diclofenac 150 mg (n=268)	52
Day et al (2000)[17]	040	1998	Osteoarthritis (n=809)	Rofecoxib 12·5 mg (n=244) Rofecoxib 25 mg (n=247)	Placebo (n=74) Ibuprofen 2400 mg (n=249)	6
Hawkey et al (2000)[18]	045	1998	Osteoarthritis (n=775)	Rofecoxib 25 mg (n=195) Rofecoxib 50 mg (n=193)	Placebo (n=194) Ibuprofen 2400 mg (n=193)	24
Saag et al (2000)[19]	033	1998	Osteoarthritis (n=736)	Rofecoxib 12·5 mg (n=219) Rofecoxib 25 mg (n=227)	Placebo (n=69) Ibuprofen 2400 mg (n=221)	6
Saag et al (2000 A)[48]	034	1998	Osteoarthritis (n=693)	Rofecoxib 12·5 mg (n=231) Rofecoxib 25 mg (n=232)	Diclofenac 150 mg (n=230)	52
Ehrich et al (2001)[13]	029	1998	Osteoarthritis (n=523)	Rofecoxib 12·5 mg (n=144) Rofecoxib 25 mg (n=132) Rofecoxib 50 mg (n=97)	Placebo (n=145)	6
Unpublished extension of Ehrich et al (2001)[13]	029-10	1998	Osteoarthritis (n=438)	Rofecoxib 12·5 mg (n=102) Rofecoxib 25 mg (n=146) Rofecoxib 50 mg (n=100)	Diclofenac 150 mg (n=90)	26
Geba et al (2001)[20]	090	2000	Osteoarthritis (n=978)	Rofecoxib 12·5 mg (n=390)	Placebo (n=196) Nabumetone 1000 mg (n=392)	6
Truitt et al (2001)[21]	058	1998	Osteoarthritis (n=341)	Rofecoxib 12·5 mg (n=118) Rofecoxib 25 mg (n=56)	Placebo (n=52) Nabumetone 1500 mg (n=115)	6
Truitt et al (2001 A)[22]	096	2001	Rheumatoid arthritis (n=909)	Rofecoxib 12·5 mg (n=148) Rofecoxib 25 mg (n=311)	Placebo (n=301) Naproxen 1000 mg (n=149)	12
Unpublished extension of Truitt et al (2001 A)[58]	096-P2	2001	Rheumatoid arthritis (n=673)	Rofecoxib 25 mg (n=335) Rofecoxib 50 mg (n=114)	Naproxen 1000 mg (n=224)	49
Geusens et al (2002)[25]	097	2001	Rheumatoid arthritis (n=1958)	Rofecoxib 25 mg (n=315) Rofecoxib 50 mg (n=297)	Placebo (n=299) Naproxen 1000 mg (n=147)	12
Unpublished extension of Geusens et al (2002)[96]	097-P2	2001	Rheumatoid arthritis (n=893)	Rofecoxib 25 mg (n=253) Rofecoxib 50 mg (n=392)	Naproxen 1000 mg (n=248)	40
Hawkey et al (2003)[27]	098/103	-	Rheumatoid arthritis (n=660)	Rofecoxib 50 mg (n=219)	Placebo (n=221) Naproxen 1000 mg (n=220)	12
Katz et al (2003)[28]	-	-	Chronic low back pain (n=690)	Rofecoxib 25 mg (n=233) Rofecoxib 50 mg (n=229)	Placebo (n=228)	4
Lisse et al (2003)[29]	102	2000	Osteoarthritis (n=5586)	Rofecoxib 25 mg (n=2799)	Naproxen 1000 mg (n=2787)	12
Kivitz et al (2004)[97]	085	2000	Osteoarthritis (n=1042)	Rofecoxib 12·5 mg (n=424)	Placebo (n=208) Nabumetone 1000 mg (n=410)	6

Table 1: Characteristics of randomised controlled trials and extensions of trials of therapeutic doses of rofecoxib in chronic musculoskeletal disorders

abstracts and obtained the full-text articles for the remaining 64 reports. 11 observational studies met inclusion criteria.[8–10,29–36]

Characteristics of trials, patients, and interventions

Table 1 shows the characteristics of trials. The 18 trials included a total of 25 273 patients. 12 trials were done in patients with osteoarthritis,[13–25] five in individuals with rheumatoid arthritis,[4,26–27] and one in people with low back pain.[28] Three trials had two arms,[4,13,23] seven had three arms,[14,15,20,22,24,27,28] and eight had four arms.[15–19,21,25,26] Most trials with more than two arms included several rofecoxib arms of different doses. 14 trials included a placebo arm.[13,15–22,24–28] Trial duration ranged from 4 weeks to more than 1 year. The median incidence of myocardial infarction in control groups was 1·45 per 1000 patient-years (IQR 0–5·2)

Five trials[15,21,24–26] were extended after the original protocol had ended, and patients initially allocated to placebo or low doses of rofecoxib were randomly allocated to different groups. For example, patients from placebo and 5 mg rofecoxib groups of protocol 029[13] were allocated to diclofenac, rofecoxib 12·5 mg, or rofecoxib 25 mg in an extension phase. One extension was excluded because no cardiovascular safety data were reported.[21] Therefore, a total of 22 comparisons contributed to analyses. All randomised controlled trials were sponsored by Merck. Four trials described adequate concealment of allocation.[13,17,21,28] Cardiovascular events were externally reviewed in eight trials.[4,20,22,23,25–28]

Cardiovascular risk from randomised controlled trials

The analysis of the primary endpoint—myocardial infarction—was based on 64 events from

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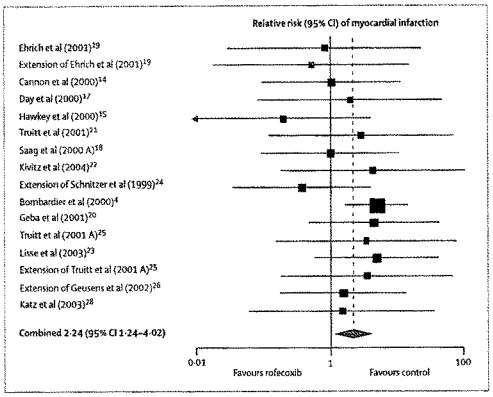

Figure 2: Meta-analysis of randomised trials comparing rofecoxib with control

16 comparisons between rofecoxib and control, with 52 events in rofecoxib groups and 12 in control groups. As figure 2 shows, the combined relative risk was 2·24 (95% CI 1·24–4·02), with little evidence of between trial heterogeneity (I^2=0%, p for heterogeneity=0·82). Table 2 presents results from stratified analyses. Estimates of relative risk varied depending on whether rofecoxib had been compared with placebo, an NSAID other than naproxen, or naproxen, but 95% CIs were wide and a test of interaction was not significant (p=0·41). Similarly, there was little evidence that relative risks differed depending on the dose of rofecoxib or the duration of trials. The estimated relative risk of myocardial infarction was greater in trials with an external endpoint committee compared with trials without such a committee (p=0·011).

	Relative risk (95% CI)	p for interaction
All comparisons	2·24 (1·24–4·02)	
Type of control		
Placebo	1·04 (0·14–3·12)	0·41
Non-naproxen NSAIDs	1·55 (0·55–4·36)	
Naproxen	2·93 (1·36–6·33)	
Daily dose		
12·5 mg	2·71 (0·99–7·44)	0·69
25 mg	1·37 (0·52–3·61)	
50 mg	2·85 (1·24–6·43)	
Trial duration		
≥6 months	2·17 (1·03–4·59)	0·82
<6 months	2·33 (0·80–6·03)	
Concealment of allocation		
Adequate	2·04 (0·32–12·93)	0·96
Unclear	2·26 (1·22–4·19)	
External endpoint committee		
Yes	3·88 (1·88–8·02)	0·011
No or unclear	0·79 (0·29–2·13)	

Table 2: Relative risk of myocardial infarction comparing rofecoxib with control, from stratified meta-analyses

Cumulative meta-analysis (figure 3) showed that an increased risk of myocardial infarction became evident in 2000, when 14 247 patients had been randomised and 44 events had occurred. At the end of 2000 (52 myocardial infarctions, 20 742 patients) the relative risk was 2·30 (95% CI 1·22–4·33, p=0·010). Subsequent trials brought the number of patients to 21 432 and the number of events to 64. Although this resulted in a narrowing of the CI, point estimates remained similar. The most recent data became available in October, 2001; later trials did not report on cardiovascular outcomes.

A total of 44 strokes were recorded in 11 comparisons, with 25 events in rofecoxib groups and 19 in control groups. The combined relative risk was 1·02 (95% CI 0·54–1·93). Nine comparisons contributed to the analysis of cardiovascular death, with 18 deaths in rofecoxib groups and 13 in control groups and a pooled relative risk of 0·79 (0·29–2·19). Finally, 17 comparisons contributed to the analysis of serious cardiovascular events, with 85 events in rofecoxib groups and 38 in control groups (combined relative risk 1·55 [95% CI 1·05–2·29]). Again, there was little evidence of between-trial heterogeneity for these outcomes (I^2 0%, 27%, and 0%, respectively).

Cardioprotective effect of naproxen

For the analysis of naproxen there were eight case-control studies and three retrospective cohort studies (table 3). All studies except one[30] used data from large administrative or clinical databases. Four studies were based on the UK General Practice Research Database. Figure 4 shows the meta-analysis of results from primary analyses. The combined estimate was 0·86 (95% CI 0·75–0·99). Almost identical results were obtained when analyses were based on comparisons with non-naproxen NSAIDs (0·86 [0·75–0·99]). In both analyses, there was considerable between-study hetereogeneity (I^2 68% and 43%, respectively). Meta-regression analysis indicated that the funding source largely explained between-study heterogeneity, with studies funded by Merck indicating larger cardioprotective effects of naproxen (p=0·001 and p=0·056, respectively, by test of interaction). There was little evidence for an association with study design or adjustment for aspirin use (p>0·30).

Discussion

The voluntary withdrawal of rofecoxib by its manufacturer, Merck, on the basis of a fairly small trial that was designed for a different purpose raises several questions.[17] In particular, we must establish whether the drug should have been withdrawn earlier. Our cumulative meta-analysis of randomised controlled trials indicates

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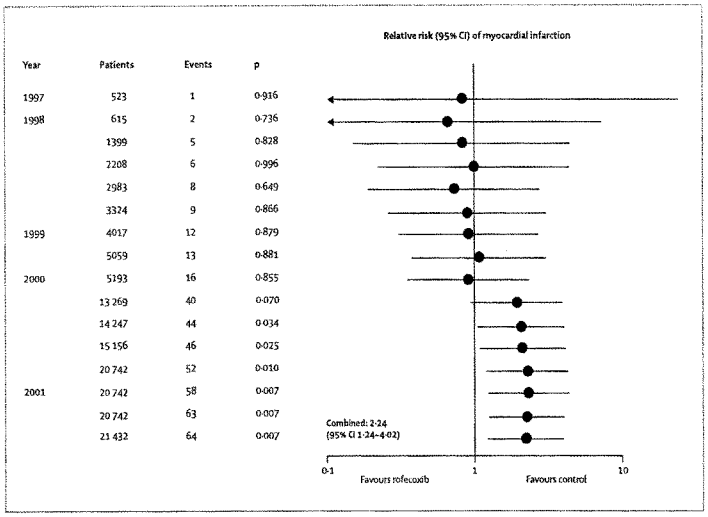

Figure 3: Cumulative meta-analysis of randomised trials comparing rofecoxib with control
See figure 2 for sequence of trials.

that an increased risk of myocardial infarction was evident from 2000 onwards. At the end of 2000, the effect was both substantial and unlikely to be a chance finding.

We found an increased risk of myocardial infarction in trials of both short and long duration, which is in contrast to the unpublished results from the APPROVe trial.[1] Our findings thus indicate that patients are at risk even if rofecoxib is taken for a few months only. Therefore, the reassuring statement by Merck, that there is no excess risk in the first 18 months,[1] is not supported by our data. Similarly, we recorded no evidence to support the notion that rofecoxib's cardiovascular toxicity is dose-dependent.[6,39] The reported increase in risk was greater in trials with an external endpoints committee (relative risk 3·9), suggesting that misclassification of coronary events could have biased results in trials that did not include external appraisal of safety outcomes. The inclusion of an independent endpoints committee should be the rule, and exceptions to this rule should be justified.

The difference in coronary risk in the VIGOR trial has been widely interpreted as being due to a cardioprotective effect of naproxen, rather than an adverse effect of rofecoxib.[4,39,40] We examined this hypothesis by stratifying results from randomised trials according to the control intervention and found that the increase in risk was indeed greater in trials comparing rofecoxib with naproxen, but that this finding was probably attributable to chance (p=0·41). The possible cardioprotective effect of naproxen has also been examined in several observational, pharmacoepidemiological studies. Taken together, the data from these studies indicate that if a protective effect of naproxen exists, it is probably small, and, as pointed out earlier,[6,20] not large enough to explain the findings of VIGOR.[4]

By contrast to our findings, two earlier meta-analyses from Merck Research Laboratories showed no evidence of a rise in cardiovascular risk[41] or an increase in risk that was restricted to trials comparing rofecoxib with naproxen.[7] Possible explanations for these discrepant results include: confounding by trial, in analyses inadequately pooling individual patients' data; use of composite cardiovascular endpoints, which will have diluted any increase in risk of myocardial infarction; and inclusion of safety data that had not undergone independent adjudication. Pooled analyses of industry-sponsored drug trials, undertaken by the company manufacturing the drug in question, are becoming increasingly common. To clarify the reasons behind the

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	Source population (study period)	Design	Case/outcome definition	Definition of exposure to naproxen	Reference group in primary analysis	Control for confounding	Funding source
Jick et al (2000)[11]	NSAID users attending general practices* (1996–98)	Matched case-control study	First acute MI	Use in previous 3 months based on prescription data	Diclofenac users	Exclusion of patients with history of CVD	Boehringer Ingelheim
Rahme et al (2002)[9]	Elderly people covered by Quebec Health Care Fund (1988–94)	Matched case-control study	Acute MI	Current and chronic use based on prescription data	Users of other NSAIDS	Exclusion of patients with recent MI; adjustment for drugs to treat cardiovascular disease, previous cardiovascular diseases, comorbidity	Merck
Ray et al (2002)[10]	Middle-aged and elderly people enrolled in Tennessee Medicaid programme (1987–98)	Retrospective cohort study	Acute MI or death from CHD	Current use based on prescription data	People not using NSAIDS	Adjustment for risk score based on prescriptions, hospital admissions, emergency room visits	AHRQ and FDA
Ray et al (2002 A)[10]	Middle-aged and elderly people enrolled in Tennessee Medicaid programme (1999–2001)	Retrospective cohort study	Acute MI or death from CHD	Current use based on prescription data	People not using NSAIDS	Adjustment for risk score based on prescriptions, hospital admissions, emergency room visits	AHRQ, US Public Health Service and FDA
Schlienger et al (2002)[12]	Patients attending general practices* (1992–97)	Matched case-control study	First acute MI	Current use based on prescription data	People not using NSAIDS	Exclusion of patients with history of CVD; adjustment for smoking status, BMI, hormone replacement therapy, aspirin use	No specific funding
Solomon et al (2002)[8]	New Jersey Medicaire, Medicaid or Pharmaceutical Assistance for the Aged and Disabled Program enrolees (1991–95)	Matched case-control study	Acute MI	Use in previous 6 months based on prescription data	People not using NSAIDS	Exclusion of patients with history of CVD; adjustment for Medicaid enrolment, nursing home residency, diabetes, hypertension, congestive heart failure, comorbidity index, drug prescriptions, hospitalisations	Arthritis Foundation and NIA
Watson et al (2002)[13]	Patients with rheumatoid arthritis attending general practices* (1988–99)	Matched case-control study	Acute MI	Current use based on prescription data	People not using naproxen	Adjustment for smoking, prescriptions, diabetes, other comorbidity, and cardiovascular risk score	Merck
Mamdani et al (2003)[14]	Elderly Ontario residents (1998–2001)	Retrospective cohort study	Acute MI	Current use based on prescription data	People not using NSAIDS	Adjustment for hospitalisations, procedures, and prescriptions	CIHR
García Rodríguez (2004)[15]	Patients attending general practices* (1987–2000)	Matched case-control study	Acute MI or death from CHD	Current use based on prescription data	People not using NSAIDS	Adjusted for smoking, diabetes, hypertension, hyperlipidaemia, BMI, CHD, cerebrovascular disease, alcohol intake, aspirin and other drugs	Pharmacia
Graham et al (2004)[16]	NSAID users enrolled in Kaiser Permanente managed care organisation (1999–2001)	Unmatched case-control study	Acute MI or sudden cardiac death	Current use based on prescription data	Past users of NSAIDs	Adjusted for risk score based on prescriptions, hospital admissions, emergency room visits	FDA
Kimmel et al (2004)[17]	Cases from 36 hospitals and community controls resident in five counties surrounding Philadelphia (1998–2001)	Unmatched case-control study	First non-fatal MI	Use within 1 week based on telephone interview	People not using NSAIDS	Adjustment for smoking, CHD, BMI, health services utilisation, diabetes, hypertension, hypercholesterolaemia, education	NIH, Pharmacia, Merck

MI=myocardial infarction, CHD=coronary heart disease, CVD=cardiovascular disease, BMI=body mass index, AHRQ=Agency for Healthcare Research and Quality, FDA=Food and Drug Administration, NIA=National Institutes of Ageing, CIHR=Canadian Institutes of Health Research, *UK General Practice Research Database (UK GPRD).

Table 3: Characteristics of observational studies of naproxen use and myocardial infarction

misleading results of Merck's meta-analyses of cardiovascular events in clinical trials of rofecoxib will be important. Also, the notion that meta-analyses of individual patients' data are always superior to meta-analyses of published work might have to be revised.[42]

We recorded little evidence of an increased risk of stroke, although the number of events was small and 95% CIs wide. The rofecoxib trials were done in patients at low cardiovascular risk and the discrepant results for myocardial infarction and stroke mirror what is noted

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with antiplatelet treatment: risk of myocardial infarction, but not stroke, is reduced in individuals at low risk of cardiovascular disease.[43] This situation is consistent with opposite patterns of inhibition of the COX1 selective aspirin and the COX2 selective rofecoxib, with the two drugs inversely affecting the balance between COX1 and COX2 activity.[44]

Because of restrictive inclusion criteria, most trials included only few individuals with a history of cardiovascular disease. This contrasts with the situation encountered in routine clinical settings. For example, in middle-aged and elderly people from the Tennessee Medicaid programme, Ray and colleagues[30] reported that more than 40% of rofecoxib users had a history of cardiovascular disease and that, compared with trial populations, the risk of fatal or non-fatal myocardial infarction was eight times higher (11·6 *vs* 1·45 per 1000 patient-years). This risk translates into numbers needed to treat for 1 year to cause one myocardial infarction of 556 patients in trial populations, but only 70 patients in routine populations in Tennessee.

Some limitations need to be noted. Our analysis was restricted to trials in patients with chronic musculoskeletal disorders. Safety data were available from FDA files for most of these trials, but this was not the case for more recent trials in Alzheimer's disease and colon adenoma. Only one trial in people with Alzheimer's disease presented results for myocardial infarction (three events in 122 individuals assigned to rofecoxib and one event in 229 individuals assigned to naproxen or placebo).[45] The APPROVe trial in patients with a history of colorectal adenomas[1] was recently presented at the Annual Scientific Meeting of the American College of Rheumatology, but different cardiovascular outcomes were not reported separately. Furthermore, we were unable to adjust for possible duplication of data between the four case-control studies based on the UK General Practice Research Database. Adjustment would have shifted the pooled estimate towards the null and would have inflated CIs. Therefore, our meta-analysis might overestimate naproxen's cardioprotective potential.

What lessons should be learned for the future? First, we can never be sure that we know all there is to know about mechanisms. The VIGOR study group presented the myocardial infarction data exclusively as "a reduction in the risk of myocardial infarction in the naproxen group",[4] on the basis of the documented inhibition of platelet aggregation by naproxen, but not rofecoxib.[46] That rofecoxib could increase the risk was not discussed, despite the fact that, since the mid 1990s, the drug has been known to reduce production of prostacyclin, a vasodilator and inhibitor of platelet aggregation.[47] In the context of hormone replacement therapy and cardiovascular outcomes, Petitti recently pointed out that we should resist being seduced by mechanisms, that we should suspend our beliefs, and allow healthy scepticism when interpreting data.[48] Clearly, the same holds true when reporting and interpreting unexpected results of randomised trials, and ultimately when writing prescriptions for patients.

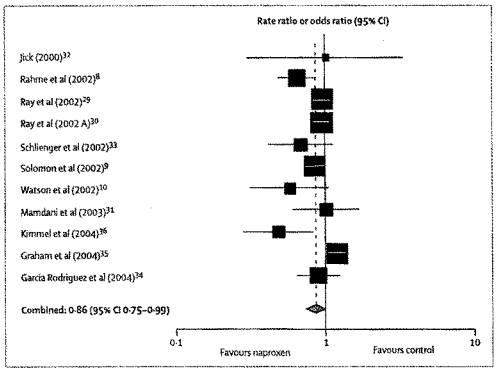

Figure 4: Meta-analysis of observational studies of naproxen and risk of myocardial infarction

Second, the FDA and other drug licensing authorities should review their procedures, and identify and remove the obstacles to making continuously updated summary information available to decision makers.[11] The present analysis would not have been possible without access to the proceedings of the FDA, which underscores the importance of free access to these files. In some instances, important discrepancies were noted between published data and figures in FDA files. For example, the VIGOR Study Group reported a four-fold increased risk of myocardial infarction,[4] whereas the figures available from FDA files indicated a five-fold increase in risk.[49] Making important safety data accessible to interested researchers and the public at large does, of course, not absolve authorities from their duty to carefully and continuously monitor the evidence on the adverse effects of drugs. Clearly, this has not happened in the case of rofecoxib: the most recent labelling information in the USA, for example, mentioned only three trials. Had the accruing data been analysed cumulatively as soon as they became available, appropriate and timely decisions could have been taken.

If Merck's statement in their recent press release that "given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take"[1] was appropriate in September, 2004, then the same statement could and should have been made several years earlier, when the data summarised here first became available. Instead, Merck continued to market the safety of rofecoxib.

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Contributors

P Jüni had the idea for the study, was responsible for protocol development, study supervision, and statistical analysis, and contributed to data extraction and management, quality assessment, and interpretation of data. M Egger contributed to protocol design, study supervision, data extraction, quality assessment, statistical analysis, and interpretation of data. L Nartey, S Reichenbach, and R Sterchi contributed to protocol design, data extraction and management, and data interpretation. P Dieppe contributed to protocol development, study supervision, and data interpretation. M Egger and P Jüni wrote the first draft of the paper, and all authors contributed to the final draft.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

This study was funded by the Swiss National Science Foundation's National Research Programme 53 (grant numbers 3200-066378.01 and 405340-104762). We thank Bettina Lässer for bibliographic work, Beat Jordi for database development, and Nicola Low for helpful comments on earlier drafts of this paper.

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Vioxx, the implosion of Merck, and aftershocks at the FDA

Published online November 5, 2004 http://image.thelancet.com/extras/04cmt396web.pdf

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Today we publish results from a cumulative meta-analysis which show that the unacceptable cardiovascular risks of Vioxx (rofecoxib) were evident as early as 2000—a full 4 years before the drug was finally withdrawn from the market by its manufacturer, Merck. This discovery points to astonishing failures in Merck's internal systems of post-marketing surveillance, as well as to lethal weaknesses in the US Food and Drug Administration's regulatory oversight. In a recent Editorial, we commended Merck for acting promptly in the face of new findings about the safety of Vioxx.[1] Our praise was premature. The evidence showing that Vioxx caused significant adverse events was apparent well before data from the APPROVe trial triggered Merck's overdue intervention. This week's report by Peter Jüni and colleagues will add significant weight to ongoing litigation against Merck by patients who believe they were harmed by this drug.

These findings also come in the wake of new disclosures that suggest Merck was indeed fully aware of Vioxx's potential risks by 2000. Investigations by the *Wall Street Journal*[2] have revealed e-mails that confirm Merck executives' knowledge of their drug's adverse cardiovascular profile—the risk was "clearly there", according to one senior researcher. Merck's marketing literature included a document intended for its sales representatives which discussed how to respond to questions about Vioxx—it was labelled "Dodge Ball Vioxx". Given this disturbing contradiction—Merck's own understanding of Vioxx's true risk profile and its attempt to gloss over these risks in their public statements at the time—it is hard to see how Merck's chief executive officer, Raymond Gilmartin, can retain the confidence of the public, his company's most important constituency.

The FDA's position is no less comfortable. The public expects national drug regulators to complete research, such as that published by Jüni and colleagues, in their ongoing efforts to protect patients from undue harm. But, too often, the FDA saw and continues to see the pharmaceutical industry as its customer—a vital source of funding for its activities—and not as a sector of society in need of strong regulation.

Worse still, the FDA's Office of Drug Safety co-exists in the same centre—the Centre for Drug Evaluation and Research (CDER)—as the Office of New Drugs, the part of the agency that works most closely with industry to license new medicines. Once a licensing approval has been made it is naturally in CDER's own interests to stand by its original decision. CDER's reputation would be damaged if its licensing judgments were constantly challenged by its own staff. This understandable but dangerous tendency to discourage dissent makes the Office of Drug Safety, which sits lower in the hierarchy of CDER than the Office of New Drugs, weak and ineffective. The inherent precedence that licensing of new drugs takes over safety evaluation is a serious flaw in FDA's complex regulatory structure.

In the case of Vioxx, FDA was urged to mandate further clinical safety testing after a 2001 analysis suggested a "clear-cut excess number of myocardial infarctions".[3] It did not do so. This refusal to engage with an issue of grave clinical concern illustrates the agency's in-built paralysis, a predicament that has to be addressed through fundamental organisational reform.

On Nov 2, 2004, the FDA tried to shore up its tarnished reputation by posting on its website an early version of a recently completed observational study into the safety of Vioxx. The report comes with a warning that it has "not been fully evaluated by the FDA and may not reflect the official views of the agency". The FDA investigators estimate that over 27 000 excess cases of acute myocardial infarction and sudden cardiac death occurred in the USA between 1999 and 2003. "These cases", they write, "would have been avoided had celecoxib been used instead of rofecoxib". This study is presently under review at *The Lancet*. It is unclear why the FDA could not have waited for the fully evaluated report to have been scrutinised, revised, and published according to the norms of scientific peer review. Bypassing independent peer review smacks of panic in the FDA, which is under intense reputational pressure. And yet its decision to try to undermine the integrity of this work again shows that the agency's senior management is more concerned with external appearance than rigorous science.

The licensing of Vioxx and its continued use in the face of unambiguous evidence of harm have been public-health catastrophes. This controversy will not end with the drug's withdrawal. Merck's likely litigation bill is put at between US$10 and $15 billion. The company has seen its revenues and market capitalisation slashed. It has been financially disabled and its reputation lies in ruins. It is not at all clear that Merck will survive this growing scandal.

But the most important legacy of this episode is the continued erosion of trust that public-health institutions will suffer. Failure to act decisively on signals of risk might minimise short-term political criticism for regulators, or shareholder unrest for company chief executives. But the long-term consequence of prevarication is a tide of public scepticism about just whose interests drug makers and regulators truly represent.

It is no good saying, as some academic physicians have said to me, that one must expect pharmaceutical companies to do all they can to protect their products, even in the face of clear evidence of risk. And it is of little help to suggest that regulators have a nearly impossible job of balancing harms and benefits. Defenders of our systems of drug regulation argue that the blame for the Vioxx debacle in-

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Comment

stead rests on allegedly credulous specialists who should have asked tougher questions about the drug they were prescribing. Why clinical investigators studying Vioxx did not do more to raise concerns is a fair question that needs to be answered. But in doing so, we must not diminish the importance of the covenant of trust that society has established with powerful commercial and governmental institutions. For with Vioxx, Merck and the FDA acted out of ruthless, short-sighted, and irresponsible self-interest.

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Response to Article by Juni *et al.* Published in *The Lancet* on Nov. 5

In an article that appeared in Lancet on Nov. 5, 2004, Juni *et al.* present a meta-analysis of rofecoxib data and conclude that an increased risk for cardiovascular events on rofecoxib was apparent in the year 2000. These conclusions are based on an analysis that violates the basic principle of meta-analyses to combine "like with like". In this analysis, the authors combined data from studies with 3 different kinds of comparators. The conclusion by Juni *et al.* of a difference in myocardial infarction (MI) risk for rofecoxib regardless of comparator is driven by the difference between rofecoxib and a single comparator, naproxen, especially by the results of VIGOR (Bombardier C, *et al. N Engl J Med* 2000; **343:** 1520–28). The data in this article had already been included in the first rofecoxib pooled analysis published in 2001 by Konstam *et al.* (*Circulation* 2001;104:2280) and again in 2003 (*Am Heart J* 2003;146:591). These pooled analyses demonstrated a difference in cardiovascular risk between rofecoxib and naproxen but not between rofecoxib and non-naproxen NSAIDs or placebo.

Juni *et al.* combined data from a subset of VIOXX studies analyzed by Konstam *et al.* Juni *et al.* conclude that, until mid 2000, there was no evidence of a difference in the relative risk of an MI on VIOXX compared to other drugs but that, starting in 2000, there was a difference. Careful review of their analysis reveals that studies published before 2000 compared rofecoxib to either placebo or to the non-naproxen NSAIDs ibuprofen, diclofenac, or nabumetone (Table 1). The study in 2000 that accounted for the difference noted by the authors was VIGOR, preliminary results of which first became available and were immediately disclosed in March 2000, were then published in November, and received wide attention. The final data were provided to the FDA in the fall of 2000 and published on the FDA's website in February, 2001. After VIGOR, the majority of the patient data in studies cited by the authors continued to involve comparisons of VIOXX with naproxen (Table 1).

The authors' analysis by comparator confirms that the only statistically significant difference in MI risk was between rofecoxib and naproxen, not between rofecoxib and either placebo or non-naproxen NSAIDs. The authors justify combining the data across the comparators because confidence intervals against individual comparators were wide and the statistical test for interaction was not significant. This use of an underpowered statistical test as the sole justification for combining the data is scientifically inappropriate and fails the requirement to combine "like with like"; there are known different biologic effects of the comparators on platelet function and the data demonstrate large differences in relative risk between the comparator groups (Table 2). In a complete analysis of the individual patient data using Cox proportional hazards regression, a more statistically powerful technique, Konstam *et al.* found substantial heterogeneity between naproxen-controlled studies and other studies, validating the appropriateness of segregating naproxen-controlled data (Table 2). The inappropriate combining of heterogeneous data by Juni *et al.* invalidates the results and conclusions of their meta-analysis.

In addition, Juni *et al.* did not use all available data, notably the large placebo-controlled Alzheimer's Disease studies comparing rofecoxib to placebo. Cardiovascular data from

these studies were included in the US labeling for rofecoxib. The MI data are available on the FDA website at http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_01_merck.pdf. There were 9 MIs on rofecoxib and 12 on placebo out of more than 2000 patients treated for approximately 1 year. There is no scientific reason to exclude these data as there is no basis for a difference in MI risk between Alzheimer's Disease patients and other patients included, such as osteoarthritis or chronic low back pain patients. This selective omission of a large placebo-controlled dataset available in 2001 after VIGOR and which showed no difference between rofecoxib and placebo limits the authors' conclusions.

The authors consider possible differences between their analysis and previously cited rofecoxib pooled analyses. They claim that use of a combined endpoint could obscure findings restricted to one of its components. Examination of the data in Konstam *et al.* show that this is not the case; there is consistency between the APTC combined endpoint and MI (see table 6 in Konstam *et al.*). Indeed, the principle difference between Juni *et al.* and the other rofecoxib combined analyses is not in the endpoint but in the inappropriate pooling of comparators by Juni *et al.* as noted above. The authors also claim that the relative risk between rofecoxib and comparators was the same in studies ≥6 months and <6 months. However, as with the meta-analysis of all trials, this result is confounded by comparator.

In summary, the data contained in the meta-analysis by Juni *et al.* had been previously disclosed and analyzed. As in the pooled analyses of randomized rofecoxib controlled clinical trials published in 2001 and again in 2003, the Juni *et al.* meta-analysis shows no significant difference with rofecoxib versus placebo, no significant difference with rofecoxib versus non-naproxen NSAIDs and a significantly lower risk with naproxen versus rofecoxib. However, Juni *et al.* went on to combine all the data in a scientifically inappropriate manner, counter to basic principles of meta-analysis. All their conclusions for a signal beginning in 2000 were driven by the comparison to naproxen, largely by VIGOR. Prior to APPROVe, in placebo- and non-naproxen NSAID-controlled studies, the data did not support an increased risk of cardiovascular events with rofecoxib. In the APPROVe trial, for the first time, there was an increased risk of confirmed cardiovascular events beginning after 18 months of treatment in patients taking rofecoxib compared to those taking placebo. Within one week of learning those results, Merck acted in what it believed was the best interest of patients and voluntarily withdrew VIOXX from the market.

Table 1
Sequence of Studies and Comparator Usage in Juni *et al.* Figure 3

Protocol Number	Comparators	Year
029	Placebo	1997
029 extension	Diclofenac	1998
035	Diclofenac	1998
040	Placebo, Ibuprofen	1998
045	Placebo, Ibuprofen	1998
058	Placebo, Nabumetone	1998
034	Diclofenac	1999
085	Placebo, Nabumetone	1999
068 ext	**Naproxen**	2000
088, 089 (VIGOR)	**Naproxen**	2000
090	Placebo, Nabumetone	2000
096	**Placebo, Naproxen**	2000
102 (ADVANTAGE)	**Naproxen**	2000
096 ext	**Naproxen**	2001
097 ext	**Naproxen**	2001
120, 121	Placebo	2001

Table 2
Relative Risk of Cardiovascular Events in Published Pooled and Meta-Analyses

	Konstam *et al.*, 2001	Reicin *et al.*, 2002	Weir *et al.*, 2003	Juli *et al.*, 2004
Endpoint	APTC	Investigator reported CV thrombotic event	APTC	MI
Placebo	0.84 (0.51, 1.38)	0.94 (0.31, 2.92)	0.93 (0.57, 1.53)	1.04 (0.34, 3.12)
Non-naproxen NSAIDs	0.79 (0.40, 1.55)	1.04 (0.49, 2.21)	0.84 (0.45, 1.63)	1.55 (0.55, 4.36)
Naproxen	1.69 (1.07, 2.69)		1.69 (1.07, 2.69)	2.93 (1.36, 6.33)
	MI=myocardial infarction			
	APTC=Non-fatal cardiac, non-fatal and total CV, hemorrhagic, and unknown deaths			
	Investigator-reported cardiovascular events=Coronary artery disease, MI, unstable angina, cerebrovascular accident, transient ischemic attack, deep venous thrombosis			

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 48

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APPROVe ESMB MEETING MINUTES

Mtg Date: 23-Jan- 2002

Attendees: John Baron, David Bjorkman, James Bolognese, Candice Conway, Marvin Konstam, Susan Loftus, Richard Logan, James Neaton, Bettina Oxenius, Hui Quan, Robert Riddell, Robert Sandler, Thomas Simon

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Open Session

The session started with the introduction of each attendee.

Then, Jim Bolognese briefly presented the draft Data Analysis Plan. During the presentation, a question was raised whether the alpha level of 0.0025 for the primary hypothesis and the first secondary hypothesis was too stringent. The concern was that it is difficult for a study to be positive with such a small alpha level. Suggestions were made to use alpha level of 0.05 or 0.01 in the DAP. If the ultimate p-value reaches 0.05, the study is at least a scientifically positive study. Although this may not satisfy the FDA's previously stated requirement for an indication, the FDA's position may change. An opinion from the regulatory group of Merck will be obtained before making any changes on this respect.

Jim Bolognese also presented issues related to the DAP to get ESMB's opinion. The first issue was whether there is any scientific concern that the primary hypothesis will be tested based on the increased risk patient population instead of the entire randomized population. The consensus was that there is no concern at this point. Most patients (approximately 85%) have at least one factor considered to increase risk; therefore patient characteristics should be comparable across the two treatment groups and there should be no bias for between treatment comparisons for this population.

The second issue was whether additional sensitivity analyses should be performed. The attendees felt the sensitivity analyses specified in the DAP are sufficient.

The third issue was the proposal of the unblinding of CV data within a small group of Merck personnel. This issue was discussed in more detail when Tom Simon presented additional issues related to the study (see below).

The fourth issue was whether we should impose a stopping rule that the study will be stopped if rofecoxib is worse than placebo in adenomas at the level of 0.01 at the Year 1 analysis. The ESMB felt the term of 'guideline' is better than 'stopping rule' since the ESMB's recommendation of stopping the study will be based on the overall results and consistency of the results rather than a single p-value.

After Jim Bolognese's presentation, Tom Simon presented addition potential issues related to the study.

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The first issue was that MRL is planning to conduct CV meta-analysis for the entire Vioxx program. The draft DAP for this study states that 'A very small group of SPONSOR employees (except the unblinded statistician) may be unblinded to some specific safety data like CV data' in order to include data from this study in the meta-analysis. Even though the meta-analysis results will be shared with the ESMB, the ESMB raised serious concerns about the ability to maintain the integrity of the trial if this will occur; especially, when there is a chance of publishing the meta-analysis results. This occurred for a previous CV analysis. The ESMB felt if there was concern on the CV safety based on the interim analyses from this study, they prefer to share the concern with the DSMBs of other studies in a private manner, rather than involve the sponsor. Tom Simon/Jim Bolognese will report this issue to the Merck senior management and report back to the ESMB about the solution.

The second issue Tom Simon presented was the potential unblinding of some executive committee members who are also an investigator or pathologist of the study. This could theoretically occur if the ESMB were to disclose patient-level unblinded information in conjunction with discussion of a recommendation to change or modify the study. The ESMB and the chair of the executive committee will keep this in mind when they come to this point and they will withhold patient-level information when they share the interim results with the other executive members.

The third issue Tom Simon presented was the fourth issue Jim Bolognese presented and mentioned above, regarding the Year 1 stopping rule.

Summary of the Closed Session That Can Be Shared with Study Leadership

1. The ESMB recommends that the study continue as planned.

2. The ESMB noted that according to the Data Analysis Plan that thrombotic and PUB events are adjudicated. The ESMB would like a copy of the adjudication protocol and a description of the procedures in place to review and adjudicate these events. For example, what events go to adjudication? What are the criteria for confirmation? How timely is the adjudication?

3. The ESMB would like more information on the nature of the patient population and the general conduct of the trial. For example, a table summarizing final enrollment by site and strata and baseline characteristics would be helpful. Quarterly, we would like a brief report from the study leadership that provides an update on patient follow-up (e.g., completion of required visits, and number of colonoscopic examinations performed and missing) and treatment discontinuations. The ESMB charter mentions data quality will be monitored by reviewing WCQAR reports. We have not seen these reports.

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APPROVe ESMB CLOSED SESSION MEETING MINUTES
Not for Sharing Outside of the ESMB

Mtg Date: 23-Jan- 2002

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan

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The committee reviewed adverse event data, including deaths, and reasons for treatment discontinuation. Dr. Quan noted that he had only been unblinded the week before the meeting and that safety data had to be pulled from several sources. The data were not "clean". There were some trends noted in serious adverse clinical events and in thromboembolic events, but it was not clear whether thromboembolic events had been adjudicated and what the process was for adjudicating events. The committee requested additional information on the adjudication process and also suggested several additional analyses (see below) for future reports. Due to the concerning nature of the trends, even though the numbers are small, we will be exercising diligence to review the data once they are cleaner and urge expeditious updating of the event database for the next look.

The ESMB will meet again by teleconference on February 13 at noon EST to obtain a better understanding of the adjudication process and to review the additional analyses that were requested. As it might not be possible to prepare all analyses by February 13, another teleconference may be held in early March.

1. Separate analyses of adjudicated/confirmed thrombotic and PUB events. For example, table 1 should have a line for all reported thromboembolic events, a separate line for adjudicated thromboembolic events, and a 3rd line for adjudicated/unadjudicated events (this line would use the findings of the adjudication committee if present, otherwise, use what the site reported.) A summary table from which we can tell how many reported events have not met committee criteria should also be provided. (If it is possible to occur, also tally events not considered to be thrombotic by the site which the committee considers to be thrombotic.)

2. Give hazard ratios (p-value and 95% CI) for each line in Table 1 (including new ones requested) as well as risk differences.

3. Tabulate the number of CVD deaths (should include sudden deaths) or thrombotic events (combined endpoint).

4. Tablulate the type of thrombotic events, e.g., MI, angina, other. We may want to modify this when we see the adjudication protocol.

5. Classify the edema-related and hypertension-related events by severity.

6. Clarify what a "hypertension-related" AE is. Also summarize BP differences between treatment groups during follow-up.

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7. Prepare K-M curves for all serious AEs, edema AEs, hypertension-related AEs, thrombotic AEs, and death.

8. Summarize all discontinuations by treatment group and prepare a K-M curve for time to discontinuation. Also prepared K-M curve for discontinuation due to a clinical AE.

9. Summarize serious clinical AEs by body system.

10. Summarize serious clinical AEs and thrombotic separately for the two stratum according to use of low dose aspirin at entry.

11. Prepare a brief narrative for each death concerning the circumstances surrounding death.

The ESMB will meet by teleconference on 13 February at noon EST. On that call we will review the adjudication protocol for thrombotic events, an update of AE data, and any of the new analyses for AEs that are requested above that are available. A 2nd teleconference will be held in early March to review all of the new analyses that have been requested.

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APPROVe ESMB CLOSED SESSION MEETING MINUTES
Not for Sharing Outside of the ESMB

Mtg Date: 13-Feb- 2002

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan

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An ESMB teleconference was held to review the minutes of the previous ESMB meeting, the SOP for adjudication of thromboembolic serious AEs, results of updated safety data including the additional safety analyses requested at the last meeting, and to set the time/date for the next ESMB teleconference.

The minutes were accepted as written. The terms for defining the thromboembolic serious AEs specified in the SOP were discussed and clarified. The major concern raised during the meeting was the delay of the adjudication process which has left out significant number of potential cases. Approximately half the events have not been adjudicated. Dr. Neaton will write a letter to express this ESMB's concern and urge MRL to expedite the adjudication process. In addition, the ESMB would like to review the packages (i.e., case descriptions) which have been adjudicated, both those confirmed as thromboembolic events and those not confirmed.

A suggestion was made for additional analyses to classify the adjudicated events as indicated in the adjudication SOP: 1) coronary; 2) peripheral vascular; and 3) cerebrovascular. The number of patients who develop an event in each category should be tabulated as well as the number in any of the three categories. Also, congestive heart failure, pulmonary edema, or cardiac failure events should be tabulated both separately and as a combined endpoint with the cardiovascular adjudicated events in the 3 categories of events mentioned above.

The ESMB recommends the study continue as planned.

The ESMB will meet again by teleconference on May 16 at 10 AM EST to review updated safety data.

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APPROVe ESMB MEETING MINUTES
Not for Sharing Outside of the ESMB

Mtg Date: 16-May- 2002

Open Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan, Tom Simon, Jim Bolognese, Alise Reicin, Bettina Oxenius, John Baron

In the open session, Tom Simon presented the results of the combined analysis of cardiovascular thrombotic events in all Phase IIb to Phase V clinical trials of refecoxib that were at least 4 weeks or more in duration. Presently the APPROVe data are not included in the meta-analysis. It was noticed that while the overall hazard ratio for APTC events for refecoxib versus placebo was 0.94 (95% CI: 0.62 to 1.42), it varied between the Alzheimer trials and the other (primarily arthritis) trials. One possible explanation, other than chance (the numbers were small for the other trials), was the difference in treatment durations between these types of trials. Another possible explanation might be due to death as the competing risk of thrombotic events in the much older Alzheimer patients. The ESMB would like to see some results of all-cause deaths in the combined analysis. The next update of the meta-analysis will be in approximately one year and will include data from APPROVe.

Then, Bettina Oxenius updated the progress of the trial. A total of 2612 patients were randomized into the trial. Excluding those 26 patients who were originally randomized into rofecoxib 50 mg group and later either went to open label treatment on rofecoxib 25 mg or discontinued from the study, there will be a total of 2586 patients in all future analyses. As of May 9, 13.4% of the patients have discontinued from the study. To reduce patient discontinuations, a patient retention strategy will be discussed in a future investigator's meeting. Also, as of May 9, there are a total of 61 reported thrombotic events. Among them, 46 have been adjudicated, 8 are waiting for adjudication and 7 are ineligible. The ESMB was pleased with MRL's effort for expediting the adjudication process. Currently, approximately 50% of patients have had their 12 month colonoscopy. One-year data for all patients should be available for review by early 2003.

Closed Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan

Results of updated safety data were reviewed. There were trends noted particularly in reported thromboembolic events, hypertension-related AEs, AEs of cardiovascular system, and serious clinical AEs. The number of adjudicated thromboembolic serious adverse events was small and did not differ substantially by treatment group (11 for Treatment A and 16 for Treatment B). Three other observations were made: 1) trends

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for adjudicated thromboembolic events, thromboembolic events that did not meet study criteria, and events not yet adjudicated; all trended in the same direction against treatment; 2) since the last review, the numbers of serious AEs reported were similar for the two groups, attenuating the difference observed on the previous review; and 3) the meta-analysis of placebo-controlled studies, which is now based on 117 adjudicated thromboembolic events, showed no overall effect of refecoxib. Based on this review, the ESMB recommends the study continue as planned. However, the data on thromboembolic serious adverse events and cardiovascular events warrant close monitoring, so another review will be held in approximately 3 months.

A separate question was raised whether the ESMB members could keep the safety report themselves rather than returning the report to Hui Quan each time after the meeting. That would permit easy comparison of the safety results over time to assess how safety trends change. After the meeting, Hui Quan consulted with MRL managements on this issue. Based on the ESMB guidelines, they suggested that ESMB members send the safety report back to Hui Quan after each meeting. He will return the previous report together with the new one to each ESMB member before each meeting or summarize key data from the previous reports in each new report prepared.

The ESMB decided to meet again by teleconference on August 7 at 10 AM EST to review updated safety data.

May 28, 2002

Thomas Simon, M.D.
BL 1-4
10 Sentry Parkway
Blue Bell, PA
19422

Dear Tom:

This letter is to you inform you that the External Safety Monitoring Board (ESMB) for the *APPROVe* study met by teleconference on February 13 and May 16, 2002 to review unblinded safety reports. Following each teleconference, the ESMB recommended that the study continue as planned. This recommendation is reflected in the confidential summary of our closed session held by Hui Quan. I apologize for not communicating this to you earlier.

The teleconference on February 13 included a review of the adjudication protocol for thromboembolic vascular events and as you know following that teleconference I sent you a letter on February 25 requesting that the adjudication of thromboembolic events be expedited. The improved timeliness of these reviews was reflected in our most recent data summary that we reviewed. Thank you for your help with this. Our next teleconference will be on August 6. It will be important for that teleconference also to have up to date adjudication of events.

Sincerely,

James D. Neaton, Ph.D.
Professor of Biostatistics
ESMB Chair

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APPROVe ESMB MEETING MINUTES
Not for Sharing Outside of the ESMB

Mtg Date: 7-August- 2002

Open Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan, Jim Bolognese, Susan Loftus, Alise Reicin, Tom Simon, Janet van Adelsberg

In the open session, Dr. Tom Simon first updated the status of the APPROVe trial. As of July 31, 15.4% of the patients have discontinued from the study. Actions are continuously taken to contact investigators to improve the conduct of the trial. The percentage of patients for whom a 12 month colonoscopy is available is not currently available but the information is being assembled for future review. Also, as of July 31, there are a total of 64 reported thrombotic events. Among them, 54 have been adjudicated, 2 are currently being adjudicated and 8 are waiting for adjudication.

The possible expansion of the DSMB for other trials was discussed. There is a plan to combine the CV data from the Victor, APPROve and the up coming Prostate Cancer Prevention trials as an alternative to a CV outcomes study for Vioxx. The objective of the combined analysis is to show the non-inferiority of Vioxx compared to placebo. The pooled analysis will have 90% power to establish if the upper bound of the confidence interval for the Vioxx/Placebo ratio for CV events is less than 1.3. The proposal is to expand the responsibilities of the ESMB for the APPROVe trial to include being the DSMB for the Prostate Cancer Prevention Trial and the monitoring board for reviewing the combined CV data of the Victor, APPROVe and Prostate Cancer Prevention trials. The ESMB would be expanded by adding another cardiologist and an oncologist/urologist. A report documenting the timelines for the trials, protocols and monitoring plan will be prepared by MRL. Dr. Jim Neaton will write a letter to inform MRL of the ESMB's willingness to take on these additional responsibilities.

Closed Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan

Results of updated safety data up to 7/25/02 were reviewed. There were still some trends noted in adjudicated/confirmed thromboembolic CV combined with CHF AEs, hypertension-related AEs, edema- related AEs and AEs of cardiovascular system. On the other hand, there was a continued reduction of the treatment difference in overall serious clinical AEs.

More patients on treatment are experiencing stage 2 or 3 hypertension during follow-up. Also, many patients with elevated BP at a follow-up visit do not have hypertension AEs.

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A discussion of this led to two action items: 1) Dr. Neaton will write a latter to MRL informing them of the overall percent of patients experiencing stage 2/3 hypertension (even in the control group this percent exceeded 10%) and request that procedures be put in place (if not already established) for referring such patients for re-measurement of BP (confirmation) and if necessary treatment or treatment modification; and 2) Dr. Neaton will ask MRL what the definition of hypertension-related AEs and serious hypertension-related AEs are and why some patients who have BP elevations during follow-up do not have AE reports and why some who do, do not appear to have elevated follow-up BPs.

A table for the percentage of patients whose DBP≥100 or SBP≥160 by treatment will be added to the safety report for future reviews. Also, a line will be added to the summary table that included non-CVD deaths as well as CVD deaths with thromboembolic AEs. In addition, narrative summaries for serious hypertension-related AEs will be provided to the ESMB for their next review..

The number of CV adverse events is still small and treatment differences for the primary and secondary outcomes are not nominally significant. Although there appear to be clear differences in BP and edema events between treatments, treatment differences for serious clinical AEs, which number 241 total, have become smaller. Therefore, other than the recommendation stated above for referring hypertensives for further evaluation, the ESMB recommends the study continue as planned..

The ESMB will meet again by teleconference on November 26 at 2:00 PM EST to review updated safety data.

August 20, 2002

Thomas Simon, M.D.
Merck Research Laboratories
BL 1-4
10 Sentry Parkway
Blue Bell, PA
19422

Dear Tom:

This letter is to you inform you that the External Safety Monitoring Board (ESMB) for the *APPROVe* study met by teleconference on August 7, 2002 to review unblinded safety reports. The ESMB noted that overall, for both treatment groups combined, that approximately 18% of patients had stage 2 or higher hypertension at least once during follow-up (systolic blood pressure $\geq$ 160 mm Hg or diastolic blood pressure $\geq$ 100 mm Hg). We believe that unless there is already a provision in the protocol that such patients should be referred for re-measurement of blood pressure and initiation or modification of antihypertensive therapy as necessary. We also noted that 279 patients had a "hypertension-related" adverse event and 6 patients had a serious "hypertension-related" adverse event. It is not clear to us how these events are defined. We examined the follow-up blood pressures for those with serious events and some patients did not appear to have marked elevations in blood pressure at follow-up visits. We have requested the narrative summary for these events. We point this out because there appears to be an inconsistency between follow-up blood pressure readings (e.g., defining events as stage 2 or 3 hypertension) and adverse event reports and we are uncertain about the reliability of the hypertension-related adverse event data we are monitoring.

Other than the recommendation above concerning establishment of protocol procedures for handling elevated blood pressure, we recommend the study continue as planned. Our next review is scheduled for 26 November at 2PM EST.

Sincerely,

James D. Neaton, Ph.D.
Professor of Biostatistics
ESMB Chair

August 20, 2002

Alise Reicin, M.D.
RY34 B-264
126 E. Lincoln Ave.
Rahway, NJ
07065

Dear Alise:

This letter is a follow-up to the discussion we had on the teleconference on August 7 concerning the possible extended responsibilities of the *APPROVe* External Safety Monitoring Board (ESMB). We discussed this briefly in our closed session as well. We would like to reaffirm our interest in assuming the responsibility for the monitoring of the proposed prostate cancer prevention trial and of the pooled cardiovascular data from *APPROVe*, VICTOR, and the prostate cancer study. As we indicated during the open session, we believe this will require the addition of a cardiologist and an oncologist/urologist to the ESMB.

We think it is important that the VICTOR leadership and data monitoring committee be made aware of this proposed monitoring plan and we propose the following for your consideration and theirs:

1. Establish an open line of communication between our monitoring committee and the VICTOR monitoring committee so that a decision on early termination due to safety can be shared before it is formalized. In our discussion we conjectured that because of the nature of the VICTOR trial, it is more likely that we would make a recommendation for early termination if it turned out that there was an increased risk of cardiovascular events due to rofecoxib, because of the different potential benefits of treatment between the VICTOR study and the other trials. We also considered the merits of adding someone from the VICTOR monitoring committee to our monitoring committee. We felt that was not advisable as it could place that individual in an awkward position during reviews of the VICTOR data. Instead, we think a plan for exchange of safety information when deemed appropriate by either monitoring committee was the preferred way to operate.

2. Arrange a conference telephone call among members of the two monitoring committees or at least the chairs to discuss logistics of communication and issues

around early release of the cardiovascular data. For example, if the combined data from the three trials indicated that there was a safety concern, or as you indicated on the call, the required number of events for the overview were obtained before the end of VICTOR and the prostate cancer prevention trial, what would be the plan and the implications to the ongoing trials for the release of that data?

3. We like to plan a future meeting to review the monitoring guidelines for the prostate cancer prevention trial and for the pooled analysis of cardiovascular events. What is your timetable for the availability of these documents? If these are available in the Fall, we may consider changing our planned teleconference on November 26 for *APPROVe* to a face-to-face meeting on another date.

Thank you for sending us the timeline for completion of the three studies and the combined analysis. It appears our group will be busy for some time.

Sincerely,

James D. Neaton, Ph.D.
Professor of Biostatistics
ESMB Chair

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APPROVe ESMB MEETING MINUTES

Mtg Date: 26-November- 2002

Open Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan, Jim Bolognese, Tom Simon, Ray Joseph, Bettina Oxenius, John Baron, Albert Leung, Celia Harms, Jennifer Ng, Deborah Shapiro, Janet van Adelsberg

1. APPROVe

In the open session, Dr. Oxenius first updated the status of the APPROVe trial. As of middle November, 18.1% of the patients have discontinued from the study. There were a total of 17 PUBs, 16 deaths and 636 reported serious adverse events. Thirty-one of the reported serious adverse events were drug-related. Whether a serious adverse event is drug-related or not relies upon local investigator's judgement based on the definition provided in the protocol. Also, there were a total of 78 reported thrombotic events. Among them, 67 had been adjudicated, and 11 were waiting for adjudication. Dr. Oxenius also presented the tentative timelines for Year 1 interim analysis: the file for analysis will be frozen on April 21; statistical analyses will be completed by May 5; and results will be ready for ESMB review by May 12, 2003.

The ESMB sent a letter to MRL in August informing them of the overall percent of patients experiencing hypertension and requested that procedures be put in place (if not already established) for such patients. Dr. Joseph indicated that a letter from MRL was sent out to all investigators in September to remind them of hypertension as a possible side effect of NSAIDs including VIOXX. Additionally, the letter reminded the investigators that Vioxx might interfere with the control of hypertension. Finally, the letter recommended procedures to be followed for following hypertensive patients in the study. Subsequently, Dr. Joseph clarified the use of the term "hypertension-related" adverse events, and the reporting requirements for any AEs in the study. Then, Dr. Joseph briefly reviewed the six cases that were deemed hypertension SAEs – of a total of six cases five were hospitalized, and the other patient had systolic readings in excess of 200 associated with dizziness. Only two of the six cases had no prior history of hypertension. All six patients were treated, and three continued in the study.

Merck and FDA have been communicating regarding the design of the study. In a recent communication regarding APPROVe, FDA indicated that 3- year data are not sufficient to fully study cardiac and other adverse events, including mortality. The FDA also indicated that follow-up after stopping treatment is necessary to assess rebound (the recurrence rate of the active treatment group would be higher than that of the placebo group). The FDA proposed to extend the treatment period to 5 years, with colonoscopies at Years 1, 3, and 5 (on-drug), followed by another colonoscopy at Year 6 (after 1 year

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off drug). The protocol team's current thinking is that the pre-planned cardiovascular combined analysis of three trials including APPROVe would provide a more meaningful safety assessment than continuation of the colon polyp study, because it would provide much greater power. Therefore, the team is considering addressing the rebound concern with a 1 year off-drug follow-up colonoscopy (at year 4), and addressing the safety concern with the pre-planned cardiovascular combined analysis. This proposal is still under discussion within MRL.

2. Prostate Cancer Prevention Trial

Dr. Leung presented the VIOXX prostate cancer prevention protocol. He summarized the design, the patient population, the endpoint, and the inclusion/exclusion criteria for the study. The ESMB for APPROVe will be expanded to include a cardiologist and an oncologist/urologist and will serve as the ESMB for the prostate cancer prevention trial. Dr. Shapiro will be the blinded statistician and Dr. Ng will the unblinded statistician for the prostate cancer trial. FDA is currently reviewing the protocol. The study will be started in January 2003 if FDA approves the protocol.

3. CV Combined Analysis

Dr. van Adelsberg then presented the plan for a prospective combined analysis of CV data from three VIOXX trials: APPROVe, Victor (an on going study conducted by Oxford University and sponsored by Merck with approximately 7000 patients, 2 and 5 year active treatment periods) and the prostate cancer prevention trial. The primary objective of the combined analysis is to show the non-inferiority of Vioxx compared to placebo with respect to CV events. Patients in these trials will have a spectrum of baseline cardiovascular risk and will be exposed to rofecoxib or placebo on a chronic basis. These patients may be skewed toward male sex and thus have increased incidence of CV events compared to the general OA or RA patients. The ESMB for the APPROVe and prostate cancer prevention trial will serve as the ESMB for this combined analysis. The analysis will be performed after the accrual of 611 events. Thus, the timeline of the analysis will mainly depend on the enrollment of the prostate cancer prevention trial along with other factors, and probably will occur near the end of 2005. Currently, there is no plan to combine CV data from these three trials with those of other VIOXX trials for another meta analysis. This analysis is designed as a stand-alone, independent, prospectively designed assessment of non-inferiority of VIOXX in comparison to placebo. The protocol will be ready for ESMB review after incorporating FDA's comments. Certain stopping rules may be employed during the monitoring of the CV data. These stopping rules will be drafted and then reviewed by the ESMB before reviewing interim results.

Closed Session -- Not for Sharing Outside of the ESMB

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan

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Results of updated safety data up to 11/11/02 were reviewed. There were still some trends noted in adjudicated/confirmed thromboembolic CV combined with CHF AEs, hypertension-related AEs, edema- related AEs and AEs of cardiovascular system. On the other hand, there was a continued reduction of the treatment difference in overall serious clinical AEs.

More patients on treatment are experiencing stage 2 hypertension during follow-up. As mentioned in the minutes for open session, a letter from MRL has been sent out to all investigators to remind them of hypertension as a possible side effect of NSAIDs including VIOXX.

The number of CV adverse events is still small and treatment differences for the primary and secondary outcomes are not nominally significant. Although there appear to be clear differences in BP and edema events between treatments, treatment differences for serious clinical AEs, which number 300 total, have become smaller. Therefore, the ESMB recommends the study continue as planned.

The ESMB will meet again face-to-face in Boston on May 15, 2003 to review the Year 1 interim analysis results and updated safety data.

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December 16, 2002

Thomas Simon, M.D.
Merck Research Laboratories
BL 1-4
10 Sentry Parkway
Blue Bell, PA
19422

Dear Tom:

This letter is to you inform you that the External Safety Monitoring Board (ESMB) for the *APPROVe* study met by teleconference on November 26, 2002 to review unblinded safety reports. Based on our review, we recommend the study continue as planned. Our next review is scheduled for 15 May 2003 in Boston.

Sincerely,

James D. Neaton, Ph.D.
Professor of Biostatistics
ESMB Chair

cc John Baron

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APPROVe ESMB MEETING MINUTES

Mtg Date: 26-November- 2002

Open Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan, Jim Bolognese, Tom Simon, Ray Joseph, Bettina Oxenius, John Baron, Albert Leung, Celia Harms, Jennifer Ng, Deborah Shapiro, Janet van Adelsberg

1. APPROVe

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The ESMB sent a letter to MRL in August informing them of the overall percent of patients experiencing hypertension and requested that procedures be put in place (if not already established) for such patients. Dr. Joseph indicated that a letter from MRL was sent out to all investigators in September to remind them of hypertension as a possible side effect of NSAIDs including VIOXX. Additionally, the letter reminded the investigators that Vioxx might interfere with the control of hypertension. Finally, the letter recommended procedures to be followed for following hypertensive patients in the study. Subsequently, Dr. Joseph clarified the use of the term "hypertension-related" adverse events, and the reporting requirements for any AEs in the study. Then, Dr. Joseph briefly reviewed the six cases that were deemed hypertension SAEs – of a total of six cases five were hospitalized, and the other patient had systolic readings in excess of 200 associated with dizziness. Only two of the six cases had no prior history of hypertension. All six patients were treated, and three continued in the study.

Merck and FDA have been communicating regarding the design of the study. In a recent communication regarding APPROVe, FDA indicated that 3- year data are not sufficient to fully study cardiac and other adverse events, including mortality. The FDA also indicated that follow-up after stopping treatment is necessary to assess rebound (the recurrence rate of the active treatment group would be higher than that of the placebo group). The FDA proposed to extend the treatment period to 5 years, with colonoscopies at Years 1, 3, and 5 (on-drug), followed by another colonoscopy at Year 6 (after 1 year

off drug). The protocol team's current thinking is that the pre-planned cardiovascular combined analysis of three trials including APPROVe would provide a more meaningful safety assessment than continuation of the colon polyp study, because it would provide much greater power. Therefore, the team is considering addressing the rebound concern with a 1 year off-drug follow-up colonoscopy (at year 4), and addressing the safety concern with the pre-planned cardiovascular combined analysis. This proposal is still under discussion within MRL.

2. Prostate Cancer Prevention Trial

Dr. Leung presented the VIOXX prostate cancer prevention protocol. He summarized the design, the patient population, the endpoint, and the inclusion/exclusion criteria for the study. The ESMB for APPROVe will be expanded to include a cardiologist and an oncologist/urologist and will serve as the ESMB for the prostate cancer prevention trial. Dr. Shapiro will be the blinded statistician and Dr. Ng will the unblinded statistician for the prostate cancer trial. FDA is currently reviewing the protocol. The study will be started in January 2003 if FDA approves the protocol.

3. CV Combined Analysis

Dr. van Adelsberg then presented the plan for a prospective combined analysis of CV data from three VIOXX trials: APPROVe, Victor (an on going study conducted by Oxford University and sponsored by Merck with approximately 7000 patients, 2 and 5 year active treatment periods) and the prostate cancer prevention trial. The primary objective of the combined analysis is to show the non-inferiority of Vioxx compared to placebo with respect to CV events. Patients in these trials will have a spectrum of baseline cardiovascular risk and will be exposed to rofecoxib or placebo on a chronic basis. These patients may be skewed toward male sex and thus have increased incidence of CV events compared to the general OA or RA patients. The ESMB for the APPROVe and prostate cancer prevention trial will serve as the ESMB for this combined analysis. The analysis will be performed after the accrual of 611 events. Thus, the timeline of the analysis will mainly depend on the enrollment of the prostate cancer prevention trial along with other factors, and probably will occur near the end of 2005. Currently, there is no plan to combine CV data from these three trials with those of other VIOXX trials for another meta analysis. This analysis is designed as a stand-alone, independent, prospectively designed assessment of non-inferiority of VIOXX in comparison to placebo. The protocol will be ready for ESMB review after incorporating FDA's comments. Certain stopping rules may be employed during the monitoring of the CV data. These stopping rules will be drafted and then reviewed by the ESMB before reviewing interim results.

Closed Session – Not for Sharing Outside of the ESMB

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan

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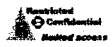
Results of updated safety data up to 11/11/02 were reviewed. There were still some trends noted in adjudicated/confirmed thromboembolic CV combined with CHF AEs, hypertension-related AEs, edema- related AEs and AEs of cardiovascular system. On the other hand, there was a continued reduction of the treatment difference in overall serious clinical AEs.

More patients on treatment are experiencing stage 2 hypertension during follow-up. As mentioned in the minutes for open session, a letter from MRL has been sent out to all investigators to remind them of hypertension as a possible side effect of NSAIDs including VIOXX.

The number of CV adverse events is still small and treatment differences for the primary and secondary outcomes are not nominally significant. Although there appear to be clear differences in BP and edema events between treatments, treatment differences for serious clinical AEs, which number 300 total, have become smaller. Therefore, the ESMB recommends the study continue as planned.

The ESMB will meet again face-to-face in Boston on May 15, 2003 to review the Year 1 interim analysis results and updated safety data.



December 16, 2002

Thomas Simon, M.D.
Merck Research Laboratories
BL 1-4
10 Sentry Parkway
Blue Bell, PA
19422

Dear Tom:

This letter is to you inform you that the External Safety Monitoring Board (ESMB) for the *APPROVe* study met by teleconference on November 26, 2002 to review unblinded safety reports. Based on our review, we recommend the study continue as planned. Our next review is scheduled for 15 May 2003 in Boston.

Sincerely,

James D. Neaton, Ph.D.
Professor of Biostatistics
ESMB Chair

cc John Baron

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APPROVe ESMB MEETING MINUTES

Mtg Date: 15-May- 2003

Open Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan, Jim Bolognese, Tom Simon, Ray Joseph, Bettina Oxenius, John Baron, Albert Leung, Jennifer Ng, Deborah Shapiro, Alise Reicin, Janet van Adelsberg

1. ViP Trial

Dr. Leung presented the status of VIOXX prostate cancer prevention trial (ViP). The trial will enroll approximately 15000 patients, 10000 in US and 5000 internationally. The protocol originally specified that biopsy would be performed only on patients with high PSA values. A amendment to the protocol had been made that biopsy will be performed on all patients at the end of the trial. Dr. Baron mentioned that a NCI trial experienced difficulty to get biopsy from patients. Dr. Leung will consult Dr. Baron after the meeting to get more detail of the NCI experience. The original timeline to have 40% of the enrollment early next year may not be possible due to delays in opening some sites. The ESMB will review safety data at their next meeting in early 2004..

2. APPROVe

Dr. Oxenius updated the status of the APPROVe trial. As of late April, 22% of the patients had discontinued from the study. There have been a total of 36 potential PUBs, 15 of them had been adjudicated. The next study newsletter will remind all sites to report future potential PUB events immediately. There have been22 deaths (some of them occurred before randomization and therefore were not included in any analyses) and 803 reported serious adverse events. Also, there have been a total of 97 reported thrombotic events. Among them, 89 had been adjudicated, and 8 were waiting for adjudication. Dr. Oxenius also presented the protocol for the 1-year off-drug extension protocol. The objective for the extension study is to assess the recurrence of adenoma 1 year after stopping study therapy. The timelines for the extension study are First Patient In (FPI) in 07/2003 and Last Patient Out (LPO) in 11/2005.

3. Vioxx Low-Dose Aspirin Endoscopy Study

Dr. Joseph presented results from the VIOXX low-dose aspirin endoscopy study. A total of 1615 OA patients were randomized into the study with approximately 400 patients in each of placebo, EC aspirin 81 mg/day, Vioxx 25 mg plus EC aspirin 81 mg/day and ibuprofen 800 mg 3 times/day treatment groups. Post randomization endoscopies were performed at Weeks 6 and 12. Incidence of ≥3 mm ulcers was the primary endpoint and incidence of ≥5 mm ulcers was also evaluated. The conclusions of the study are: Vioxx

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plus low-dose aspirin is 'similar' to ibuprofen alone; Vioxx plus low-dose aspirin as well as ibuprofen are associated with more ulceration than low-dose aspirin alone. The relevance of this endoscopy study to APPROVe trial is that approximately 16% of the patients in APPROVe trial use low-dose aspirin. Thus, in the trial, patients with treatments of Vioxx and low-dose aspirin may have the similar GI adverse experiences as with treatment of ibuprofen.

4. CV Combined Analysis DAP

Mr. Bolognese presented the Data Analysis Plan for the CV outcomes combined analysis which will combined CV data from APPROVe, Victor and ViP of more than 24000 patients. The primary endpoint is the confirmed thrombotic CV SAEs, the secondary endpoint is investigator-reported CV SAEs and confirmed APTC events. There are other exploratory endpoints. The primary hypothesis for the combined analysis is the non-inferiority of Vioxx 25 mg to placebo on the primary endpoint and the secondary hypothesis is the superiority of Vioxx 25 mg to placebo. Interim analyses will be performed based on pre-specified α spending function. There are no pre-specified plans to stop the trial due to non-inferiority of rofecoxib. However, should the ESMB decide to stop the study early for any reason (e.g., patient safety, superiority, non-inferiority), early decision rules are specified in the Data Analysis Plan. It was proposed that a cardiologist and a urologist/oncologist would be added to the current APPROVe ESMB to form the ESMB for the ViP trial and this CV combined analysis.

Closed Session -- Not for Sharing Outside of the ESMB

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan

The ESMB first discussed the role of the additional members proposed (a cardiologist and urologist/oncologist) for the prostate cancer trial and the CV outcomes combined analysis. Since there have already been several meetings of the APPROVe ESMB, the ESMB for APPROVe recommended that these two new members only be added to the ESMB for the ViP trial and the CV outcomes combined analysis and not the APPROVe study. The logistics for future ESMB meetings could be having a single open session for all parties, followed by two separated closed sessions, one for the ViP trial and CV outcomes analysis, and another for APPROVe. A letter from Prof. Neaton will be sent to Dr. Simon to indicate this recommendation.

Results from the Year 1 colonoscopy data were reviewed. The Year 1 colorectal adenoma recurrence results supported the Year 1 efficacy hypotheses specified in the protocol and data analysis plan. The Year 1 recurrence rate for Treatment B was significantly lower than Treatment A for both the increased risk patient population and general patient population. These results were consistent across all subgroups considered.. In addition, the Year 1 mean number and mean maximum size of adenomas of Treatment B were significantly smaller than those of Treatment A for both patient populations. There were approximately 10% of the patients who had no Year 1 adenoma recurrence data. These

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10% of the patients could not be included in this Year 1 efficacy analysis. It was noted that there was some imbalance across treatments on the number of patients with missing Year 1 adenoma recurrence data. The letter from Prof. Neaton to Dr. Simon will remind MRL to further make effort to ensure that near 100% of colonoscopies at Year 3 are obtained. It is also important to have histological evaluations on all biopsy samples in order to obtain non-missing adenoma recurrence data. An analysis will be performed to assess the number of patients who had a colonoscopy but had missing adenoma recurrence data (due to either the biopsy samples got lost or histologic evaluations on the biopsy samples were not performed).

Cumulative safety data up to 4/21/03 were reviewed. There were still some trends noted in adjudicated/confirmed APTC/thromboembolic CV combined with CHF AEs (It was not a pre-specified AE analysis), hypertension-related AEs, edema- related AEs, confirmed PUBs, AEs of cardiovascular system and AEs of musculoskeletal and connective tissue disorders. In addition, as before, more patients on treatment are experiencing stage 2 hypertension during follow-up.

The number of CV adverse events was still small and between-treatment differences for the primary and secondary outcomes have become smaller. It was recommended that plots of the Kaplan-Meier curves be prepared and that an assessment of whether hazard ratios in the early part of treatment are different from those later . Although there appear to be clear differences in BP and edema events between treatments, treatment difference for serious AEs (404 patients in total) was not nominally significant. Therefore, the ESMB recommended the study continue as planned.

The ESMB planned to meet in person again early next year. The timing will depend on the availability of all parties. Also, the ESMB hopes to take the first look at the ViP safety data at that meeting.

DRAFT LETTER

May 19, 2003

Thomas Simon, M.D.
Merck Research Laboratories
BL 1-4
10 Sentry Parkway
Blue Bell, PA
19422

Dear Tom:

This letter is to you inform you that the External Safety Monitoring Board (ESMB) for the *APPROVe* study met in Boston on May 15, 2003 to review the 12 month colonoscopy results and other safety data. Based on our review, we recommend the study continue as planned.

As discussed with you by teleconference during the open session of our meeting, we encourage the Executive Committee to evaluate the completeness of the Week 52 colonoscopy data by site and patient baseline characteristics and to make plans to ensure that near 100% of colonoscopies at 3 years are obtained. It is important that the 3-year colonoscopies be performed for patients who have discontinued treatment as well as those who remain on blinded treatment.

The ESMB also considered the role of the additional members proposed (a cardiologist and urologist/oncologist) for the prostate cancer trial and the CV outcomes combined analysis. Since there have already been several meetings of the APPROVe ESMB, we recommend that these two new members only be added to the ESMB for those two studies and not the APPROVe study.

We plan to meet in person again early next year and we will work with you on meeting logistics so that the review of all three studies can be accomplished. For example, one possibility would be to have a single open session for all parties, followed by two closed sessions, one for APPROVe and one for the prostate trial and CV outcomes analysis.

Sincerely,

James D. Neaton, Ph.D.
Professor of Biostatistics
ESMB Chair

cc John Baron. M.D.

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APPROVe ESMB MEETING MINUTES

Mtg Date: 24-November- 2003

Open Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan, Jim Bolognese, Tom Simon, Ray Joseph, Bettina Oxenius, John Baron, Alise Reicin, Ned Braunstein

1. Regulatory Issues Related to ESMBs

In order to protect the integrity of its studies, MRL had requested waivers from the FDA not to unblind treatment assignment in safety reports of adverse experiences that involve cardiovascular endpoints in the Arcoxia and Vioxx cardiovascular outcomes studies. Dr. Braunstein updated the ESMB on issues related to the FDA's response requesting to review data from the Arcoxia CV Outcomes Study. The FDA told MRL that whatever approach is agreed on for the Arcoxia outcome trials will apply to the Vioxx outcome trials. MRL will inform the APPROVe ESMB about any future developments on this matter and will ask an ESMB representative to participate should there be discussions related to providing data by treatment group.

2. APPROVe

Dr. Oxenius updated the ESMB on the status of the APPROVe trial. As of November 2003, there have been 985 reported serious adverse events and 25 reported deaths (three of them occurred before randomization and therefore were not included in any analyses). There have been a total of 38 reported PUBs, 35 of them had been adjudicated. Also, there have been a total of 133 reported thrombotic events. Among them, 115 had been adjudicated. Among the 633 (24%) discontinued patients, 200 patients discontinued due to withdrawal of consent (175) or lost to follow up (25). Questions were raised whether safety or efficacy data could be obtained from these patients after their discontinuations. All discontinued patients are offered the opportunity to come back for their scheduled colonoscopy. Some of them may come back and some of them may not. Also, based on the protocol, the investigators were required to report all serious AEs which occurred within 14 days after discontinuation of study therapy. AEs including deaths which occurred more than 14 days after discontinuation may be spontaneously reported. A letter from Dr. Neaton will be sent to MRL to suggest to systematically collect mortality data for all participants until the end of the trial.

The FPI for off-drug extension of the trial occurred in August 2003. It is estimated that around 600 patients per treatment group will be available to assess between-treatment difference in Year 4 adenoma recurrence rates.

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Dr. Joseph discussed the closure of Site 128. The site screened 25 patients and randomized 21 patients. Two patients discontinued prior to Visit 5. Subsequently, 18 were dispensed the wrong medication at Visit 5 and Visit 6 (Year 1). An APPROVe Team monitoring visit revealed further allocation errors involving Visits 7 and 9. The validity of the data from this site can not be ascertained. Thus, the primary modified ITT analysis will not include data from the site. However, these results along with a detailed explanation will be provided in an appendix of the study report. Additionally, since the number of randomized patients from the site (21) is small and all patients at the site are to be dropped, it is unlikely that any bias would result from including or excluding these patients. Nonetheless, these patients will be included in the safety analyses.

3. Updated Vioxx CV Data

Dr. Reicin presented updated Vioxx CV data from the Alzheimer trials. There are three placebo-controlled Alzheimer trials (Protocols 078, 091 and 126). Since Protocol 126 was terminated early and only had small amount of short term safety data, per FDA's request, Protocol 126 was not included in the update. Based on data from Protocols 078 and 091, the relative risk for thrombotic CV events for Rofecoxib 25 mg versus placebo was 1.010. The corresponding relative risk for APTC events was 1.03. Both relative risks were very close to one. Dr. Reicin briefly reviewed the results of the all cause mortality analysis.

The ESMB would like to see the full safety reports for these two studies combined including results of deaths, SAEs, edema-related AEs and hypertension-related AEs when they are available.

Currently, only around 600 patients have been enrolled into the ViP trial. CV data from the Victor trial may not be available for the May (2004) combined analysis of CV data due to the departure of programmer for the Victor study. Thus, the updated CV data for the planned May 2004 face-to-face meeting will probably include data from APPROVe and ViP only.

Closed Session – Not for Sharing Outside of the ESMB

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan

Cumulative safety data up to 11/11/03 were reviewed. Treatment differences were noted in many categories of AEs including all reported CV events excluding non-CVD deaths, adjudicated/confirmed APTC/thromboembolic CV combined with CHF AEs , drug-related AEs, serious AEs, drug-related serious AEs, hypertension-related AEs, edema-related AEs, reported PUBs, AEs of cardiovascular system and AEs of renal and urinary disorders. In addition, as before, more patients on treatment are experiencing stage 2 hypertension during follow-up.

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The ESMB recommended the tabulation of discontinuation rates due to withdrawal of consent and lost to follow up by treatment group in the future updates. Adjudicated PUB results should also be provided. In addition, the ESMB would like to see some kind of assessment of the relationship between blood pressure levels and CV events.

The number of primary CV adverse events (APTC) was still small and the between-treatment difference was not statistically significant. For these "harder" clinical events there was no convincing evidence of a safety problem; however, the trend for the APTC hard endpoints and the differences for the other safety outcomes noted above were worrisome and the ESMB felt close monitoring of accumulating data was important.

The ESMB recommended the study continue as planned with one exception. The ESMB would like MRL to consider the collection of mortality data on all participants through the end of the trial irrespective of whether the participants are taking study treatment, discontinue from the trial or stay in the trial.

The ESMB plans to meet by teleconference on February 18, 2004 to review updated safety data from APPROVe and the data analysis plan for the ViP trial.

November 25, 2003

Thomas Simon, M.D.
Merck Research Laboratories
BL 1-4
10 Sentry Parkway
Blue Bell, PA
19422

Dear Tom:

This letter is to you inform you that the External Safety Monitoring Board (ESMB) for the *APPROVe* study met by teleconference on November 24, 2003 to review safety data. Based on our review, we recommend the study continue as planned with one exception. We would like you and the Administrative Committee to consider the collection of mortality data on all participants through the end of the trial irrespective of whether participants are taking study treatment. We understand that deaths that occur14 days after treatment is discontinued may be spontaneously reported. However, given the discontinuation rate (24%), we believe it is important to have a plan to systematically collect mortality data for all participants until the end of the study.

We plan to meet by teleconference in February. We tentatively set a date and time -- February 18, 2004 at noon EST. On that teleconference, we will review updated safety data for the *APPROVe* study and the data analysis plan for the ViP study.

Finally, we appreciate the update on the final results of CVD outcomes for Protocols 091 and 078. As discussed on the teleconference, we would like to see the full safety reports for these two studies when they are available.

Sincerely,

James D. Neaton, Ph.D.
Professor of Biostatistics
ESMB Chair

cc John Baron, M.D.

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APPROVe ESMB MEETING MINUTES

Mtg Date: 18-February- 2004

Open Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan, Ray Joseph, Bettina Oxenius, Susan Loftus, John Baron, Alise Reicin, Jennifer Ng, Deborah Shapiro, Jim Bolognese

1. APPROVe

Dr. Oxenius updated the ESMB on the status of the APPROVe trial. As of February 2004, there have been 1042 reported serious adverse events and 28 reported deaths (three of the deaths occurred before randomization and therefore were not included in any analyses). There have been a total of 39 reported PUBs, 37 of them had been adjudicated. Also, there have been a total of 139 reported thrombotic events. Among them, 127 have been adjudicated. Among the 676 (25.9%) discontinued patients, 302 of them are expected to come back for the ITT Year 3 colonoscopy and 42 of them have already come back and completed the ITT Year 3 colonoscopy. There have been 396 patients who have completed the base study per protocol and 366 patients who have been enrolled into the off-drug extension study.

Dr. Joseph summarized MRL's effort to collect mortality data for all discontinued patients following the ESMB's recommendation. The collection of all mortality information would require both a protocol amendment and a 'new' consent form for all discontinued patients. Though implementation of the amendment and revision of the consent form to enable collection of mortality data on previously discontinued patients may present some practical problems, MRL will proceed with the ESMB's recommendation. It was noted that approval of an amendment may take up to 8 months based on previous IRB experience (Five domestic sites and 14 international sites are still pending IRB/ERC approval of the protocol for the extension study). Hence, the base study may be completed prior to IRB/ERC approval. The ESMB is pleased with MRL's effort and encourages MRL to continue the data collection plan.

2. Additional Combined Safety Results from Prots. 078&091

Dr. Reicin summarized the key safety results from two placebo-controlled Alzheimer trials (Protocols 078 and 091). The primary analysis of all-cause mortality was based on the on-drug population. All-cause deaths for the on-drug population included all deaths which occurred while on study therapy or within 14 days after the final dose of study therapy, or could potentially have been related to a nonfatal adverse experience which started while the patient was receiving study therapy.

Mortality was greater on rofecoxib than placebo. The overall relative risks were very close to 1.0 for both adjudicated confirmed thrombotic CV events and APTC events based on data from Protocols 078/091. However, the constant hazard ratio assumption did not hold for both types of events. The adjudication criteria for CV events are the same across all studies including APPROVe.

The ESMB would like to see the all-cause mortality result based on the ITT population from Protocols 078/091 and also the safety report from the other Alzheimer trial (Protocol 126) which was terminated early.

3. Status Update for ViP and timelines for Combined CV Analysis

Dr. Ng updated the status of the ViP trial. Currently, only 1374 patients (9.2% of the total N) have been enrolled into the trial. It was predicated that the 40% enrollment would not be achieved until 3Q04. The Data Analysis Plan for the trial will be sent to the ESMB sometime in March-April. The first safety data review for ViP trial may occur in May. The formats of the safety result presentations (tables and plots) should be consistent with those of the APPROVe trial.

Closed Session – Not for Sharing Outside of the ESMB

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan

Cumulative safety data up to 2/4/04 were reviewed. Treatment differences, not all nominally significant, were noted in many categories of AEs including adjudicated/confirmed APTC/thromboembolic CV events, adjudicated/confirmed thromboembolic CV events, all reported CV events excluding non-CVD deaths, adjudicated/confirmed APTC/thromboembolic CV events combined with CHF AEs or deaths , drug-related AEs, serious AEs, drug-related serious AEs, hypertension-related AEs, edema- related AEs, confirmed/unconfirmed PUBs, AEs of cardiovascular systems, AEs of renal and urinary disorders, and AEs of reproductive system and breast disorders. In addition, as before, more patients on Treatment B than Treatment A are experiencing stage 2 hypertension during follow-up.

After this review meeting, the ESMB recommended additional analyses for assessing the relationship between blood pressure and CV events. A follow-up ESMB closed session was held on 3/1 to review results from these additional analyses. The results revealed that over 150 patients with stage 2 hypertension were randomized into the trial. Numerically, risk of CV events was higher for Treatment B than A across baseline blood pressure levels - relative between-treatment differences were higher for those with lower blood pressure at baseline. More patients with elevated blood pressure at baseline in Treatment B discontinued from the trial. Stage 2 hypertension during follow-up was associated with about 2.5 fold increased risk for CV events. CV event rates were higher among patients more likely to develop Stage 2 hypertension in both treatment groups -

between-treatment differences were greater for those at lower risk of developing Stage 2 hypertension in the control group during treatment.

The number of primary CV adverse events (APTC) was still small (16 versus 26) and the between-treatment difference was not statistically significant. However, the trend for the APTC hard endpoint and the differences for the other safety outcomes noted above continued to be worrisome. It was noted that trends in the APTC endpoint at earlier interim analyses had become smaller on subsequent reviews. The difference in APTC outcomes could be due to chance; however, that is less likely for all reported thromboembolic outcomes where the difference is larger. Since few events will occur between now and the end of the trial due to completion of year 3 examinations and discontinuations, the safety data in the report is not likely to change much.

The ESMB considered all of these data and decided it was important to finish the trial to obtain the Year 3 efficacy data so that an overall benefit/risk assessment could be made.The ESMB recommended the study continue as planned with one exception. The ESMB would like MRL to more agressively treat patients who have hypertension and to discontinue treatment for those patients whose blood pressure is not controlled. Dr. Neaton will write a letter to inform MRL regarding this recommendation.

The next ESMB meeting for APPROVe will be probably in August - September.

March 2, 2004

Kevin Horgan, M.D.
Merck Research Laboratories
BL 1-2
10 Sentry Parkway
Blue Bell, PA
19422

Dear Dr. Horgan:

This letter is to you inform you that the External Safety Monitoring Board (ESMB) for the *APPROVe* study met by teleconference on February 18 and March 1, 2004 to review unblinded safety data. Based on these reviews, we have the following recommendations:

1. The number of participants with hypertension remains high. It is well known that NSAIDs and COX-2 inhibitors raise blood pressure. We recommend that you take a more aggressive approach to monitoring and treating blood pressure. If blood pressure cannot be controlled, study treatment should be discontinued. You indicate in the protocol that participants with uncontrolled hypertension are to be excluded and that those with medically controlled hypertension (diastolic blood pressure $\leq$ 95 mm Hg, systolic blood pressure $\leq$165 mm Hg may participate. Thus, we suggest you use these criteria to define uncontrolled hypertension during the treatment phase of the study and if blood pressure is > 95 mm Hg diastolic or >165 mm Hg systolic with antihypertensive medication, discontinue study treatment.

2. We are pleased that you are planning a 3-year colonoscopy and the collection of mortality status on all randomized participants irrespective whether study treatment was discontinued. We continue to feel this is very important.

We plan to schedule our final review of the interim data in August or September.

Sincerely,

James D. Neaton, Ph.D.
Professor of Biostatistics
ESMB Chair

cc John Baron, M.D.

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Final

APPROVe ESMB MEETING MINUTES

Mtg Date: 17-September- 2004

Closed Session

Attendees: David Bjorkman, Marvin Konstam, Richard Logan, James Neaton, Hui Quan

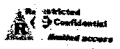
Cumulative safety data up to 8/16/04 were reviewed. Significant between-treatment differences were observed in many categories of AEs including adjudicated/confirmed APTC and adjudicated/confirmed thromboembolic CV events. These adjudicated findings were supported by the unadjudicated (all reported) event analysis and by adverse trends in a heart failure, pulmonary edema and cardiac failure composite outcome. In addition, as before, more patients on treatment B than treatment A are experiencing stage 2 hypertension (DBP 100+ or SBP 160+ mmHg) during follow-up. It appears the average DBP and SBP are increased by about 2 and 4 mmHg, respectively, with treatment B.

The trend for excess risk for treatment B for confirmed APTC events has continued to grow at each meeting over the last 1-2 years. In May 2003, the hazard ratio was 1.2; in November 2003 it was 1.4; last February it 1.8; and currently it is 2.2. Whereas there was an excess of 2 events on treatment B in May 2003, there are now 17.

Based on the K-M plots and event rates in 6-month time intervals, there was a trend for the-treatment differences for major CVD outcomes to increase over time. For example, during the first year of follow-up there were 7 confirmed APTC events on A and 8 on B; in the 2nd year there were 7 on A and 10 on B; after 2 years there were 2 events on A and 15 on B.

The ESMB noted that the changing relative risk with increasing follow-up indicating adverse effects with longer treatment exposure was also present in the Alzheimer analyses reviewed by the ESMB last February.

Even though the study is close to its completion, the ESMB considered all of these data and decided it was important to communicate their safety concerns to the Executive Committee. The ESMB unanimously recommends that the Executive Committee be unblinded to the safety data and that participating patients be instructed to discontinue study treatment. In their deliberations the ESMB considered the impact this might have on the completion of the 3-year colonoscopies, which they feel is very important, and they believe that this would not adversely impact the planned efficacy analysis using the Year 3 colonoscopy results. These data are obviously important for a full assessment of risk/benefit in this population.



Other related issues that the ESMB will discuss with the sponsor are:

- Timetable for notification (and possible reconsent) of patients;
- Communication of APPROVe results with other study groups carrying out trials of rofecoxib;
- The importance of further analyses to understand the extent to which BP differences between treatment groups explains the adverse CVD findings (prior analyses for VIGOR study may be relevant);
- Inclusion of heart failure outcomes in pooled analysis; and
- Importance in future studies of collecting all CVD events occurring in the study including those that occur more than 2 weeks after treatment discontinuation.

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 49

MERCK

VIOXX TIMELINE
Key Dates for VIGOR and Long-term, Placebo-controlled Studies Implemented to Provide Cardiovascular Safety Data

1993	Studies published in which indobufen (Circulation, 1993, 87:162-164) and the non-selective NSAID flurbiprofen (European Heart Journal, 1993, 13, 951-957) are shown to reduce cardiovascular (cv) events.
1998	
April	Results of FitzGerald study first presented. Among the results of the study was the surprising discovery that COX-2 specific inhibitors reduced the urinary excretion of prostacyclin metabolite. Based on these results, it was, for the first time, hypothesized that COX-2 specific inhibitors may alter the balance between prostacyclin and thromboxane and thereby increase the risk of cv events.
	Trial of VIOXX versus placebo in the prevention of Alzheimer's in patients with Mild Cognitive Impairment (MCI) begins.
Nov	Vioxx New Drug Application (NDA) submitted to the U.S. Food & Drug Administration (FDA). The application included data on approximately 5,400 osteoarthritis patients who participated in 8 double-blind, placebo-controlled and active-comparator studies. In these studies, similar rates of investigator-reported thrombotic cardiovascular adverse events were seen with VIOXX, placebo, and comparator NSAIDs (ibuprofen, diclofenac, or nabumetone).
1999	
Jan	VIOXX Gastrointestinal Outcomes Research[1] (VIGOR) trial initiated.
Feb	First trial of VIOXX versus placebo for the treatment of Alzheimer's disease begins.
April	Public meeting of FDA Advisory Committee on VIOXX NDA.
May	VIOXX approved by the FDA.
Oct	Adenomatous Polyp Prevention On VIOXX[2] (APPROVe) trial protocol finalized.

2000

Feb	APPROVe trial enrollment begins.
March	Preliminary results from VIGOR become available to Merck.
March	News release on preliminary results of VIGOR issued by Merck.
March	Preliminary VIGOR results submitted to the FDA.
March	Merck unblinded to safety data from two ongoing Alzheimer's studies – one for prevention and one for treatment – that compare VIOXX to placebo. These data show no difference in cardiovascular event rates between VIOXX and placebo.
April	Second trial of VIOXX versus placebo for the treatment of Alzheimer's begins.
May	Preliminary VIGOR data submitted to the *New England Journal of Medicine* for publication.
May	VIGOR presented at Digestive Disease Week.
June	Final VIGOR data submitted to FDA in a Supplemental New Drug Application, which included draft prescribing information.
Nov	The GI and cardiovascular safety findings from VIGOR published in *The New England Journal of Medicine*.
	First VIOXX versus placebo trial in the treatment of Alzheimer's disease ends.
	In preparation for VIGOR Advisory Committee, second interim analysis of safety data from Alzheimer's prevention and treatment trials conducted, again showing no difference in cardiovascular event rates between VIOXX and placebo.

2001

Feb	Public meeting of FDA Advisory Committee on VIGOR.
May	Second trial of VIOXX versus placebo for treatment Alzheimer's disease stopped.
Oct	Pooled analysis of cardiovascular data from Phase II/III studies published in Circulation. Analysis demonstrated that VIOXX was not associated with excess cardiovascular thrombotic events compared with either placebo or non-naproxen NSAIDs.
Sept	Merck and Oxford University sign letter of intent to conduct the VIOXX in Colorectal Cancer Therapy: definition of Optimal Therapy[3] (VICTOR) trial.
Nov	APPROVe enrollment completed.

2002

April	U.S. Prescribing Information for VIOXX updated with VIGOR information and data from two placebo-controlled studies
April	First patient is enrolled in VICTOR trial.
June	Pooled analysis of placebo-controlled studies in patients with Alzheimer's and MCI presented at EULAR. The incidence of

serious cardiovascular adverse events in this population was similar on VIOXX and placebo.

2003

March	VIOXX in Prostate cancer (ViP) trial protocol finalized.
April	Trial of VIOXX versus placebo in MCI ends.
June	ViP trial enrollment begins.
	Updated pooled analysis of Alzheimer's treatment and MCI data presented at EULAR. The cardiovascular event rate in patients taking VIOXX 25 mg continued to be similar to the rate in patients taking placebo; mean duration of treatment was 1.2 years in VIOXX group and 1.3 years in placebo group.
Oct	Updated pooled analysis published in the American Heart Journal. Analysis demonstrated that VIOXX was not associated with excess cv thrombotic events compared with either placebo or non-naproxen NSAIDs.

2004

Sept	APPROVe External Data Safety Monitoring Board notifies Merck of its recommendation to end APPROVe trial.
Sept	APPROVe, ViP and VICTOR trials terminated early.
Sept	Merck voluntarily withdraws VIOXX from the market
Nov	APPROVe trial scheduled to end.

2005

Aug	ViP trial enrollment scheduled to be completed.

2011

Aug	ViP trial scheduled to end.

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[1] In VIGOR, Vioxx 50 mg once daily (n=4,047) – a dose twice the highest recommended chronic dose -- was compared to a common therapeutic dose of naproxen 500 mg twice daily (n=4,029) in patients with rheumatoid arthritis (median length of participation was nine months). The study assessed the incidence of serious GI events and the most serious, or "complicated," GI events, which included perforations, obstructions or major bleeding (PUB) in the upper GI tract. The study was designed to exclude patients requiring aspirin for cardioprotection.

In VIGOR, Vioxx 50 mg once daily significantly reduced the risk of serious GI events by 54 percent and the risk of complicated GI events by 57 percent compared to naproxen 500 mg twice daily. A total of 56 patients treated with Vioxx experienced a serious GI event compared to 121 patients taking naproxen, and a total of 16 patients receiving Vioxx had a complicated GI event versus 37 patients taking naproxen. In the study, the reduction in risk for serious and complicated GI events with Vioxx was maintained in patients both at high risk for developing a PUB and in patients without risk factors. Such

risk factors include: prior history of a PUB, age of 65 or older, *Helicobacter pylori* infectionor concomitant use of corticosteroids.

In VIGOR, a statistically significant higher incidence of serious cardiovascular thrombotic events was seen in patients receiving Vioxx 50 mg once daily compared to patients treated with naproxen 500 mg twice daily. A total of 45 serious cardiovascular thrombotic events occurred among 4,047 patients taking Vioxx compared to 19 among 4,029 taking naproxen. This was largely due to a difference in the incidence of non-fatal heart attacks: 18 for Vioxx and 4 for naproxen. The number of cardiovascular thrombotic deaths was similar in patients treated with Vioxx (n=7) compared to naproxen (n=6).

[2.] APPROVe was a multi-center, randomized, placebo-controlled, double-blind study to determine the effect of 156 weeks (3 years) of treatment with rofecoxib on the recurrence of adenomatous polyps of the large bowel in patients with a history of colorectal adenomas. The study included approximately 2600 patients aged 40-96; approximately 62% male. Aspirin was allowed in the study.

In APPROVe there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment for patients taking VIOXX as compared to placebo. Results for the first 18 months of the study did not show an increased risk of confirmed CV events on VIOXX and in this respect, the results are similar to the results of two prior placebo controlled studies described in the current U.S. labeling for VIOXX.

Merck followed the recommendation of the study's External Safety Monitoring Board and terminated this trial on September 30, 2004.

[3.] VICTOR was a randomized, double-blind, placebo-controlled, international, multicenter study of VIOXX in 7,000 colorectal cancer patients following potentially curative therapy. The primary hypothesis tested in the study was that VIOXX administered for two years will result in greater overall survival compared with placebo. CV events were monitored by the VICTOR trial investigators and Merck as part of the adverse events monitoring conducted as part of the study. The study was stopped on September 30, 2004.

[4.] ViP was a randomized, double-blind, placebo-controlled, multicenter study to evaluate the effects of VIOXX in decreasing the risk of prostate cancer. The study protocol called for 15,000 male patients, aged = 50 and = 75 years, with a life expectancy of greater than 6 years, with PSA = 2.5 ng/mL and = 10 ng/mL to be enrolled. The primary hypothesis to be tested in the study was that the risk of developing prostate cancer over six years of treatment will be lower in patients treated with VIOXX 25 mg/day than in patients treated with placebo; and that treatment with VIOXX would be generally safe and well tolerated. Cardiovascular adverse events were monitored by an external safety monitoring board as a part of the study. The trial was halted on September 30, 2004.

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Forward-Looking Statement

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MERCK

Timeline of Epidemiological Studies Involving VIOXX or NSAIDs[1]

Jan 2002 — A retrospective cohort study by **Ray et al** is published in *The Lancet*. Objective was to measure the effects of non-aspirin NSAIDs, including naproxen, on risk of serious coronary heart disease (CHD). Study concludes that in a high-risk patient population of people 50 years and older, non-selective non-aspirin NSAIDs neither increased nor decreased risk of serious CHD. Analysis evaluated 6,362 cases from the Tennessee Medicaid program during 181,441 periods of new NSAID use in 128,002 people and the same number of periods of non-use of NSAIDs among 134,642 people.

May 2002 — Three separate case-control studies are published in *Archives of Internal Medicine*. Each showed that use of naproxen reduced the risk of heart attacks. These studies were first presented at the American College of Rheumatology meeting in 2001.

Solomon et al: Objective was to determine whether NSAIDs have a similar effect or whether they differ in their effects on the risk of acute myocardial infarction (AMI). Study concludes that the findings do not support a relationship between the use of NSAIDs as a group and risk of heart attacks. However, use of naproxen was associated with a significant reduction in the risk of AMI (adjusted odds ratio, 0.84; 95% confidence interval, 0.72-0.98; P =.03). Analysis evaluated 4,425 cases from the N.J. Medicare/ Medicaid Program against a control group of 17,700 subjects.

Watson, et al: Objective of the study was to examine the risk of acute thromboembolic cardiovascular events (heart attack, sudden death and stroke) with naproxen use among patients with rheumatoid arthritis. The study concludes that patients with rheumatoid arthritis and a current prescription for naproxen had a reduced risk of acute major thromboembolic CV events relative to those who did not take naproxen in the past year. Analysis evaluated 809 cases from British General Practice Research Database against a control group of 2,285 subjects. Study sponsored by Merck.

Rahme, et al: Objective of the study was to compare the effect of naproxen to other NSAIDs in the prevention of acute myocardial infarction (AMI) in an elderly population. The study concludes that compared to other NSAIDs, concurrent use of naproxen has a protective effect against AMI. Analysis evaluated 4,163 cases from Canadian RAMQ and Med-Echo databases against a control group of 14,160 subjects. Study sponsored by Merck.

[1] **Editor's Note:** Timeline is not an exhaustive list of every study ever conducted to evaluate the safety of NSAIDs and COX-2 inhibitors; selected studies have been identified to illustrate the wide divergence of results from observational studies.

Oct 2002 A retrospective cohort study by **Ray et al** is published in *The Lancet*. Objective was to assess occurrence of serious coronary heart disease (CHD), specifically acute myocardial infarction (AMI) and cardiac death, in patients taking Vioxx, celecoxib or other NSAIDs. Study concludes use of Vioxx at doses greater than 25 mg could be associated with an increased risk of serious CHD; in contrast, there was no evidence of increased risk among users of Vioxx at doses of 25 mg or less, celecoxib, naproxen or ibuprofen. Analysis evaluated 5,316 events from the Tennessee Medicaid program among 251,046 NSAID users and 202,916 non-users.

Oct 2002 A database cohort analysis by **Levy et al** is presented at the American College of Rheumatology meeting. Objective was to assess the correlation between COX-2 use and heart attacks among persons prescribed a COX-2 inhibitor, ibuprofen, or naproxen for at least 50 consecutive days. Study concludes long-term use of either of the COX-2 inhibitors (Vioxx and celecoxib) separately is not associated with an increase risk of heart attack compared with naproxen or ibuprofen. When users of COX-2 inhibitors were combined, there was an increased risk compared with users of ibuprofen or naproxen combined. Analysis evaluated 645 events from the Kaiser Permanente database among 172,260 subjects.

Feb 2003 A population-based, retrospective cohort study by **Mamdani et al** is published in *Archives of Internal Medicine*. Objective was to compare the rates of acute myocardial infarction (AMI) among elderly patients taking COX-2 inhibitors, naproxen and non-aspirin NSAIDs. Study concludes no increased short-term risk of AMI among users of COX-2 inhibitors and no short-term reduced risk of AMI with naproxen. Analysis evaluated 701 events from administrative health care databases in Ontario among 66,964 users and 100,000 non-users.

Nov 2003 A case-control study by **Kimmel et al** is presented at the American Heart Association annual meeting. Objective was to determine the risk of nonfatal heart attacks in users of COX-2 inhibitors compared with users of non-aspirin NSAIDs. Study concludes there was no increased risk of heart attacks overall from COX-2 inhibitors, or from VIOXX separately and that nonselective, non-aspirin NSAIDs were associated with a reduced risk of heart attack. Analysis evaluated 1,718 cases against 6,800 controls from the Delaware Valley Case-Control Network. Study sponsored by Merck and Pharmacia.

Mar 2004 A population-based analysis by **Whelton et al** is presented at the American College of Cardiology meeting. Objective was to determine the risk of acute myocardial infarction (AMI) or stroke with Vioxx, celecoxib, and non-selective NSAIDs in hypertensive patients. Study concludes Vioxx significantly increases the risk of AMI or stroke compared with non-users of NSAIDS and there was no increased risk among users of celecoxib or non-selective NSAIDs. Analysis evaluated 3,723 users against 1,798 users from a private medical insurance healthcare claims database. Study sponsored by Pfizer.

Mar 2004 A case-control study by **Kimmel et al** is published in the *Journal of the American College of Cardiology*. Objective was to determine the risk of nonfatal heart attacks in users of non-selective, non-aspirin NSAIDs and the interaction between non-aspirin NSAIDs and aspirin. Study concludes non-selective, non-aspirin NSAIDs are associated with a reduced risk of heart attack. Analysis

evaluated 581 events from the Philadelphia community among 4,153 control subjects.

Apr 2004 A case-control study by **Solomon et al** is published in *Circulation*. Objective was to assess the risk of acute myocardial infarction (AMI) among users of Vioxx, celecoxib, and NSAIDs in an elderly population. Study concludes Vioxx all doses combined was associated with a significant increased risk of AMI compared to celecoxib. Non-significant differences were found comparing Vioxx to ibuprofen, naproxen, other NSAIDs and to those not taking NSAIDs. The risk was higher in persons taking greater than 25 mg of Vioxx and during the first 90 days of use but not thereafter. Analysis evaluated 10,895 cases from two state-sponsored pharmaceutical benefits program in the U.S. among 54,475 patients 65 years and older. This study was first presented at the American College of Rheumatology meeting in 2003. Study sponsored by Merck.

May 2004 A population-based retrospective cohort study by **Mamdani et al** is published in *The Lancet*. Objective was to compare the rates of admission for congestive heart failure (CHF) in elderly patients who were given COX-2 inhibitors or non-selective NSAIDs. Study concludes there is a higher risk of admission for CHF in users of Vioxx and non-selective NSAIDs (diclofenac, naproxen and ibuprofen) but not celecoxib in comparison to non-users of NSAIDs. Analysis evaluated 654 events from administrative healthcare databases in Ontario among 45,097 users of NSAIDs/COX-2 inhibitors and 100,000 non users.

June 2004 A cohort study by **Garcia Rodriguez et al** is published in *Circulation*. Objective was to estimate the effect of non-aspirin NSAIDs on the occurrence of AMI and death from CHD. Study concludes there was no risk reduction of NSAIDs on the occurrence of MI. Analysis evaluated 4,975 cases from the General Practice Research Database in the U.K. against a control of 20,000 subjects.

Aug 2004 A case-control study by **Graham et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to determine if NSAID use increases the risk of AMI or sudden cardiac death (SCD) and if the risk is similar among COX-2 selective agents. Study concludes Vioxx use at doses greater than 25 mg increases the risk of AMI and SCD; Vioxx at 25 mg or less had an increased risk compared with celecoxib; and that several other NSAIDs increased the risk of AMI and SCD. Analysis evaluated 8,199 cases from Kaiser Permanente against a control group of 32,796 subjects. Funding provided by FDA.

Aug 2004 A retrospective cohort study by **Rahme et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to assess the rates of hospitalizations for acute myocardial infarction (AMI) in an elderly cohort. 52,029 patients were taking non-selective NSAIDs and 71,543 patients were taking rofecoxib, with 14,056.4 and 37,371.0 person-years of exposure, respectively. Based on the regression model, the adjusted hazard ratios of hospitalizations for MI was 1.03 (0.83-1.27) for rofecoxib vs. ibuprofen/diclofenac. Study concludes there was no difference in the rate of hospitalizations for AMI among Vioxx and the non-selective NSAIDs ibuprofen and diclofenac. Study sponsored by Merck.

Aug 2004 A retrospective cohort study by **Shaya et al** is presented at the International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Objective was to examine the cardiovascular risk of COX-2 inhibitors compared to non-specific NSAIDS in a high risk Medicaid population. Analysis evaluated medical and prescription claims for Maryland Medicaid enrollees, COX-2 users numbered 1208 and non-naproxen NSAID users numbered 5274. Study concludes that COX-2 inhibitors did not increase cardiovascular risk over non-naproxen NSAIDs in a high risk population.

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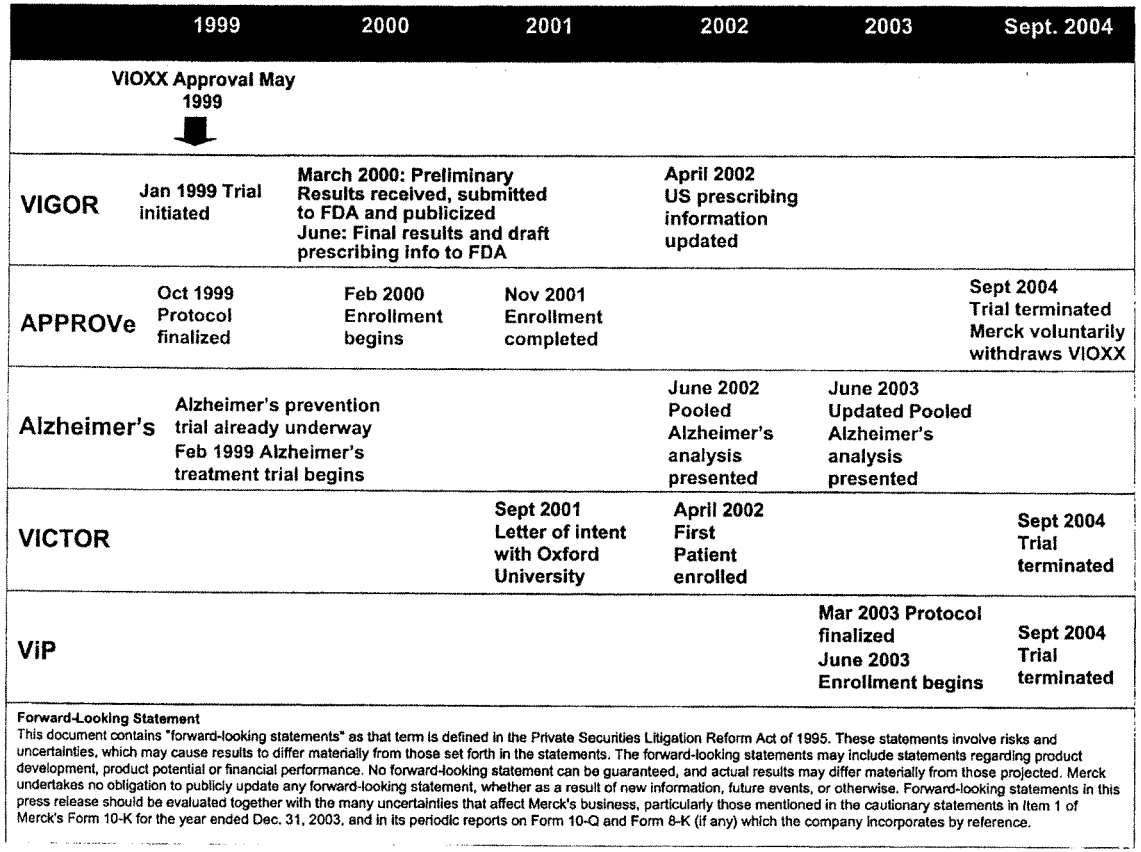

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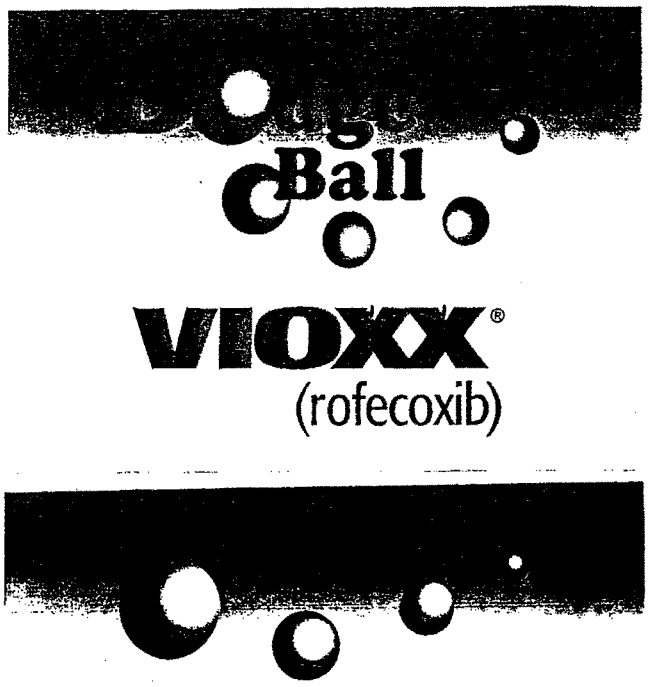
"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 50



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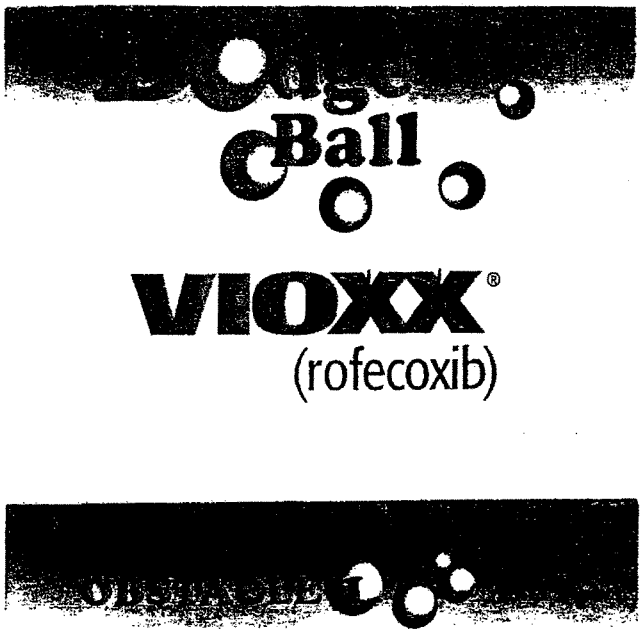
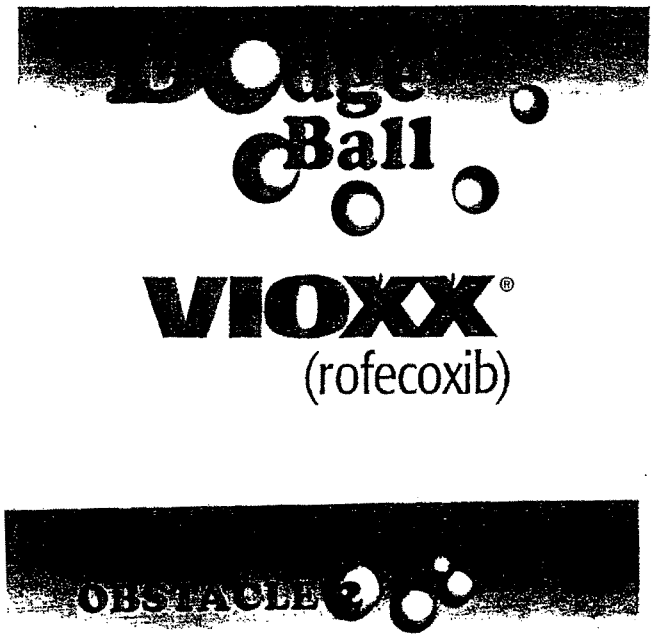
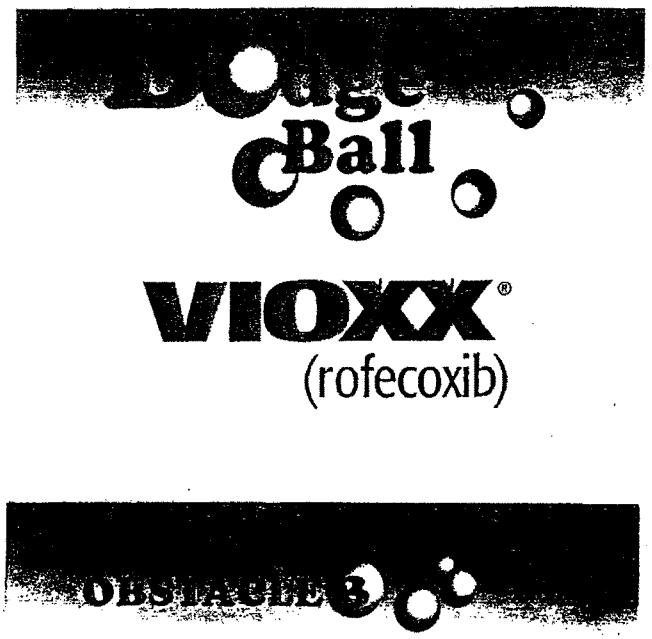


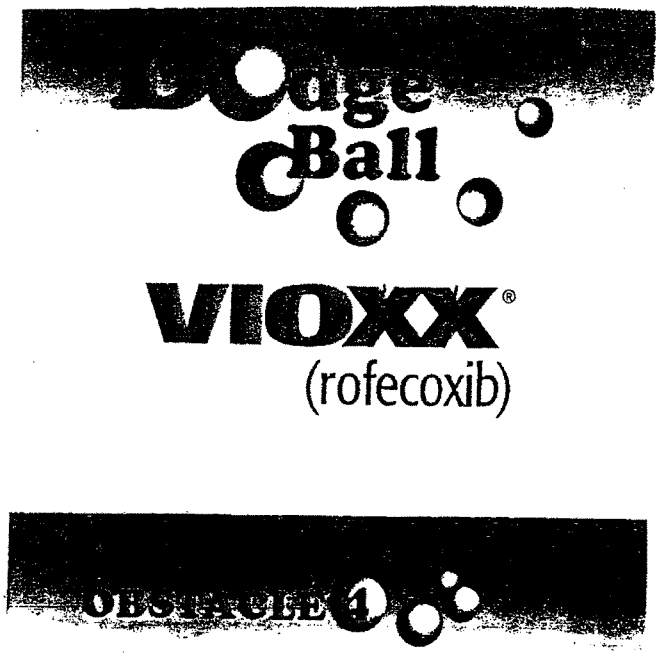
"I am concerned with the potential edema that occurs with Vioxx."



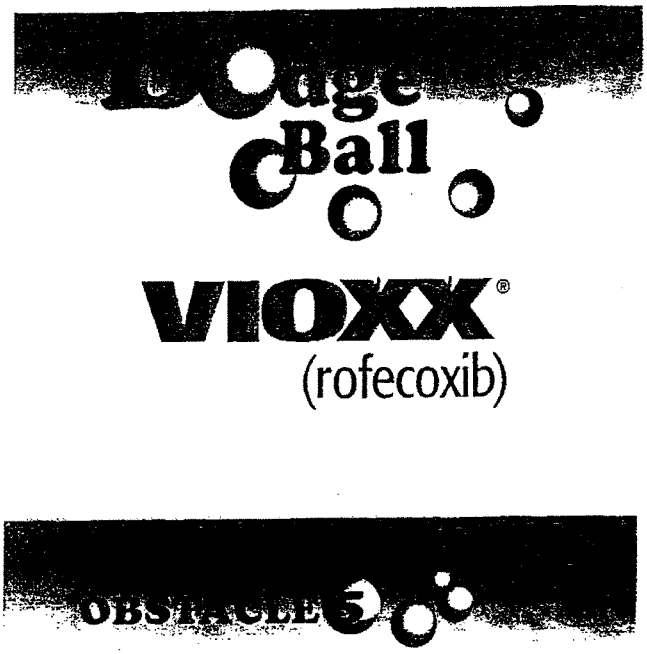
"I am concerned with dose-related increases in hypertension with Vioxx."



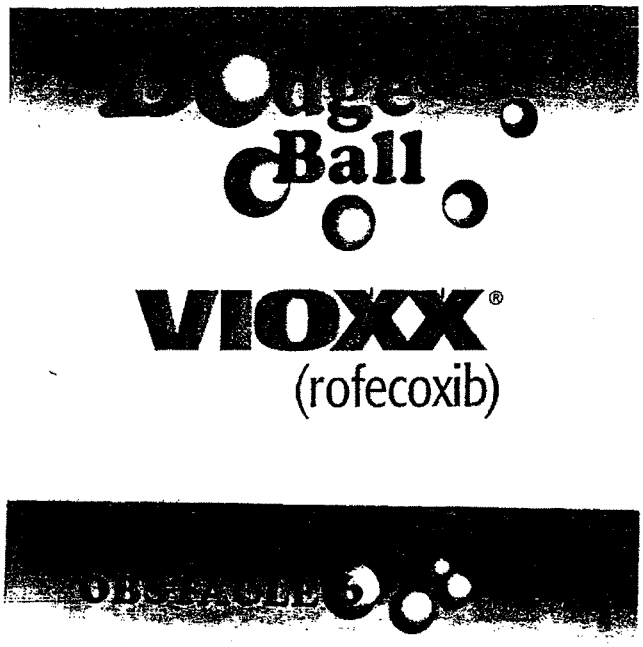
"Can Vioxx be used in patients using low dose aspirin?"



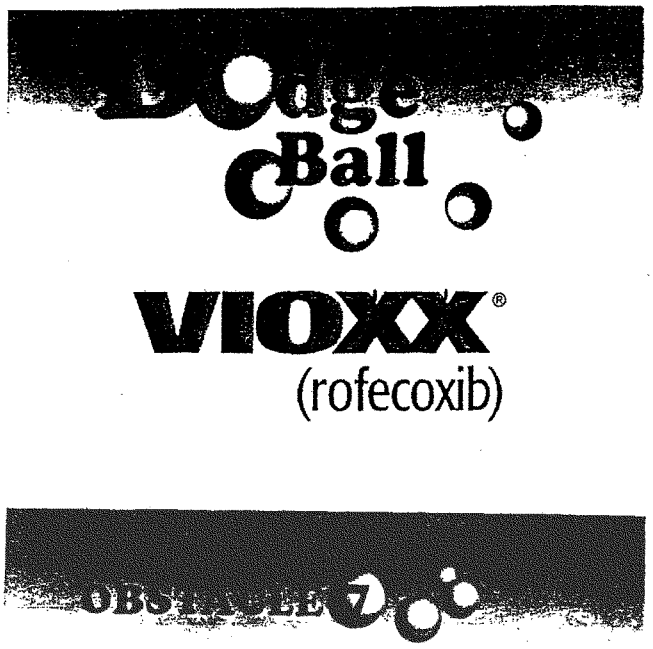
"I am concerned about the cardiovascular effects of Vioxx?"



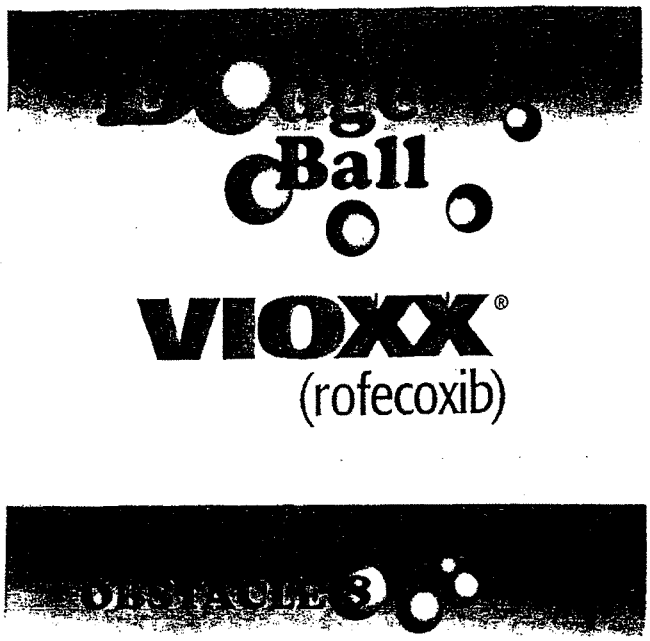
"The competition has been in my office telling me that the incidence of heart attacks is greater with Vioxx than Celebrex."



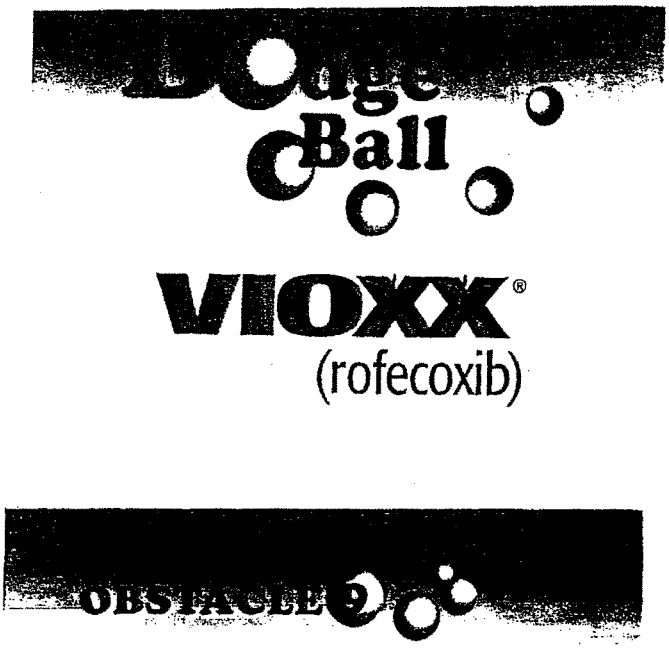
"There is no difference between Vioxx and Celebrex, why should I use Vioxx?"



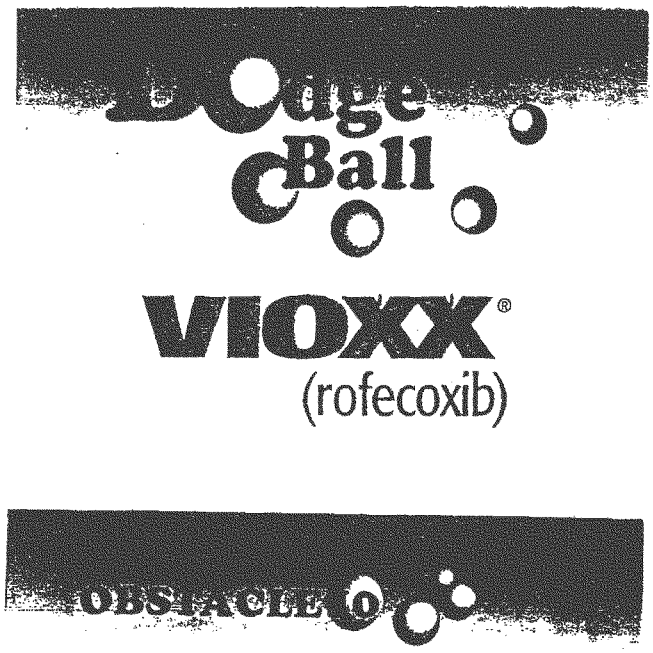
"Vioxx cannot be used for longer than five days when treating patients for acute pain?"



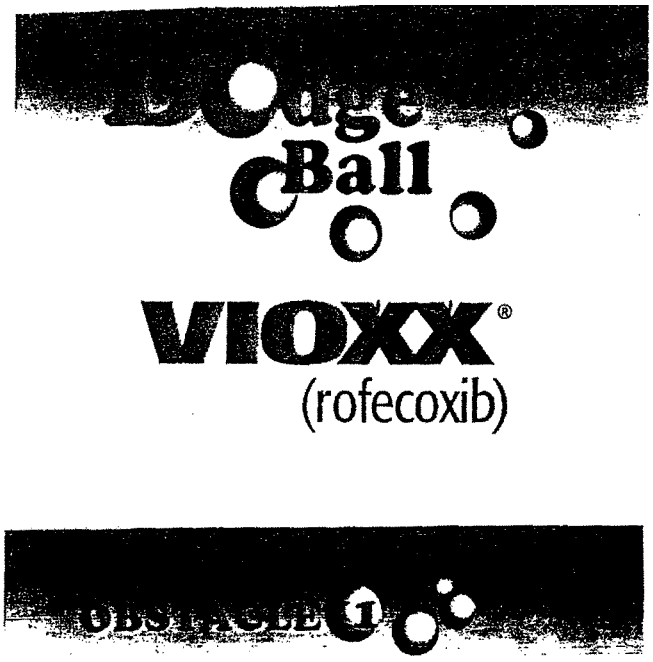
"I use Celebrex. I'm concerned about the safety profile with Vioxx?"



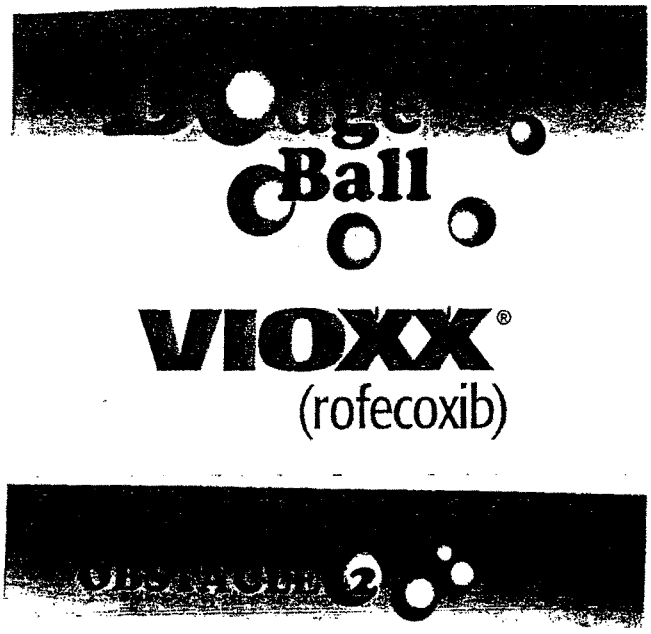
"I understand the new COXIB, Mobic, was just approved."



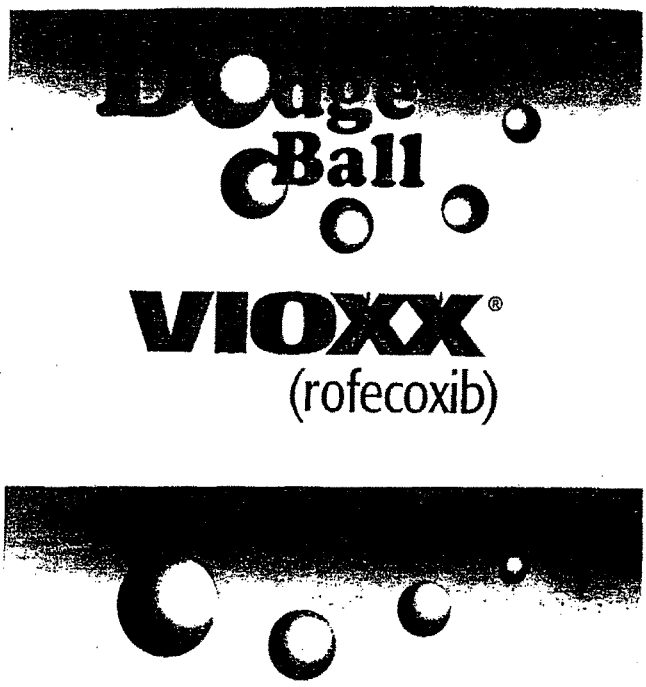
"Searle/Pfizer just presented me with data which showed Celebrex 800 mg daily did not exhibit dose dependent increases in side effects compared to the OA and RA doses, and that Vioxx exhibited dose dependent increases in side effects with the 50 mg dose."



"The new narcotic data looks great, now I'll use Vioxx for all my acute pain patients."



"I can't use Vioxx because the HMO's require the patients to be on generic NSAIDS first."



DODGE!

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Exhibit 51

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By Order of the United States District
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3T99 REFOCUS FOR VIOXX®

LEADER'S GUIDE FOR OBR REPRESENTATIVE MEETING

PRODUCT STRATEGY

Overtake Celebrex Through Clear Product Differentiation

CORE MESSAGES

Strength. Safety. QD Simplicity.

VERBATIM

Once daily power.

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GROUPS PARTICIPATING

- Office Based Sales Group

EQUIPMENT & RESOURCES NEEDED

- Overhead projector/proxima; flipchart
- 4 Physician profiles (Appendix)
- Message Grid (Appendix)
- 14 Questions To Ask Your Celebrex Representative (Appendix)
- Obstacle Response Guide for VIOXX®
- JeopardXX questions & answers (Appendix)

OVERVIEW

The primary purpose of this workshop is to give Office Based Representatives time to review and practice their understanding of VIOXX® and the top two competitors in their district, to identify the location of key messages in the package insert/detail aid for VIOXX® and the competitive package inserts, to practice obstacle handling, and to practice full product discussions. Representatives will be certified on how well they deliver product discussions using the detail piece, the package inserts for VIOXX® and competitors, and effective obstacle handling.

PLANNED OUTCOMES

At the completion of the workshop(s), participants will be able to do the following:

- Deliver differentiating and confident product discussions for VIOXX®, supported by the Top 5 Messages for VIOXX® and the detail aid for VIOXX®.
- Identify the segments within the detail aid for VIOXX®, package insert for VIOXX®, and competitive package inserts that support responses to obstacles and competitive challenges.
- Confidently handle obstacles for VIOXX® and transition back into a product discussion.

DISTRICT WORKSHOPS

Topic	Time	Method	Slide /Materials
Team Presentations - VIOXX® and Competitors	1 Hour	• Power Point presentations	
Identification of Key Messages in Detail aid and Package Inserts	1 Hour 30 Minutes	• Group exercise	
Discussion of Top Obstacles	30 Minutes	• Group exercise	

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	Obstacle JeopardXX	30 Minutes	• Team competition	
	Progressive Discussion	1 Hour	• Role-play Activity	
	Sales Discussion and Certification	30 Minutes	• Role-play Activity	
	TOTAL TIME	5 Hours		

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TEAM PRESENTATIONS - VIOXX® AND COMPETITORS

Time: 1 Hour

At A Glance - Material/Media	Instruction
Set-up	■ Presentations by pre-selected teams on VIOXX® and top two competitors.
Planned Outcomes	■ This workshop will enable Representatives to understand the differences between VIOXX® and the top two competitors for the district. Representatives will give a ten minute overview of a pre-selected product that will focus on key areas of differentiation between that product and VIOXX®, leading representatives to conduct persuasive product discussions for VIOXX®. Teams will identify how to use the competitive package insert or the detail aid/package insert for VIOXX® to effectively sell VIOXX® against the competitor.
Workshop Kick-off by Trainer	■ **Begin** the workshop by reviewing and reiterating the importance of two key elements: ✓ ***Detail piece and Package Insert*** ✓ ***Top 5 Messages for VIOXX® (overhead)***
Instructions	■ **Instruct** the representatives to move into their pre-assigned groups according to the product they were given (VIOXX® or a competitor).
Physician Profiles	■ **Ask** for the groups with a competitive product to present first, leaving the group with VIOXX® to go last. ⇒ **Explain** to teams that their task is to present the attributes of the competitive product that are necessary to know to conduct effective product discussions of VIOXX®. ⇒ **Note:** the trainer and manager should monitor each presentation and add any missing points of differentiation. ⇒ **Allow** teams approximately 10 minutes to present their assigned product, then 10 minutes for a group discussion of their successful product discussions on territory. ■ **Call time** after 1 hour. ■ **Comment** on each presentation, pointing out key areas to leverage strengths and areas for improvement. **Allow** as much time for discussion and questions from other teams as practical.

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At A Glance – Material/Media	Instruction
Transition	■ **Transition** to the next activity by saying that participants will have an opportunity to identify the key messages for VIOXX® within both the resources for VIOXX® and the competitive resources.
Learning Point	**Learning Point:** ***Learning about your competitors will be invaluable in your success with VIOXX®.***

IDENTIFICATION OF KEY MESSAGES IN DETAIL AID AND PACKAGE INSERTS

Time: 1 hour, 30 Minutes

At A Glance – Material/Media	Instruction

Set-up	■ **Ask** all representatives to have their detail aid for VIOXX®, package insert for VIOXX®, and competitive package inserts ready.
	■ **Look** at the key messages of VIOXX®:
	  ■ Top 5 Messages for VIOXX®
	  ■ 3x3
	■ **Explain** that this workshop will deepen their understanding of what to reference in the detail aid for VIOXX®, package insert for VIOXX®, and the competitive package insert when conducting product discussions for VIOXX® in a competitive environment.

Instructions	■ **Divide** participants into 4 groups.
	■ **Explain** that each group represents a Key Messages team. Each team will have 30 minutes to identify the Top 5 Messages for VIOXX® and the 3x3 in whichever resource they are assigned.
	■ **Divide** the teams in the following way:
	  ■ detail aid for VIOXX®
	  ■ package insert for VIOXX®
	  ■ Celebrex package insert
	  ■ Other competitor package insert

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At A Glance - Material/Media	Instruction
	⇒ **Note:** The teams that are assigned the detail aid for VIOXX® and the package insert for VIOXX® should be able to complete the assignment as given. The team with that uses the competitive package inserts should identify areas within the package insert that are targeted by the Top 5 Messages for VIOXX® and the 3x3. ⇒ Note: Trainers should use the Message Grid (appendix) that is provided to check the responses for the detail aid for VIOXX®, package insert for VIOXX®, and the package insert for Celebrex. Trainers are responsible for completing this exercise for the other competitor. ■ **Call** time after 30 minutes. ■ **Allow** each group 15 minutes to present their findings and explain how they would use the resource within their product discussions for VIOXX®.
Transition	■ **Transition** to the next activity by saying that participants will have an opportunity to discuss the current obstacles and the competition for VIOXX®.
Learning Point	**Learning Point:** ***You can be very successful in a competitive selling environment if you understand all of the resources available to you.***

DISCUSSION OF TOP OBSTACLES

Time: 30 Minutes

At A Glance - Material/Media	Instruction
Set-up	■ **Ask** the representatives to return to their original seats. ■ **Explain** that now they will have the opportunity to discuss the obstacles for VIOXX® that they hear on territory.
Instructions	■ **Ask** the representatives to share the most common obstacles for VIOXX® they hear on territory. ■ **Flip** their responses.

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Transition

- **Ask** the representatives to rank the top five obstacles for VIOXX® from their original list.
- **Highlight** or flip the top five most common obstacles for VIOXX®.
- **Review** each obstacle for VIOXX® by asking the following questions:
  - How do you usually respond to this obstacle?
  - How do the physicians usually react to your response?
  - How are you successful when handling this obstacle?
  - Which resources do you use when handling this obstacle?

  ⇒ **Note:** verify that all obstacle responses match the responses found in the Obstacle Response Guide for VIOXX®.
- **Take** 5 minutes to discuss each obstacle (25 minutes total).
- **Transition** to the next activity by saying that participants will have an opportunity to practice their obstacle handling responses in the following team activity.

Learning Point

Learning Point:

Effective obstacle handling will help representatives to confidently deliver product discussions for VIOXX®.

OBSTACLE JEOPARDXX

Time: 30 Minutes

At A Glance – Material/Media	Instruction
Set-up	■ Display JeopardXX game board slide on O/H. Trainer obtains JeopardXX hardcopy of Q&A in Appendix.
Planned Outcomes	■ Representatives will compete in 3 teams. ■ This fun, interactive activity will help keep participants energized and maintain district momentum into the final workshop (*Sales Discussion & Certification*). Just as important, "Obstacle JeopardXX" reinforces Obstacle Handling knowledge that Representatives need to master

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regarding messages competitive products, and obstacle resolution.

Instructions

- **Divide** participants into 3 groups.
- **Explain** that each group represents an Obstacle JeopardXX team. Each team's goal is to answer the most questions correctly and to score the most points.
  - ⇒ **Note:** It is suggested that each team rotate the individual answering for each new question. That way, everyone gets an opportunity to participate.
  - ⇒ **Note:** There should be a judge who specifically rules on which team raised their hand first to answer the question (it is difficult to read the question and monitor the hands at the same time).
- **Display** the Obstacle JeopardXX gameboard slide. Keep this slide visible for the duration of the activity, so the Representatives know which categories and point values are available.
  - ⇒ As each category/point value is selected, use a marker to *X-out* that box.
- **Keep** score on a flipchart page divided into 3 columns.
- **Note:** Use the "14 Questions To Ask Your Celebrex Representative" as an additional category during Obstacle Jeopardxx (found in the Appendix to this Leader's Guide). The first question can be phrased: "Recite one of the 14 Questions To Ask Your Celebrex Representative." Additional questions can be phrased: "Recite the Question To Ask Your Celebrex Representative that includes an FDA rejection." (Insert the topic of each question here).
- The game will end when all questions have been asked, or when you run out of time.

Overhead Slide

At A Glance – Material/Media	Instruction
	■ **Note:** Obstacle JeopardXX questions and answers can be found in the Appendix to this Leader's Guide.
Transition	■ **Transition** to the next activity by saying that participants will have an opportunity to put all they have learned to use in an interactive skill practice session that follows.
Learning Point	**Learning Point:** ***Consistent practice of obstacle handling and competitive issues will help***

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representatives to confidently deliver product discussions for VIOXX®.

PROGRESSIVE DISCUSSION

Time: 1 hour

At A Glance - Material/Media	Instruction
Set-up Instructions	■ **Divide** into 2-3 groups. ■ **Explain** that you and the business manager will play the role of physician, the physician will role-play with several different representatives to complete a sales discussion. ■ **Explain** that you will throw a koosh ball to a representative, who must open the discussion, using appropriate materials and messages. ■ Next, that representative throws the koosh ball to a different representative to deliver the next portion of the discussion. ■ The koosh ball is thrown to a new representative for each discrete section of the discussion.

At A Glance - Material/Media	Instruction
	■ **Explain** that the koosh should be thrown back to the trainer (or physician) when appropriate within the product discussion (i.e., when questions are being asked, when representatives needs to check-in to make sure the physician is in agreement throughout the discussion, etc.). ■ **Note to Facilitator:** This segment is meant to be fun and spontaneous. It should generate ideas that representatives can use when developing their sales discussions during the role-play/skill practice session. ■ This is also an opportunity for the trainer or business manger to provide constructive feedback either after each participant response (toss of the koosh) or after the entire discussion is over. This feedback should direct them in their later role-play/skill practicing. ■ Take each round of the koosh toss to the "close" or Call to Action.

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	■ Note to Facilitator: There may be times when the trainer/business manager needs to stop the round and ask the group "where they are and what is needed next in the call". ■ *Optional:* Trainer and business manager may choose to conduct a sample progressive discussion to provide participants with a model of "what good looks like". ■ Several progressive discussions will be completed, each lasting approximately 10-15 minutes (including feedback to the group). This allows each representative several opportunities to practice their product discussion skills, and will allow you to observe each representative.
Transition	■ Transition to the next activity by saying that participants will have an opportunity to put all they have learned to use in a role-play/skill practice session that follows.
Learning Point	**Learning Point:** ***Constant practice of product discussions will help representatives to incorporate creative ideas and to prepare for their skill practice.***

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SALES DISCUSSION AND CERTIFICATION

Time: 30 Minutes

At A Glance - Material/Media	Instruction
Skill Practice Process Two 15 minute Rounds: - 3 minutes prep - 5 minutes role-play - 5 minutes feedback - 2 minutes transition **Skill Practice Roles** **Representative Role** Physician Profile to prep **Physician/Observer Role** Physician Profile to prep, record observations	■ **Explain** that during this session, they will have an opportunity to practice formulating and delivering their product messages and using detail aids and/or package inserts. ■ **Ask** participants to group into pairs. ■ **Explain** that skill practice sessions will consist of **two – 15 minute Rounds. Pre-Prepare** flipchart showing break down of Rounds. ■ Rounds consist of: ⇒ 3 minutes prep ⇒ 5 minutes role-play ⇒ 5 minutes feedback ⇒ 2 minutes transition ■ **Remind** participants that they will be rotating in and out of two roles – representative and physician/observer. **Pre-Prepare** flipchart outlining each role.

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At A Glance - Material/Media	Instruction
Physician Profiles **Feedback Process** First – Representative Role Second – Physician/Observer Role	■ **Explain** that each role-play group will be given two **Physician Profiles.** ■ **Explain** that based on the direction and focus of the discussion, representatives should also incorporate an appropriate "close" or Call to Action in their discussion. **Emphasize** that feedback should be focused on all components of the Needs Based Selling process. ■ **Explain** that order for giving feedback is as follows: Representative first, physician/observer second. **Pre-Prepare** flipchart outlining feedback process.
Feedback Forms	■ **Ask** pairs to begin ***Round 1*** of the skill practice. ■ **Call time** at each interval: prep, discussion, feedback, transition. ■ **Call time** at **15 minutes** and ask pairs to transition to ***Round 2*** of skill practice. ■ **Note to Facilitator:** Trainer and manager should circulate and provide feedback to pairs. Reference the Obstacle Handling Guide for VIOXX® when giving feedback.
Obstacle Handling Guide for VIOXX® 	■ **Ask** how playing different roles helped them to see the sales discussion from a different perspective. Ask what lessons they learned through this experience. ■ **Note to facilitator: Prepare a flipchart by placing a horizontal line at the top and a vertical line down the middle. On the left-hand column header write the word "Do's"; on the right hand column header write "Don'ts".** ■ **Ask** representatives to share out the key learning points (do's and don'ts) and insights that they gained by playing the roles of representative and physician/observer on a flipchart. ■ **Thank** representatives for their participation.

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OBSTACLE JEOPARDXX

"I'm concerned about the potential edema that occurs with VIOXX"	"What hepatic effects can I expect with VIOXX"?	"I'm concerned about the CV effects of VIOXX"	"VIOXX cannot be used for longer than 5 days when treating pediatrics for acute pain"	Overtake Celebrex	MYSTERY??
100	100	100	100	100	100
200	200	200	200	200	200
300	300	300	300	300	300
400	400	400	400	400	400
500	500	500	500	500	500

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"I'm concerned about the potential edema that occurs with VIOXX."

Question:

A) Provide a clarifying statement, and

B) State two possible specific concerns a physician may have regarding edema.

Answer:

A) Clarifying statement: What are your specific concerns regarding edema?

B) Two possible specific concerns: 1) *overall* incidence of edema, 2) *dose related* increase of edema with once daily VIOXX® 50 mg.

- 100 -

"I'm concerned about the potential edema that occurs with VIOXX."

Question:

A) What drug comparators are included in the AE Table

B) State the overall incidence for VIOXX each comparator.

Answer:

A) Ibuprofen, diclofenac, placebo

B) VIOXX - 3.7%

Ibuprofen - 3.8%

Diclofenac - 3.4%

Placebo - 1.1%

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- 200 -

"I'm concerned about the potential edema that occurs with VIOXX."

Question:

State the response if the physician is specifically concerned about the overall incidence of edema.

Response:

Doctor, edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition in the kidney. Clinical trials with once daily VIOXX® 12.5 and 25 mg have shown renal effects such as edema similar to those observed with comparator NSAIDs. In these studies, the incidence rates for lower extremity edema were as follows: (in the AE table, point to row on edema under Body As A Whole)

–VIOXX® 12.5 mg or 25 mg once daily - 3.7%
–Ibuprofen 2400 mg – 3.8%
–Diclofenac 150 mg –3.4%
–Placebo – 1.1%

- 300 -

"I'm concerned about the potential edema that occurs with VIOXX."

Question:

State the response if the physician is concerned about a dose related increase in edema with once daily VIOXX 50 mg.

Response:

Doctor, edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition in the kidney.

Regarding the safety of once daily VIOXX® 50 mg, let me explain where the use of 50 mg is recommended. 50 mg is recommended for use in acute pain in adults and is not recommended for OA. In the analgesia studies, the renal effects of once daily VIOXX® – such as edema-were generally similar to comparator NSAIDs.

The 50 mg dose, while not recommended for OA, has been studied in clinical trials for up to 6 months. In these trials, the incidence of lower extremity edema was 6.3% for 50 mg. In the 6-week to 6-month studies with 12.5 or 25 mg, the incidence of lower extremity edema was 3.7%. Are you concerned about a 3.7% incidence rate of lower extremity edema in your OA patients?

- 400 -

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Wild Card

Question:
What were the three endpoints once daily VIOXX demonstrated comparable efficacy to ibuprofen 2400 mg in a 6-week OA study?

Answer:
Primary - Pain on walking
Secondary - Physical function
Tertiary - Joint Tenderness

- 500 -

"What hepatic effects can I expect with VIOXX?"

Question:
A) Provide a clarifying statement, and
B) State two possible specific concerns a physician may have regarding hepatic effects.

Answer:
A) Clarifying statement: What specific hepatic effects are you concerned about?
B) Two possible specific concerns: 1) increase in liver function testing (LFTs), 2) metabolism of once daily VIOXX® 50 mg.

- 100 -

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Wild Card

Question:
Enzyme ***Induction*** can lead to an _____ (increased/decreased) rate of drug metabolism and corresponding _____ (increases/decreases) in the availability of the parent drug.

Answer:
increased, decreases

- 200 -

"What hepatic effects can I expect with VIOXX?"

Question:
In placebo-controlled trials, what percentage of patients taking once daily VIOXX 12.5 or 25 mg had notable elevations of ALT or AST?

Response:
Once daily VIOXX - approximately 0.5%
Placebo - 0.1%

- 300 -

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"What hepatic effects can I expect with VIOXX?"

Question:
If the physician is concerned about the potential increase in liver function tests, how would you respond?

Response:
In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking once daily VIOXX 12.5 or 25 mg and 0.1% of patients taking placebo had notable elevations of ALT or AST. A patient who has an abnormal liver test while on once daily VIOXX should be monitored carefully for evidence of a more severe hepatic reaction.
Use of VIOXX is not recommended in patients with moderate or severe hepatic insufficiency.

- 400 -

"What hepatic effects can I expect with VIOXX?"

Question:
If the physician is concerned about the metabolism of once daily VIOXX, how would you respond?

Response:
Doctor, metabolism of once daily VIOXX is primarily mediated through reduction by cystolic enzymes in the liver. It is not primarily metabolized by the P450 system and is not known to inhibit the P450 system in the liver.

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"I am concerned about the cardiovascular effects of VIOXX."

Question:
Provide a clarifying statement to uncover the physician's true obstacle.

Answer:
What is your specific concern?

- 100 -

"I am concerned about the cardiovascular effects of VIOXX."

Question:
State two possible specific concerns a physician may have regarding the potential CV effects of once daily VIOXX.

Answer:
(1) "I am hesitant to use VIOXX in my patients because it may worsen CHF"
(2) "VIOXX has the potential to increase the risk of MI"

- 200 -

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Wild Card

Question:
The general safety profile of once daily VIOXX 50 mg q.d. in OA clinical trials of up to six months was similar to that with the recommended OA doses, except for a higher incidence of _____, _____, and _____.

Answer:
GI symptoms, lower extremity edema(6.3%), and hypertension (8.2)

- 300 -

"I am concerned about the cardiovascular effects of VIOXX."

Question:
If the physician is concerned that once daily VIOXX® may worsen CHF, how would you respond?

Response:
Doctor, as you know, there are precautions you should take when prescribing any NSAID for your patients with CHF. Because once daily VIOXX is an NSAID, you should consider taking these same precautions when considering the use of once daily VIOXX® for this specific patient population.

Clinical trials with once daily VIOXX® 12.5 mg and 25 mg have shown renal effects such as hypertension and lower extremity edema similar to those observed with comparator NSAIDs. VIOXX® should be used with caution and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or edema.

- 400 -

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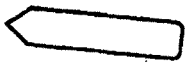

"I am concerned about the cardiovascular effects of VIOXX."

Question:
If the physician is concerned about a potential increase in the risk of MI, how would you respond?

Response:
Doctor, once daily VIOXX has no effect on platelet aggregation. Once daily VIOXX® is therefore is not a substitute for aspirin for cardiovascular prophylaxis. However, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low dose (81 mg daily) aspirin.

- 500 -

"VIOXX cannot be used for longer than five days when treating patients for acute pain"

Question:
According to the PI for VIOXX, what is the appropriate dosing for the management of acute pain?

Response:
The recommended initial dose of VIOXX is 50 mg once daily. Subsequent doses should be 50 mg once daily as needed. Use of VIOXX for more than 5 days in management of pain has not been studied.

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Wild Card

Question:
In the postorthopedic surgical pain study, patients on once daily VIOXX consumed a significantly smaller amount of additional _____ medicine than patients treated with placebo during the entire five-day study.

Answer:
analgesic

- 200 -

"VIOXX cannot be used for longer than five days when treating patients for acute pain"

Question:
Explain the rationale for the 5 day duration of the pain studies for VIOXX.

Response:
To obtain an indication for the management of acute pain in adults, all analgesic drugs are studied in short-term standard pain models as defined by the FDA. The maximum duration of these studies for once daily VIOXX® was 5 days.

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Overtake Celebrex

Question:
Name two questions for the doctor to ask his/her Celebrex Representative.

Answer:
Refer to list.

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Overtake Celebrex

Overtake Celebrex

Question:
Name the Science Messages for VIOXX.

Answer:

- VIOXX has demonstrated no effect on platelet aggregation or bleeding time; no effect on bleeding time even at doses of up to 375 mg.
- VIOXX has an effective half-life of 17 hours
- VIOXX is not contraindicated in patients with sulfonamide allergies. Celebrex is contraindicated in patients with sulfonamide allergies.
- VIOXX is not primarily metabolized via the cytochrome P450 system and there are no special considerations for patients who are cytochrome P450 2CX

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Overtake Celebrex

Mystery ?

Question:

When should physicians prescribe VIOXX® 12.5 mg, 25 mg, and 50 mg?

Response:

Whether you're treating OA or acute pain, once daily VIOXX® is always a simple once daily dose.

12.5 mg or 25 mg once daily for OA

Once daily VIOXX® 12.5mg is the starting dose for OA. If a patient requires greater pain relief, you have the flexibility to increase the dose to 25mg once daily at no additional cost to the patient.

50 mg once daily for Acute Pain and Primary Dysmenorrhea

In patients with moderate to severe acute pain, the dose is 50mg once daily. Once daily VIOXX® relieved moderate to severe pain following orthopedic surgery, dental surgery and primary dysmenorrhea.

(Appropriate balance: The use of Vioxx for more than 5 days for the management of pain has not been studied.)

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Mystery ?

Mystery ?

Question: T/F

Like Celebrex, VIOXX is contraindicated for patients allergic to sulfonamides.

Answer: FALSE!

Once daily VIOXX is not contraindicated for patients with known sulfonamide allergies, commonly known as "sulfa allergies."

Unlike Vioxx, Celebrex contains a sulfonamide group (S-NH2) which is associated with sulfonamide allergies. This contraindication is is based on the specific chemical structure of Celebrex and is not a class effect.

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Mystery ?

Question:

Mystery ?

Question:

Discuss the terms "selective" and "specific."

Answer:

The relationship between the desired and the undesired effects of a drug is termed its ***selectivity***. Expressed in another way, ***selectivity*** is defined as the *"ability of a drug to discriminate between specific targets."* Thus a truly selective drug will interact with only one specific target irrespective of the dose of drug used. If this criterion is satisfied absolutely, that drug can be referred to as being ***specific***.

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Top 5 Messages for VIOXX

Messages to deliver in the context of balanced product discussions.

*Messages 1 and 2 should be delivered in reverse order for orthopedic surgeons.

1. VIOXX demonstrated ONCE-DAILY POWER in chronic osteoarthritis (OA) pain.
   Supported by:
   - **Powerful** pain relief **all day and all night** and into the next morning
   - Power in **one small tablet once daily comparable** to ibuprofen dosed **three times a day**
   - Powerful relief of **chronic** OA pain demonstrated **over one year** (52-week data)

This document must not be copied, distributed, or shown to anyone outside the company.

2. VIOXX demonstrated FAST ONSET of pain relief; VIOXX consistently demonstrated POWERFUL RELIEF across ALL moderate-to-severe acute-pain models studied.

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3. VIOXX demonstrated **significantly fewer endoscopic ulcers** than ibuprofen, and was consistent across all studies.

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4. Safety profile of VIOXX demonstrated in patients **80 years or older.**

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5. VIOXX is **NOT** contraindicated in patients with **sulfonamide allergies.**

ONCE-DAILY POWER... One tablet, once a day, in all indications

These statements can be used by professional representatives in discussions with physicians.

This document must not be copied, distributed, or shown to anyone outside the company.

Be sure to provide appropriate balancing information as part of all product discussions.

ONCE DAILY VIOXX® (rofecoxib)

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REPRINT REVIEW

MESSAGES SUPPORTED

TYPE	TOPIC	AUTHOR/TITLE	QUAN	Strength	Safety	QD Simplicity	Science
Primary[1]	GI Safety	Laine, *A Randomized Trial Comparing the Effect of Rofecoxib, a Cyclooxygenase 2-Specific Inhibitor, With That of Ibuprofen on the Gastroduodenal Mucosa of Patients With Osteoarthritis*	2604(1)	X			
Obstacle Handling[2]	Celebrex Renal Paper	Rossat, *Renal Effects of Selective Cyclooxygenase-2 Inhibition in Normotensive Salt-Depleted Subjects*	2605(1)				X
Supporting Clinical[3]	Dental Pain	Morrison, *Analgesic Efficacy of the Cyclooxygenase-2–Specific Inhibitor Rofecoxib in Post-Dental Surgery Pain: A Randomized, Controlled Trial*	2602(1)	X		X	
	Primary Dysmenorrhea	Morrison, *Rofecoxib, a Specific Cyclooxygenase-2 Inhibitor, in Primary Dysmenorrhea: A Randomized Controlled Trial*	2603(1)	X		X	

1. Primary reprints should be used proactively during in-depth discussions with healthcare professionals.
2. Obstacle-handling reprints should only be used to address obstacles that arise during discussions.
3. Supporting clinical reprints should only be used when a healthcare professional requests additional clinical information.

ONCE DAILY
VIOXX® (rofecoxib)

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1T 2000 Top 5 Messages for VIOXX®

Messages to deliver in the context of balanced product discussions.
(*Messages #1 and #2 should be delivered in reverse order for Orthopedic Surgeons)

1. *VIOXX demonstrated ONCE DAILY POWER in chronic osteoarthritis pain.
   Supported by:
   - **Powerful** pain relief **all day and all night** and into the next morning
   - Power in **one small tablet once daily comparable** to ibuprofen dosed **three times a day**
   - Powerful relief of **chronic** OA pain demonstrated **over one year** (52 week data)

2. *VIOXX demonstrated FAST ONSET of pain relief; VIOXX consistently demonstrated POWERFUL RELIEF across ALL moderate- to- severe acute pain models studied.

3. VIOXX demonstrated **significantly fewer endoscopic ulcers** than ibuprofen, and was consistent across all studies.

4. Safety profile of VIOXX demonstrated in patients **80 years or older**

5. VIOXX is NOT contraindicated in patients with **sulfonamide allergies**

ONCE DAILY POWER... One tablet, once a day, in all indications

These statements can be used by professional representatives in discussions with physicians.
This document must not be copied, distributed, or shown to anyone outside the company.
Be sure to provide appropriate balancing information as part of all product discussions.

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 52

MERCK COPY MEMO

TO: All Field Personnel with Responsibility for VIOXX

FROM: Market Integration Team for VIOXX

SUBJECT: Top Ten Obstacle Handlers

Enclosed is the complete Obstacle Handling Guide for VIOXX. This Guide includes all obstacle responses issued since the launch of VIOXX. Though it is important for you to be familiar with all of the obstacle handlers, the following Top Ten Obstacle Handlers are the most important obstacle handlers at this time as they center around current issues in the field.

Cardiovascular Events

Obstacle Response #7- "Can VIOXX be used in patients using low dose aspirin?"

Obstacle Response #23- "I am concerned about the cardiovascular effects of VIOXX."

Obstacle Response #38- "The competition has been in my office telling me that the incidence of heart attacks {or cardiovascular events} is greater with VIOXX than Celebrex." OR "I just read {or heard} a news story stating that VIOXX has a higher incidence of heart attacks than Celebrex."

Renal Effects

Obstacle Response #4- "I am concerned about the potential edema that occurs with VIOXX."

Obstacle Response #20- "Can I use VIOXX with Ace Inhibitors?"

Obstacle Response #31- "I am concerned about dose-related increases in hypertension with VIOXX."

VIOXX 50mg Tablet

Obstacle Responses #9 and 9a- "Why wasn't VIOXX 50mg studied for longer than five days in acute pain?" OR "VIOXX cannot be used for longer than five days when treating patients for acute pain."

Obstacle Response #30- "Searle/Pfizer just presented me with new data which showed that Celebrex 800mg daily did not exhibit dose dependent increases in side effects compared to the OA and RA doses, and that VIOXX exhibited dose dependent increases in side effects with the 50mg dose."

General

Obstacle Response #26- "I use Celebrex. I'm concerned about the safety profile of VIOXX."

Obstacle Response #34- "I understand the new COX-2 agent, MOBIC, was just approved."

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OBSTACLE RESPONSE GUIDE VIOXX

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Obstacle Response Guide

List of Obstacles

1. "There is no difference between VIOXX and Celebrex. Why should I use VIOXX?"

2. "I can't use VIOXX with patients being treated with methotrexate."

3. "Is VIOXX contraindicated in patients being treated with warfarin?"

3a. I received this letter from Searle about Celebrex and warfarin. What can you tell me about it and VIOXX?

4. "I'm concerned about the potential edema that occurs with VIOXX."

5. "It is my understanding that VIOXX was denied an indication for RA by the FDA."

6. "VIOXX is not an anti-inflammatory drug."

7. "Can VIOXX be used in patients using low dose aspirin?"

8. "I understand that VIOXX has sulfur as part of its chemical structure. Is it contraindicated for patients with "sulfa allergies?"

9. "Why wasn't VIOXX 50 mg studied for longer than five days in acute pain?"

9a. "VIOXX cannot be used for longer than five days when treating patients for acute pain"

10. "Why didn't you compare VIOXX to higher doses of ibuprofen or naproxen sodium for the management of pain?"

11. "When do I prescribe VIOXX 12.5 mg, 25 mg, or 50 mg once daily?"

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12. "Can I use VIOXX in patients with renal impairment?"

13. "Why doesn't VIOXX have a 50 mg tablet?" **DELETED**

14. "How does your price compare to Celebrex and other branded NSAIDs?"

15. "Isn't a 17-hour half-life inconsistent with once daily dosing?"

16. "Since VIOXX is not primarily metabolized by the cytochrome P450 system and that is a benefit for VIOXX, should I be concerned about the fact that COZAAR is metabolized by the P450 system?"

    or

    "How is the CYP450 issue with Celebrex any different from COZAAR?"

17. "Since VIOXX is not primarily metabolized by the cytochrome P450 system and that is a benefit for VIOXX, should I be concerned about the fact that ZOCOR is metabolized by the P450 system?"

    or

    "How is the CYP450 issue with Celebrex any different from ZOCOR?"

18. "The pain studies for VIOXX were not well designed."

19. "What hepatic effects can I expect with VIOXX?"

20. "Can I use VIOXX with ACE inhibitors?"

21. "VIOXX is only comparable to a single dose of naproxen."

22. "I've been told that 45% of VIOXX is metabolized through the cytochrome P450 system."

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23. "I am concerned about the cardiovascular effects of VIOXX."

24. "Your PI states that VIOXX provided a significant reduction in OA pain after one to two weeks. Why should I use VIOXX when Celebrex states OA patients achieved significant reduction in pain within 24-48 hours after initiation of dosing?"

25. "Do I have to discontinue VIOXX pre or post-operatively?"

26. "I use Celebrex. I'm concerned about the safety profile of VIOXX. (Cumulative vs. Additive clarification)

27. "Why are you telling me not to prescribe Celebrex for sulfa-allergic patients when Hyzaar has the same contraindication?"

28. "The two recent JAMA articles showed that Celebrex provided greater reductions in events than VIOXX." OR "It looks like there are still a lot of PUB's in the VIOXX group; why is the reduction only 50% and not 100%?"

29. "I understand Celebrex just received an FDA approval for prevention of cancer. Is VIOXX receiving a similar indication soon?"

30. "Searle/Pfizer just presented me with new data which showed that Celebrex 800mg daily did not exhibit dose dependent increases in side effects compared to the OA and RA doses, and that VIOXX exhibited dose dependent increases in side effects with the 50mg dose."

31. "I am concerned with dose-related increases in hypertension with VIOXX."

32. "Celebrex must be a safer agent. Unlike VIOXX, Celebrex outcomes data did not show any increases in myocardial infarctions or stroke."

33. "Why didn't VIOXX report the p-values for its' OUTCOMES STUDY?" DELETED

34. "I understand the new COX-2 agent, Mobic, was just approved."

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35. "The Mobic representative told me that Mobic is 20% less expensive than VIOXX. I am considering using Mobic due to the cost advantage."

36. "I am impressed with Mobic's tremendous amount of worldwide experience."

37. "The Mobic representative has shown me data from two large-scale studies, the MELISSA and SELECT trials, which emphasized Mobic's GI tolerability. I find these studies very comprehensive and impressive."

38. " The competition has been in my office telling me that the incidence of heart attacks [or cardiovascular events] is greater with VIOXX than Celebrex."

OR

"I just read [or heard] a news story stating that VIOXX has a higher incidence of heart attacks than Celebrex."

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I: There is no difference between VIOXX and Celebrex. Why should I use VIOXX?

Clarify: Doctor, while they both work by inhibiting COX-2, I would like to point out some key clinical areas of distinction that may be important to you and your patients.

INDICATIONS

Once daily VIOXX is indicated for the relief of the signs and symptoms of OA, management of acute pain in adults and treatment of primary dysmenorrhea, representing all of the indications that were submitted to the FDA for approval of VIOXX.

Celecoxib is indicated for the signs and symptoms of OA and RA.

Reference:
A&A Training Program ⇒ Module 5 (NSAIDs)
VIOXX PI ⇒ Indications and Usage (V22)
Celecoxib PI ⇒ Indications and Usage (C23)

CONTRAINDICATIONS

Both VIOXX and celecoxib are contraindicated in patients who are allergic to them, aspirin or other NSAIDs. Once daily VIOXX is not contraindicated in patients with sulfonamide allergies, commonly known as sulfa allergies.

In contrast, celecoxib is contraindicated in patients with allergic-type reactions to sulfonamides. This contraindication is unique to celecoxib, due to its molecular structure, and is **not a class effect**. Sulfonamide allergies are common drug allergies in the US population and allergic reactions can range from mild to more serious.

Once daily VIOXX offers simplicity - simplified prescribing without having to worry about a sulfonamide allergy contraindication.

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Reference:
VIOXX PI ⇒ Contraindication (V23)
Celecoxib PI ⇒ Contraindication (C24)

DOSING
Doctor, VIOXX offers dosing simplicity of one tablet, once daily dosing for all indications – the relief of the signs and symptoms of OA, management of acute pain in adults, and the treatment of primary dysmenorrhea. With celecoxib, each time you see an OA patient you must decide whether to prescribe it once a day or twice a day. VIOXX also offers the option to increase the dose to 25 mg once daily for OA patients who need additional relief. Celecoxib has one dose – 200 mg, and its label states that no additional efficacy is seen with 200 mg BID.

Reference:
VIOXX PI ⇒ Dosage and Administration ⇒ Osteoarthritis (V65) and Management of Acute Pain and Treatment of Primary Dysmenorrhea (V66)
Celecoxib PI ⇒ Dosage and Administration ⇒ Osteoarthritis (C54)

METABOLISM
Once daily VIOXX is metabolized primarily through cytosolic enzymes in the liver. Unlike once daily VIOXX, celecoxib is metabolized through the cytochrome P450 system.

(Remember to provide appropriate balancing information on use in hepatic insufficiency and hepatic effects.)

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Pharmacokinetics ⇒ Metabolism (V7)

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COMPREHENSIVE CLINICAL STUDIES

Once daily VIOXX has been comprehensively studied. In OA patients, once daily VIOXX was compared to diclofenac in two 1-year studies. The endoscopy studies were six-month studies. We have data on serious upper GI events out to one year. This was the most comprehensive clinical program ever run by Merck. Let me share some of the data with you...

- VIOXX demonstrated significantly fewer endoscopic ulcers than ibuprofen and was consistent across all studies.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:

VIOXX PI ⇒ Clinical Studies ⇒ OA (V16)

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2. I can't use VIOXX with patients being treated with methotrexate.

Doctor, once daily VIOXX is not contraindicated in patients receiving methotrexate. No dosage adjustments of once daily VIOXX and no change in the standard monitoring for methotrexate are required for patients taking methotrexate with once daily VIOXX.

If probed further:

- Doctor, according to the product circular for once daily VIOXX, at doses of 75 mg (which is 3 to 6 times the OA therapeutic dose), once daily VIOXX increased plasma concentrations of methotrexate by 23%. At 24 hours post dose or at the trough period, a similar proportion of patients receiving VIOXX or placebo had methotrexate plasma concentrations below the measurable limit. According to the methotrexate label, methotrexate-toxicity is believed to be more dependent on time of exposure rather than peak levels. Again doctor, no dosage adjustments of once daily VIOXX and no change in the standard monitoring for methotrexate are required for patients taking methotrexate with once daily VIOXX.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ Methotrexate (V47)

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Q: Is VIOXX contraindicated in patients being treated with warfarin?

No. Once daily VIOXX is not contraindicated in patients taking warfarin. According to the package insert, when therapy with once daily VIOXX is initiated or changed, patients should be monitored for INR* values, particularly in the first few days. Doctor, as you know, patients on warfarin or similar agents are at an increased risk for GI bleeding when administered concomitantly with an NSAID.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

If further probed, refer to the PI:
In single and multiple-dose studies in healthy individuals receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin. Standard monitoring of INR values should be conducted when therapy with VIOXX is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

Submit a PIR if appropriate.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ Warfarin (V51)

***INR** – International Normalized Ratios. This is a standardized way of measuring the degree of anti-coagulation produced by warfarin.

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3a. I received this letter from Searle about Celebrex and warfarin. What can you tell me about it and VIOXX?

Doctor, for information about celecoxib and warfarin, you should talk to your Searle or Pfizer representative.

However, I can tell you about the concomitant use of VIOXX and warfarin. In single and multiple-dose studies in healthy individuals receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin. Standard monitoring of INR values should be conducted when therapy with VIOXX is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

Finally, doctor, as you know, patients on warfarin or similar agents are at an increased risk for GI bleeding when administered concomitantly with an NSAID.

Submit a PIR if appropriate.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ Warfarin (V51)
VIOXX PI ⇒ Warnings ⇒ GI Effects, 4th paragraph

*INR – International Normalized Ratios. This is a standardized way of measuring the degree of anti-coagulation produced by warfarin.

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"I'm concerned about the potential edema that occurs with VIOXX"

Clarify:
What are your specific concerns regarding edema?

If the physician's concern is the overall incidence of edema with once daily VIOXX, then respond:
Doctor, edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition in the kidney. Clinical trials with once daily VIOXX 12.5 and 25 mg have shown renal effects such as edema similar to those observed with comparator NSAIDs. In these studies, the incidence rates for lower extremity edema were as follows: (In the AE table, point to row on edema under Body As A Whole)

VIOXX 12.5 mg or 25 mg once daily - 3.7%
Ibuprofen 2400 mg – 3.8%
Diclofenac 150 mg –3.4%
Placebo – 1.1%

Also, it is important to note that in these same studies the discontinuation rate due to lower extremity edema was low-0.2%.

NOTE: Use the Renal Card to support this discussion.

If physician is concerned about a dose related increase of edema with once daily VIOXX 50 mg, then respond:

Doctor, edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition in the kidney.

Regarding the safety of once daily VIOXX 50 mg, let me explain where the use of 50 mg is recommended. 50 mg is recommended for use in acute pain in adults and is not recommended for OA. In the analgesia studies, the renal effects of once daily VIOXX – such as edema-were generally similar to comparator NSAIDs.

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The 50 mg dose, while not recommended for OA, has been studied in clinical trials for up to 6 **months** to evaluate the GI safety of VIOXX. In these trials, the incidence of lower extremity edema was 6.3% for 50 mg. In the 6-week to 6-month studies with 12.5 or 25 mg, the incidence of lower extremity edema was 3.7% and the discontinuation rate was low-0.2%. Are you concerned about a 3.7% incidence rate of lower extremity edema in your OA patients?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Adverse Reactions ⇒ OA ⇒ Table and second paragraph (V59)
VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

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5. "It is my understanding that VIOXX was denied an indication for RA by the FDA."

Clarify: Doctor, what is your true concern?

If physician mentions denial of an RA indication, respond:
Doctor, Merck was not denied any indications. Once daily VIOXX is indicated for relief of the signs and symptoms of OA, management of acute pain in adults, and for the treatment of primary dysmenorrhea. These represent all of the indications that Merck submitted to the FDA for the approval of once daily VIOXX.

(Note: If the physician ask specific question regarding the VIOXX GI Outcomes trial, you may provide the PIR with the recent bulletin, in accordance with the instructions in that bulletin, and submit additional PIRs as requested.)

If appropriate, state: Last month when I was in, you stated that the majority of your arthritis patients suffer from OA. I would like for us to discuss how once daily VIOXX could benefit these patients.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

(After close: If you need information on the use of VIOXX in RA, I can submit a PIR.)

If the physician is concerned about the anti-inflammatory effect, see obstacle #6.

Reference:
VIOXX PI ⇒ Indications and Usage (V22)
VIOXX PI ⇒ Clinical Pharmacology ⇒ Mechanism of Action (V3)

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6. "VIOXX is not an anti-inflammatory drug."

Doctor, the Mechanism of Action section of the package insert for once daily VIOXX clearly states: "VIOXX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and anti-pyretic activities in animal models." Once daily VIOXX 12.5 and 25 mg reduced the signs and symptoms of OA as effectively as 2400 mg of ibuprofen. Also, once daily VIOXX produced significant reductions in joint stiffness upon first awakening in the morning. Doctor, as you know, morning stiffness is one indicator of inflammation.

In addition, let me point out that in the label it also states "because of the anti-inflammatory effects of VIOXX, the pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions."

Doctor, would you agree that once daily VIOXX has anti-inflammatory effects?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Mechanism of Action (V3)
VIOXX PI ⇒ Clinical Studies ⇒ OA (V16)
VIOXX PI ⇒ Precautions ⇒ General (V31)

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7. Can VIOXX be used in patients using low-dose aspirin?

There is no contraindication for concomitant use with low-dose aspirin.

Let me share with you the experience we have on the concomitant use of once daily VIOXX and low-dose aspirin. At steady state, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin.

I should also remind you that once daily VIOXX is not a substitute for aspirin for cardiovascular prophylaxis and that concomitant administration of low-dose aspirin with once daily VIOXX may result in an increased risk of GI ulceration or other complications compared with use of once daily VIOXX alone.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ Aspirin (V41)

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3. "I understand that VIOXX has sulfur as part of its chemical structure. Is it contraindicated for patients with "sulfa" allergies?"

No. Doctor, let me show you the contraindications section of the label. Once daily VIOXX is not contraindicated for patients with known sulfonamide allergies, commonly known as "sulfa allergies."

Unlike once daily VIOXX, celecoxib is contraindicated in patients with sulfonamide allergies. Celecoxib contains a sulfonamide group (S-NH_2), which is associated with sulfa allergies. This contraindication is based on the specific chemical structure of celecoxib and is not a class effect. Sulfonamide allergies are common drug allergies in the US population and allergic reactions can range from mild to more serious.

Once daily VIOXX offers simplicity, with no sulfonamide allergy contraindication.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Contraindications (V23)

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Q: "Why wasn't VIOXX 50 mg studied for longer than five days in acute pain?"

To obtain an indication for the management of acute pain in adults, all analgesic drugs are studied in short-term standard pain models as defined by the FDA. The maximum time for these studies for once daily VIOXX was 5 days. However, let me point out that while it is not a recommended dose for OA, once daily VIOXX 50 mg was studied out to 6 months to evaluate GI safety. In these studies, the general safety profile of once daily VIOXX 50 mg was similar to the recommended doses, except for a higher incidence of GI symptoms, lower extremity edema, and hypertension. Also, let me point out that once daily VIOXX is indicated for the treatment of acute pain. The studies that support this acute pain indication lasted up to 5 days. But as I mentioned, while it is not a recommended OA dose, once daily VIOXX 50 mg was studied for up to 6 months in OA patients – so the profile is well defined in the circular.

If further probed: **"But, I'm worried about GI safety long-term."** Doctor, in two identical studies of OA patients receiving once daily VIOXX 25 or 50 mg for up to 24 weeks, once daily VIOXX demonstrated significantly fewer endoscopic ulcers than ibuprofen.

Once daily VIOXX also has GI event data from clinical trials up to one year. Among 3,357 patients who were treated with once daily VIOXX 12.5, 25, and 50 mg in controlled clinical trials of 6-weeks to 1 year, a total number of four patients experienced a serious upper GI event. Two patients experienced an upper GI bleed within 3 months (0.06%); one experienced an obstruction within 6 months; and one experienced an upper GI bleed within 12 months, for a total incidence of 0.12% over 1 year.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Analgesic Studies (V17)
VIOXX PI ⇒ Clinical Studies ⇒ OA (V16)

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Q: VIOXX cannot be used for longer than five days when treating patients for acute pain.

Doctor, that is not what the circular states. The circular states that the recommended initial dose of VIOXX for the management of acute pain and the treatment of primary dysmenorrhea is 50 mg once daily. Subsequent doses should be 50 mg once daily as needed. The use of VIOXX for more than 5 days in the management of pain has not been studied.

Let me explain why these studies were designed this way. To obtain an indication for the management of acute pain in adults, all analgesic drugs are studied in short-term standard pain models as defined by the FDA. The maximum duration of these studies for once daily VIOXX was 5 days.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

If challenged further by the physician:
However, let me also point out that while 50 mg is not a recommended dose for OA, once daily VIOXX 50 mg was studied out to 6 months in OA patients. In these studies, the general safety profile of once daily VIOXX 50 mg was similar to the recommended doses for OA, except for a higher incidence of GI symptoms, lower extremity edema and hypertension.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Indications and Usage (V22)
VIOXX PI ⇒ Dosage and Administration ⇒ Osteoarthritis (V65) and Management of Acute Pain and Treatment of Primary Dysmenorrhea (V66)

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Q: "Why didn't you compare VIOXX to higher doses of ibuprofen or naproxen sodium for the management of pain?"

To obtain an indication for the management of acute pain in adults, a drug must be studied in standard pain models as defined by the FDA. As it states in the ibuprofen PI, in clinical studies using doses of ibuprofen greater than 400mg are no more effective than the 400mg dose in analgesia. Also, the maximum recommended dose of naproxen for analgesia is 550 mg.

- In acute analgesic models of post-orthopedic surgical pain, post-operative dental pain and primary dysmenorrhea, once daily VIOXX relieved pain that was rated by patients as moderate to severe. In post-surgical dental pain studies, the onset of action with a single 50mg dose of once daily VIOXX occurred within 45 minutes.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Analgesia (V17)

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[redacted]

Whether you're treating OA or acute pain, once daily VIOXX is always a simple, one tablet, once daily dose.

12.5 mg or 25 mg once daily for OA

Once daily VIOXX 12.5mg is the starting dose for OA. If a patient requires greater pain relief, you have the flexibility to increase the dose to 25mg once daily at no additional cost to the patient.

50 mg once daily for Acute Pain and Primary Dysmenorrhea

In patients with moderate to severe acute pain, the dose is 50mg once daily. Once daily VIOXX relieved moderate to severe pain following orthopedic surgery, dental surgery and primary dysmenorrhea.

In addition to the simplicity of once daily dosing, once daily VIOXX also adds the flexibility of oral suspension for both strengths.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Dosage and Administration (V65-V67)

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2. Can I use VIOXX in patients with renal impairment?

No dosage adjustment is recommended for patients with mild to moderate renal impairment. Use of once daily VIOXX in patients with advanced renal disease is not recommended because no safety information is available regarding the use of once daily VIOXX in these patients.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Renal Effects (V33)
VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

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"Why doesn't VIOXX have a 50 mg tablet?"

Once daily VIOXX is not offered in a single 50 mg tablet and a dosage of 50mg can be easily achieved by taking two 25 mg tablets.

Transition back to strength, safety and QD simplicity messages.

Reference:
VIOXX PI ⇒ Dosage and Administration (V66)

H1 - How does your price compare to Celebrex and other branded NSAIDs?

Doctor, the catalog price for once daily VIOXX is $2.02 for both 12.5 mg and 25 mg, offering your patients one of the best values available.

The catalog price for celecoxib is $2.38 for 100mg bid and $2.02 for 200 mg qd.

The catalog price for VIOXX 12.5 and 25mg is less expensive than the catalog prices for the usual daily doses of Arthrotec, Relafen, Daypro, and Voltaren.

In addition, the catalog price for the oral suspension of once daily VIOXX is competitive with other NSAIDs at $3.00.

This price comparison does not establish that products have comparable efficacy. These prices reflect direct cost and do not reflect actual costs paid by consumers.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

(For your reference, the average wholesale price (AWP) for once daily VIOXX is $2.42 for both 12.5 mg and 25 mg. AWP for celecoxib is $2.86 for 100 mg BID and $2.42 for 200 mg qd.
AWP for the oral suspension of once daily VIOXX is competitive with other NSAIDs at $3.60.)

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Q: "Isn't a 17 hour half life inconsistent with once daily dosing?"

The 17 hour half-life of once daily VIOXX is entirely consistent with its once daily dosing. In all OA studies, lasting from 6 to 86 weeks with 3900 patients, once daily treatment with VIOXX 12.5 and 25 mg in the morning was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg once daily, the effectiveness of once daily VIOXX was shown to be comparable to ibuprofen 800mg TID and diclofenac 50 mg TID.

If probed further on half life:
Doctor, many drugs with half-lives shorter than 24 hour are effective when dosed once a day, for example Singulair, Prinivil, and Zocor.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Excretion (V8)
VIOXX PI ⇒ Clinical Studies ⇒ OA (V16)
SINGULAIR® PI ⇒ Clinical Pharmacology ⇒ Excretion
PRINIVIL® PI ⇒ Clinical Pharmacology ⇒ Excretion
ZOCOR® PI ⇒ Clinical Pharmacology ⇒ Excretion

[redacted]

or

[redacted]

Doctor, you are correct when you say that COZAAR is metabolized by cytochrome P450 enzymes. COZAAR has been evaluated for safety in more than 3300 patients treated for hypertension. The overall incidence of adverse experiences reported with COZAAR in clinical studies was similar to placebo. No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine, and phenobarbital. COZAAR has been extensively used in clinical practice and clinical study settings for over four years with millions of patients treated. Clinical experience with COZAAR is well documented.

In vitro studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its active metabolite. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

Celecoxib is metabolized by P450 2C9 and is an inhibitor of P450 2D6. The package circular states that the co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. It also states that there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6.

Doctor, let me also note that VIOXX is not primarily metabolized by cytochrome P450 enzymes and is not known to inhibit enzymes of P450.
If you have additional questions regarding the P450 system and/or the implications for the products we discussed, I would be happy to submit a Professional Information Request to our Medical Services Department.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)
COZAAR® PI ⇒ Clinical Pharmacology ⇒ General
COZAAR® PI ⇒ Adverse Reactions
COZAAR® PI ⇒ Precautions ⇒ Drug Interactions
Celecoxib PI ⇒ Precautions ⇒ Drug Interactions ⇒ General (C36)

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"Since VIOXX is not primarily metabolized by the cytochrome P450 system and that is a benefit for VIOXX, should we be concerned about the fact that ZOCOR is metabolized by the P-450 system?"

or

"How is the CYP-450 issue with Celebrex any different from ZOCOR?"

Doctor, you are correct when you say that ZOCOR is metabolized via CYP450. ZOCOR has been extensively used in clinical practice and clinical study settings for over 10 years with millions of patients treated and tens of thousands of patients studied in controlled trials. Clinical experience with ZOCOR is well documented.

For ZOCOR, we know that the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Certain drugs that inhibit this pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. Therefore, physicians contemplating concomitant therapy with ZOCOR and a drug that inhibits the P450 3A4 pathway should carefully weigh the potential benefits and risks of combined therapy and monitor for signs and symptoms of myopathy.

Celecoxib, on the other hand, is metabolized by P450 2C9 and is an inhibitor of P450 2D6. The package circular states that the co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. It also states that there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6.

Doctor, let me also note that VIOXX is not primarily metabolized by the P450 system and is not known to inhibit the P450 system.

If you have additional questions regarding the P450 system and/or the implications for the products we discussed, I would be happy to submit a Professional Information Request to our Medical Services Department.

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Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)
ZOCOR® PI ⇒ Warnings ⇒ Myopathy caused by drug interactions
Celecoxib PI ⇒ Clinical Pharmacology ⇒ Metabolism (C8)

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18. "The pain studies for VIOXX were not well designed."

Clarify: Which pain study are you referring to and why do you feel it was not well designed?

- **If the physician is concerned about the head-to-head study comparing VIOXX to Celebrex, offer to submit a PIR.**

- **If the physician is concerned because VIOXX was compared to 400 mg Ibuprofen, use the response offered in obstacle #10 in the Obstacle Response Guide and respond:**

To obtain an indication for the management of acute pain in adults, a drug must be studied in standard pain models as defined by the FDA. As it states in the ibuprofen PI, in clinical studies using doses of ibuprofen greater than 400mg are no more effective than the 400 mg dose in analgesia. Also, the maximum recommended dose of naproxen for analgesia is 550 mg.

In acute analgesic models of post-orthopedic surgical pain, post-operative dental pain and primary dysmenorrhea, once daily VIOXX relieved pain that was rated by patients as moderate to severe. In post-surgical dental pain studies, the onset of action with a single 50mg dose of once daily VIOXX occurred within 45 minutes.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Analgesia (V17)

- **If the physician is concerned about the different dosing regimens, respond:**

Doctor, this is a single dose model. It is a standard model designed to assess the analgesic effect of an agent. It was not designed to compare the dosing regimens of the agents, in this

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instance, once daily VIOXX versus 3 times a day Ibuprofen or twice daily naproxen. However, it does demonstrate the relative efficacy of the two agents on onset of action, peak effect, and total pain relief over 8 hours. On the measures, once daily VIOXX was generally similar to the comparator NSAIDs.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Analgesia (V17)

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What hepatic effects can I expect with VIOXX?

Clarify: What specific hepatic effects are you concerned about?

If physician is concerned about liver function testing (LFTs), respond:
In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking once daily VIOXX 12.5 or 25 mg and 0.1% of patients taking placebo had notable elevations of ALT or AST. A patient who has an abnormal liver test while on once daily VIOXX should be monitored carefully for evidence of a more severe hepatic reaction.

Use of VIOXX is not recommended in patients with moderate or severe hepatic insufficiency.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Hepatic Effects (V32)

If physician is concerned about metabolism, respond:
Doctor, metabolism of once daily VIOXX is primarily mediated through reduction by cystolic enzymes in the liver. It is not primarily metabolized by the P450 system and is not known to inhibit the P450 system in the liver.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)

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20. "Can I use VIOXX with ACE inhibitors?"

Doctor, as stated in the prescribing information, once daily VIOXX can be used concomitantly with ACE inhibitors. All NSAIDs may diminish the antihypertensive effect of ACE inhibitors. The prescribing information for once daily VIOXX states "In patients with mild to moderate hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mm Hg compared to ACE inhibitor alone." Remember, all NSAIDs may diminish the antihypertensive effect of ACE inhibitors. Therefore, this effect is not unique to VIOXX.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ ACE inhibitors (V40)

24. "VIOXX is only comparable to a single dose of naproxen?"

Clarify:
Doctor, why do you say that?

If the physician replies "It states in your product circular that VIOXX 50mg once daily was comparable to naproxen 550mg. This would seem to indicate that you are not comparable to 550mg bid," then respond:

Doctor, that statement is derived from single dose studies and is not intended to compare or draw conclusions about the efficacy of VIOXX or Anaprox over a 24 hour period. It was not designed to compare the dosing regimens of the agents. The single dose analgesia study was designed to compare time of onset, peak effect and total pain relief over 8 hours. In OA studies, once daily VIOXX 12.5mg and 25mg were comparable to ibuprofen 800mg tid and diclofenac 50mg tid. In each study, both 12.5mg and 25mg of VIOXX once daily were comparable to the comparator NSAIDs. Would you agree that 800 mg of ibuprofen tid and 50 mg of diclofenac tid were good NSAID comparators to demonstrate the efficacy of once daily VIOXX in OA over a full 24 hours? Will you try once daily VIOXX in your acute pain and OA patients?

If the physician replies "You only compared yourself to 550mg of naproxen in your pain studies" refer to the obstacle "The pain studies for VIOXX were not well designed" in the Obstacle Response Guide, #18.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

For Representatives background, naproxen sodium is Anaprox, and naproxen is Naprosyn.

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2. I have been told that 14% of VIOXX is metabolized through the cytochrome P450 system.

I would like to clarify that in general, once daily VIOXX is metabolized primarily through reduction by cytosolic enzymes in the liver, not primarily through the P450 system. Cytochrome P450 plays a minor role in the metabolism of once daily VIOXX.
The inhibition of P450 3A4 activity by administration of ketoconazole 400 mg daily did not affect the disposition of VIOXX. However, induction of general hepatic activity by administration of the non-specific inducer rifampin 600 mg daily produced a 50% decrease in VIOXX plasma concentrations.

If you are interested in further information on the metabolism of once daily VIOXX, I'd be happy to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)

Background Information
Cytochrome P450: Inhibition and Induction (referenced from the Analgesic and Anti-Inflammatory Training Program, Module 5, pages 31-32).

Inhibition
Inhibition of specific CYP450 enzymes can also affect the conversion of a drug to its active metabolite. Significant drug interactions may occur when NSAIDs that are metabolized through the CYP450 system are administered together with drugs that inhibit enzymes of the CYP450 systems. Concomitant administration of a drug with a known inhibitor of cytochrome P450 enzymes can alter the relative amounts of parent and metabolite that end up in the general circulation. For example, concomitant administration of fluconazole, a known inhibitor of CYP2C9, and celecoxib results in an increase in

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celecoxib plasma concentrations due to the inhibition of celecoxib metabolism via CYP2C9 by fluconazole.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by CYP2D6. Some examples of drugs that are metabolized by CYP2D6 are certain antidepressants (e.g., tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs), antipsychotics (e.g., haloperidol), and narcotics (e.g., codeine). Coadministration of these agents with celecoxib may result in increased serum concentrations of these drugs.

Induction

Drug-drug interactions can also occur when one drug induces the metabolism of another by increasing the synthesis or reducing the degradation of CYP450 enzymes, as shown in Figure 13. In this case, the clearance of the drug will be increased and the pharmacological effects decreased. Increased synthesis of CYP450 protein (which leads to an increase in CYP450) activity) can be associated with exposure to certain drugs or environmental agents. Enzyme induction can lead to an increased rate of drug metabolism and corresponding decreases in the availability of the parent drug. For example, indinavir is metabolized by CYP3A4. Therefore, the drug rifampin, a potent inducer of CYP3A4, should not be co-administered because it may lead to markedly diminished plasma concentrations of indinavir.

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"I am concerned about the cardiovascular effects of VIOXX."

Clarify:
What is your specific concern?

The physician may respond:
(A) "I am hesitant to use VIOXX in my patients because it may worsen CHF," or
(B) "VIOXX has the potential to increase the risk of MI."

Response to (A) "I am hesitant to use VIOXX in my patients because it may worsen CHF."
Doctor, as you know, there are precautions you should take when prescribing any NSAID for your patients with CHF. Because once daily VIOXX® is an NSAID, you should consider taking these same precautions when considering the use of once daily VIOXX® for this specific patient population.

Clinical trials with once daily VIOXX® 12.5 mg and 25 mg have shown renal effects such as hypertension and lower extremity edema similar to those observed with comparator NSAIDs. VIOXX® should be used with caution and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or edema.

(NOTE: If the physician asks about concomitant use with ACEIs, refer to Obstacle Response No. 20.)

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Renal Effects (V33)
VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

Response to (B) "VIOXX increases the risk of MI."

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Doctor, once daily VIOXX has no effect on platelet aggregation, and therefore would not be expected to demonstrate reductions in MI or other CV events. Agents such as low-dose aspirin are routinely prescribed for CV patients for their effect on the inhibition of platelet aggregation. Therefore, once daily VIOXX® is not a substitute for aspirin for cardiovascular prophylaxis. However, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low dose (81 mg daily) aspirin when the two were given together.

(Refer to Obstacle Response No. 7.)

If probed further:
Offer to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Aspirin (V41)

24. Your PI states that VIOXX provides a significant reduction in OA pain after one to two weeks. Why should I use VIOXX when Celebrex states OA patients achieved significant reduction of pain within 24-48 hours after initiation of dosing?

Doctor, it is important to note that the time period you refer to, 1 to 2 weeks, was the predetermined initial time intervals in the study at which pain relief was measured. Patient's pain relief was simply not assessed earlier than that by design. The objective of these trials (up to one year) was to evaluate study endpoints over the course of the trial-not onset of action. These were not studies of onset of action

If you would like specific information on the onset of action of once daily VIOXX in acute pain, let's look at the comparison to naproxen sodium (Anaprox) in dental pain which showed an onset of action of VIOXX 50 mg within 45 minutes.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI⇒Clinical Studies PI⇒OA (V16)
VIOXX PI⇒Clinical Pharmacology ⇒ Pharmacokinetics ⇒ Absorption (V4)
VIOXX PI⇒Clinical Studies□Analgesia, including Dysmenorrhea (V17)
Celecoxib PI⇒ Clinical Pharmacology ⇒ Pharmacokinetics ⇒ Absorption (C4)

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Q: Do I have to discontinue VIOXX pre or post-operatively?

Clarify: Dr. what specifically is your concern?

If the concern is with bleeding time (pre and post-operatively), respond:
Once daily VIOXX® has not been studied in a pre-operative setting. I cannot make a recommendation regarding pre-operative use.

In studies of healthy volunteers who had not undergone surgery, at multiple doses of up to 375 mg daily up to 12 days, VIOXX® had no effect on bleed time relative to placebo. Similarly, bleeding time was not altered in a single dose study with 500 or 1000mg of VIOXX®.

Additionally, VIOXX® 50 mg has shown no effect on platelet aggregation. Also, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low dose (81 mg daily) aspirin when the two were given together.

If requesting further information, please submit a request.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

If the concern is the management of acute pain, post-operatively, respond:
In order to obtain an acute pain indication, VIOXX® was demonstrated to provide effective pain relief in 3 acute pain models.

Two of the pain models involved surgery – the post-orthopedic surgical model and the post-operative dental pain model. The post-orthopedic surgery studies involved patients with knee or hip replacement. Patients received their first dose of VIOXX®, on average, 46 hours after surgical procedure (range 17 to 97 hours). In our acute dental pain study, VIOXX® provided onset of pain relief within 45 minutes.

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Dr., in contrast, Celebrex is not indicated for the management of acute pain.

If further information is requested, offer to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Platelets (V21)

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26. I use Celebrex. I'm concerned about the safety profile of VIOXX.

Clarify:
Doctor, specifically what safety concerns are you referring to?

If the physicians' concern is renal safety or edema:
Refer to obstacle # 12, 4

If the physicians' concern relates to hepatic effects or cardiovascular safety:
Refer to obstacle # 19,23

If the physicians' concern is whether the rate of ulcers increases over time when treating patients with VIOXX, respond with the following:

Doctor, in order to address your concerns, I would like to discuss the extensive GI endoscopy program that has been conducted for VIOXX®. In two identical, large trials, the **cumulative** incidence of ulcers with patients taking VIOXX 25 mg and 50 mg once daily (2 to 4X the dose used for osteoarthritis) was studied. The results with VIOXX showed significantly fewer endoscopic ulcers than with ibuprofen 2400 mg at weeks12 and 24. (Refer to VIOXX® PI, Clinical Trials.)

Doctor, I would like to bring to your attention a few important factors regarding our endoscopy study design:

First, "cumulative rates" include all patients who develop an ulcer up to a specified point in time. In other words, the rates shown at week 24 include all endoscopic ulcers detected by week 12 and all endoscopic ulcers detected between weeks 12 and 24. This method assures that patients developing ulcers at any time during the study are represented in the overall risk assessment.
As noted in the attached Laine reprint (page 780, second full paragraph), when referencing the endoscopy trials for VIOXX®,

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"Ulcer rates in the first 3 months of the study were not significantly different compared to the second three months in the rofecoxib groups or in the ibuprofen groups (4.1% vs. 5.5% in the 25 mg rofecoxib group, 7.3% vs. 7.4% in the rofecoxib 50 mg group, and 27.7% vs. 18.2% in the ibuprofen group)". Please refer to the Important Considerations for Endoscopy Studies as noted in the detail aid.

Please provide appropriate and referenced balancing throughout product discussions with healthcare professionals.

Note: We have heard reports from the field that Searle/Pfizer representatives are describing the results as "additive rates". Additive rates evaluate an increase over a specified period of time and make assumptions that rates continue to increase by the same rate into the future.

The rates reported in this study are <u>not</u> additive rates.

2. Why are you telling me not to prescribe Celebrex for sulfa-allergic patients when Hyzaar has the same contraindication?

Dr., I can appreciate your concern. Let me clarify Merck's view of this and every other contraindication for our product.

The fact remains that a contraindication is just that – a contraindication. At no time will Merck ever suggest that you prescribe an agent to a patient who is contraindicated for its use.

> As you know, use of hydrochlorothiazide in patients who are allergic to sulfonamides is contraindicated. Hyzaar, which is losartan plus hydrochlorothiazide, is contraindicated for use in patients with hypersensitivity to other sulfonamide-derived drugs. However, losartan, (Cozaar) alone is not contraindicated in these patients. We do not, have not, and never will recommend the use of Hyzaar for patients who have sulfonamide allergies. Cozaar is not contraindicated for patients who have a sulfonamide allergy and can be prescribed for these patients who need control of their BP.

Regarding the Coxib class, **VIOXX does not have a contraindication for sulfonamide allergic patients** – Celebrex does.

(Note: If you have not already discussed Cozaar/Hyzaar with this physician on this call, take the opportunity to initiate a discussion regarding these products after you close your product discussion for VIOXX. One suggested transition may be, "Just as we have discussed appropriate patients to prescribe VIOXX for, I'd like to discuss appropriate patients for therapy with Cozaar, Hyzaar 50/12.5 and Hyzaar 100/25...")

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26. "The two recent JAMA articles showed Celebrex provided greater reductions in events than VIOXX." Or "It looks like there are still a lot of PUB's in the VIOXX group. Why is the reduction only 50% and not 100%?"

Note: Physician is referring to the JAMA article, November 24, 1999 issue, Volume 282, No. 20

Representative Response:

Actually those were different types of studies. **(See below or in the cover bulletin for background information)**

The JAMA article on VIOXX is a combined analysis of PUBs, **P**erforation, symptomatic **U**lcers and **B**leeds from all 8 double bind, randomized phase 2b/3 OA trials. The Celebrex article, which is the information currently contained in their PI, is a prospective endoscopy trial with Celebrex, comparator NSAIDs and placebo. This is similar to the study I have been discussing with you from our package circular, which compares VIOXX to Ibuprofen, and placebo. The JAMA study on VIOXX was designed to compare VIOXX to the comparator NSAIDS, not placebo. No one knows what the background rate of PUBs in patients treated with placebo would be, but we know it is not zero.
It would be inaccurate to compare the JAMA articles on VIOXX and Celebrex because the endpoints (ulcers detected on surveillance endoscopy versus clinically significant events) are entirely different. Until head to head comparative trials are designed and completed, no conclusions can be drawn regarding relative GI safety between these agents.

Additional studies will need to be conducted to further support these conclusions. As stated in the VIOXX package insert (under the 044 endoscopy data), "the correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established."

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However, I can share with you information for VIOXX from our endoscopy trials. These results are listed in our package circular, in our detail aids and most recently were published in Gastroenterology. The lead author of the study was Dr. Loren Laine. Among 742 OA patients without ulcers on baseline endoscopy, the cumulative incidence of gastroduodenal ulcers $\geq$ 3mm with VIOXX (25 mg or 50 mg) was significantly ($p<0.001$) lower than ibuprofen.
Also, in controlled clinical trials summarized in our promotional literature, among 3357 patients who were treated with VIOXX 12.5 mg, 25 mg, and 50 mg, only (POB data):

- 2 of 3357 (0.06%) patients experienced a serious Clinical Upper GI event in the first 3 months
- and 4 of 3357 patients cumulative (0.12%) experienced a serious Clinical Upper GI event in the first 12 months.

Transition back to Laine reprint or detail aid to further discuss results with VIOXX and deliver Top 5 messages, provide appropriate balance and close the call.

Remember that you may not discuss or provide the JAMA article to your physicians. You must submit a PIR to address any additional concerns.

Background Information:

It is critical to understand the differences in the types of analyses that have been performed in the studies that are now being published in JAMA and Gastroenterology. Merck and Searle have both performed endoscopy studies comparing VIOXX® and celecoxib to NSAIDs. Both companies also have data from their combined clinical trials in their PIs describing what are termed "serious" upper GI events (Perforations, Obstructions and Bleeds, or POBs). These events are found during the course of clinical treatment, NOT during a scheduled endoscopy. In addition, Merck has just

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published in JAMA the results of a PUB (Perforations, symptomatic Ulcers and Bleeds) analysis, data which is not in the PI for VIOXX®.

The first type of analysis is the endoscopy study. In this study patients are randomized to study drugs (or placebo) and undergo scheduled endoscopies (in the VIOXX® trials these were at baseline 6, 12, and 24 weeks). Ulcers that are seen through the endoscope are measured and counted. This provides a basis for comparing the effect of drugs on the gastric mucosa and is seen as a surrogate for clinically significant events, even if the ulcers seen are not symptomatic and do not actually lead to bleeding or other complications. This is the type of analysis done in the Laine paper published in Gastroenterology and the Searle paper in JAMA, data in the PIs for both VIOXX® and celecoxib.

It is sometimes considered more clinically relevant to compare drugs based on the number of clinical events that occur. Thus the second type of analysis is done, looking at events that occur during the trials. These occur at much lower rates than endoscopically visualized ulcers, so it requires many more patients to see any differences between drugs. Merck chose to measure PUBs (perforations, ulcers and bleeds) while the clinical event data in the PIs for VIOXX® and celecoxib measured POBs (perforations, obstructions and bleeds). The primary difference between these is the U – Ulcers that present due to clinical signs or symptoms. In the Merck JAMA paper, if any patient underwent endoscopy for cause (that is, the patient demonstrated symptoms that the physician judged worthy of follow-up) and ulcers were detected, these were included as events, along with the POBs. This explains why the rates of POBs in the PIs for celecoxib and VIOXX® are lower than the PUB rates shown in the JAMA paper on VIOXX®.

29. "I understand Celebrex just received an FDA approval for prevention of cancer. Is VIOXX receiving a similar indication soon?"

Doctor, it would have been great news for patients if Celebrex received an indication to prevent cancer, but what Celebrex actually received was an indication for a rare genetic disorder, familial adenomatous polyposis (FAP).

The indication is:

> "to reduce the number of adenomatous polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care". The indication further states, "It is not know whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients." The label also states that "treatment with Celebrex in FAP has not been shown to reduce the risk gastrointestinal cancer or the need for prophylactic colectomy or other FAP –related surgeries."

If pressed about whether Merck is conducting studies state,

"Doctor, I am not permitted to discuss uses that not included in the labeling for VIOXX. If you would like, I can submit a request for information to our medical services department."

Transition back to the HI COXIB or HI NSAID messages for VIOXX using the following statement, "So you can see, doctor, this is a new indication for a very rare disorder. Let's discuss much more common disorder-OA."

[redacted]

Note: You may have to probe to uncover the real obstacle. It may be presented as one of the following:

- Celebrex is now proven to be safer than VIOXX.
- Celebrex is a safer agent.
- Are there safety issues with VIOXX?

CLARIFY FIRST:

"Doctor, what is your concern regarding VIOXX? Is there a particular area of concern you want to discuss?"

RESOLVE

Doctor, Searle/Pfizer may be using their new FAP data to suggest that Celebrex 400mg bid, the dose used in the FAP studies, had an adverse event profile "*similar to that reported for patients in arthritis controlled trials*". It is important to realize that the FAP study included 83 patients, who were generally younger and otherwise healthy. This is a population very different from the patient population of OA studies.

It is important to realize that VIOXX 50mg is the recommended dose for acute pain or analgesia, and not a recommended dose for OA. In fact, our product circular states,

> *"Approximately one thousand patients were treated with VIOXX in analgesia studies. The adverse experience profile in the*

analgesia studies was generally similar to those reported in the osteoarthritis studies."

Doctor, what this means is that when the 50mg dose was used in analgesia studies, it had a similar adverse experience profile as that which was seen with VIOXX 12.5 and 25mg in osteoarthritis studies.

If the doctor refers to the increased incidence of edema or hypertension listed under the Adverse Experiences table:

Doctor, the data that you are referring to are from the use of VIOXX 50mg in two, 6-month, OA, endoscopy trials, which evaluated the GI safety of VIOXX. VIOXX 50mg is not a recommended dose for the treatment of OA, but was used in these studies to determine GI safety. VIOXX, at both 25 and 50mg doses, yielded significantly fewer endoscopic ulcers than ibuprofen. Let me reiterate that in analgesia studies with VIOXX 50mg, the incidence of hypertension and edema was similar to that reported in the OA studies with VIOXX12.5 and 25mg.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

Clarify:

Doctor, what has led to your concern that VIOXX causes dose-related increases in hypertension?

Resolve:

Doctor, according to the product circular for VIOXX, the incidence of hypertension reported in OA studies, regardless of causality, was 3.5% with the 12.5 or 25mg dose. For patients who were treated with VIOXX 50mg in analgesia studies, the VIOXX product circular states,

> *"Approximately one thousand patients were treated with VIOXX in analgesia studies. The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies."*

Doctor, what this means is that when the 50mg dose was used in analgesia studies, it had a similar adverse experience profile as that which was seen with VIOXX 12.5 and 25mg in OA studies. VIOXX 50mg is not a recommended dose for OA.

If the doctor refers to the increased incidence of hypertension listed under the Adverse Experiences table:

Doctor, the data that you are referring to is from the 6-month, OA, endoscopy trials, which were used to evaluate the GI safety of VIOXX. VIOXX 50mg is not a recommended dose for the treatment of OA, but was used in these studies to evaluate GI safety. VIOXX, at both 25 and 50mg doses yielded significantly fewer endoscopic

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ulcers than ibuprofen. Let me reiterate that in analgesia studies with VIOXX 50mg, the incidence of hypertension was similar to that reported in the OA studies with VIOXX 12.5 and 25mg.

Doctor, have I addressed your concern with dose-related increases in hypertension with VIOXX?
Now let's talk about the benefits VIOXX offers you and your patients in the treatment of OA and acute pain.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

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The design of the studies differed in a number of significant respects and therefore the results of the two studies cannot be compared. So, let me tell you about the data for VIOXX from our OA clinical trials at the 12.5 mg and 25 mg doses.

In an extensive review of all of our Phase III OA clinical trials, VIOXX did not show an increase in the incidence of thromboembolic events compared to placebo or the comparator NSAIDS.

You can feel confident that Merck has conducted OA clinical trials for VIOXX 12.5mg and 25mg daily in over 3600 patients with OA; approximately 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for one year or longer. These trials included a placebo arm in the six week studies and two comparator NSAIDS, ibuprofen 2400 mg and diclofenac 150 mg daily. VIOXX 12.5mg and 25mg has shown to provide OA pain relief all day, all night and into the next morning.

Referring to the Adverse Events data, as listed in the package insert for VIOXX 12.5 mg and 25mg daily, the only Cardiovascular System adverse event experienced as occuring over 2% (in trials of six-weeks to six-months) was hypertension at **3.7 %** vs. comparators of ibuprofen 2400 mg daily at **3.0%** and diclofenac 150 mg daily at **1.6%.** In addition, stroke and MI each occurred in less than 0.1% of patients taking VIOXX in our OA clinical program.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Note: If the physician has questions regarding the hypertension & edema rates for VIOXX, please refer to obstacles #19 & #12. Also, the Renal Card (OAN #001962(1)) is an excellent resource that has been developed to directly address issues pertaining to hypertension & edema.

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~~38. Why didn't VIOXX report the p-values for its OUTCOMES STUDY?~~

Merck announced only preliminary results of the VIOXX OUTCOMES study. Data analysis is on-going. The final results with corresponding p-values and incidence rates will be presented later this year.

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34. I understand that the new COX-2 agent, Mobic, was just approved.

Doctor, Mobic is a non-steroidal anti-inflammatory drug – an NSAID – that inhibits both COX-1 and COX-2 at its therapeutic doses. It does not selectively inhibit COX-2.

If the doctor continues and asks how Mobic differs from VIOXX, respond:

> Doctor, VIOXX is indicated for the signs and symptoms of OA, acute pain in adults, and primary dysmenorrhea. Mobic is indicated for OA. VIOXX is available in three tablet strengths, 12.5 mg, 25 mg, and 50 mg, which allows you to prescribe VIOXX one tablet, once daily for all indications. Mobic is available in a 7.5 mg tablet; to increase the dose requires two 7.5 mg tablets. Finally, the two OA doses of VIOXX – 12.5 mg and 25 mg – are priced the same. The highest dose of Mobic is twice as expensive as the lowest dose because patients must take two tablets.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Alternatively, if the doctor continues and asks how Mobic's mechanism of action that you just explained differs from that of VIOXX, respond:

> Doctor, VIOXX is an NSAID that inhibits COX-2 without inhibiting COX-1 at therapeutic doses. Of course, Doctor, we would not recommend that you base your prescribing decision on the mechanism of action of the drug. Can I take a minute and share with you the clinical data on the Strength, Safety, and QD Simplicity of VIOXX?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

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"The MOBIC representative told me that MOBIC is 20% less expensive than VIOXX. I am considering using MOBIC due to the cost advantage."

Doctor, if cost is your reason for considering Mobic, let me point out that Mobic is available only in a 7.5mg tablet. That means that if you need to increase your patients dose to 15mg, the maximum recommended dose for OA, your patients cost will double. In contrast, VIOXX 12.5 and 25 mg tablets are flat priced so you can select the appropriate dose for your OA patients without regard to cost.

Let me share with you the benefits that VIOXX can provide for you and your patients.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

36. I am impressed with MOBIC's tremendous amount of worldwide experience.

Doctor, I can understand that experience with a medication is very important to you. The most valuable experience is not just what has happened abroad, but the clinical experience that you and your colleagues have developed on your own. What has been your experience with VIOXX over the last year? Have you been satisfied with your clinical experience using VIOXX over the last year?

In the last year, VIOXX has achieved a vast amount of clinical experience among many specialties-Rheumatologists, Orthopedic Surgeons, Gastroenterologists, Internists, and Primary Care Physicians. VIOXX has become second most prescribed branded NSAID in the U.S. in less than one year. Is this the kind of experience that is important to you?

Not only has VIOXX developed a tremendous amount of clinical experience within the U.S., but VIOXX has been extensively studied in clinical trials. Let me share some data with you demonstrating the safety and efficacy of VIOXX.

Transition back to the HI COXIB or HI NSAID messages for VIOXX. Be sure to emphasize the data within your Core Visual Aid as you deliver these messages. Focus on the number of patients within each study and the benefit which the results present for the doctor's patient.

Remember to provide appropriate balancing information as part of all product discussions.

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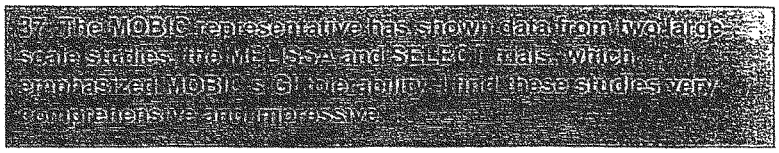


Doctor, I can understand that when choosing a medication to treat your OA patients, you would want to choose a medication with a well documented GI safety and tolerability profile.

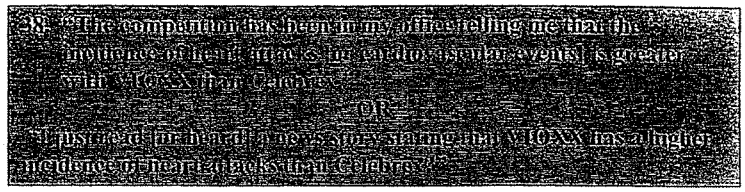
Doctor, the studies which you're referring to are not reflected in the prescribing information for MOBIC. I believe that those studies only lasted 28 days, did not include endoscopic data, and only included the 7.5mg dose of MOBIC.

Let me remind you of the extensive GI data available for VIOXX. In two studies involving over 1500 patients, VIOXX demonstrated significantly fewer endoscopic ulcers than ibuprofen and was consistent across all studies. These studies lasted 6 months, and the incidence rate of ulcers in groups receiving VIOXX did not increase over time. These studies were done with the 25mg and 50mg dose of VIOXX, although I want to remind you that the 25mg dose is the maximum recommended dose for chronic OA.

Does the duration and inclusion of endoscopy data in the VIOXX studies cause you to be more impressed with the data for VIOXX than that of MOBIC?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.



Doctor, there are no head-to-head studies comparing the cardiovascular profile of the two drugs. As a result, you cannot compare the drugs and conclude that one drug had fewer events than the other. What you may be referring to is press reports of the incidence rates in two separate studies. In the VIOXX GI Outcomes Trial (VIGOR), the incidence of MI was 0.4% with VIOXX and 0.1% with naproxen. Upon further analysis, four percent of patients in the VIOXX GI Outcomes Study had experienced a cardiac event such as a heart attack or stroke before entering the study and thus met the established criteria for the use of aspirin for secondary CV prophylaxis. In the remaining 96% of patients for whom aspirin was not indicated for secondary CV prophylaxis, the incidence of MI was lower—0.2% for VIOXX and 0.1% for naproxen. This difference was not statistically significant.

In a separate GI outcomes trial of Celebrex, the CLASS study, Searle has reported that the incidence of MI was 0.5% with Celebrex, 0.3% with diclofenac, and 0.5% with ibuprofen. They also presented data for patients who were not prescribed aspirin. In this group, the incidence of MI was 0.2% for Celebrex and 0.1% for the comparator NSAIDs Again, doctor, I want to emphasize that the results of two different studies can't be compared, and that's particularly true here when you have studies of differing duration and in different patient populations.

If needed, continue to address the physicians concerns with the cardiovascular effects of VIOXX by guiding them through the Cardiovascular Card as outlined in Roadmap for the CV Card.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

NOTE: There will be an additional PIR to address these issues available shortly.

If the doctor asks you further for the incidence of MI from the OA studies presented in the package insert for VIOXX tell them,

In the clinical OA trials for VIOXX reported in our package insert, the incidence of MI was less than 0.1% with VIOXX.

If needed, continue to address the physicians concerns with the cardiovascular effects of VIOXX by guiding them through the Cardiovascular Card as outlined in Roadmap for the CV Card.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 53

Journal of the American College of Cardiology
© 2002 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 39, No. 3, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(01)01749-1

PERSPECTIVE

Why Do Cyclo-Oxygenase-2 Inhibitors Cause Cardiovascular Events?

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This report confirms evidence that selective nonsteroidal anti-inflammatory drugs (NSAIDs), such as celecoxib, can lead to thrombotic cardiovascular events. Aspirin, a nonselective COX-1 (cyclo-oxygenase) and COX-2 inhibitor may result in gastric toxicity. For this reason, selective COX-2 inhibitors have been developed to reduce erosion of the gastric mucosa. Both selective and nonselective NSAIDs reduce prostacyclin formation in the infarcted heart; they accomplish this by tipping the balance of prostacyclin/thromboxane in favor of thromboxane, a prothrombotic eicosanoid. The relative increase in thromboxane, coupled with a diminution in prostacyclin in infarcted heart muscle, can lead to the development of thrombotic cardiovascular events. This may be prevented by the addition of a nitric oxide donor to NSAIDs. (J Am Coll Cardiol 2002;39:521–2) © 2002 by the American College of Cardiology

Cyclo-oxygenase (COX) or prostaglandin endoperoxidase H synthase inhibitors are important contributors to the treatment of arthritis and other inflammatory conditions. Cyclo-oxygenases catalyze the conversion of arachidonic acid and O_2 to PGH_2, the committed step in prostanoid synthesis (1). The two isoenzymes, COX-1 and COX-2, are encoded by separate genes located on different chromosomes. The COX-2 expression can be induced through multiple signaling pathways involving protein kinases A and C, tyrosine kinases and bacterial endotoxin, among others (1). Both isoenzymes are homodimeric, heme-containing glycosylated proteins with two catalytic sites (1). They are targets of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs); aspirin, a nonselective NSAID, acts via COX-1 to inhibit platelet thromboxane A_2 formation and, therefore, lowers mortality from ischemic heart disease (1). Inhibition of COX-2 reduces inflammation, fever and probably colon cancer (2,3). Covalent modifications of COX enzymes by aspirin cause permanent inactivation of the enzyme (1). Because of their anti-inflammatory action, COX inhibitors have been selected for long-term treatment of inflammatory conditions. The COX-2 inhibitors predispose to erosion of the gastric mucosa with subsequent hemorrhage. Both COX-2 selective and nonselective COX inhibitors cause renal toxicity with papillary necrosis and interstitial nephritis (4).

Recently, Mukherjee et al. (5) analyzed clinical trials dealing with the effect of celecoxib and rofecoxib, two selective COX-2 inhibitors, on cardiovascular events. They concluded that these two inhibitors are responsible for a significant risk of cardiovascular thrombotic events. Based on one of the clinical trials (Vioxx Gastrointestinal Outcomes Research), they showed that the relative risk of developing thrombotic cardiovascular events such as myocardial infarction or unstable angina was high as compared to naproxen, a nonselective COX inhibitor (5). The investigators conclude that COX-2 inhibition favors prothrombotic events by tipping the balance of prostacyclin/thromboxane in favor of thromboxane, a prethrombotic eicosanoid (5). Experimental data have confirmed these conclusions.

The release of prostaglandins from ischemic tissue was first demonstrated by McGiff et al. (6). The heart metabolizes arachidonic acid into different prostaglandins (7), particularly prostacyclin (8). An increase in prostaglandins in canine coronary venous blood occurs during postocclusive reactive hyperemia (9). Acute myocardial ischemia not only increases prostacyclin but also thromboxane in coronary vein blood (10). Prostacyclin increases in microsomes prepared from infarcted myocardium (10). It is likely that macrophages are the main source of prostaglandins and thromboxane (11). Production of prostacyclin and thromboxane by the infarcted heart in situ occurs in conjunction with increased activation of the inducible form of nitric oxide-synthase (iNOS) (12). The induction of iNOS in the ischemic rabbit and human heart increases the coronary arterial-venous coronary difference of NO_2 and NO_3 (NO_x). Activation of iNOS occurs primarily by activated macrophages during the inflammatory phase (12).

Both nitric oxide (NO) and prostaglandins play an important role in the infarcted heart (2). Prostacyclin is a vasodilator that prevents cardiac arrhythmias and platelet aggregation; thromboxane, in contrast, promotes platelet aggregation, acts as a vasoconstrictor and initiates ventricular arrhythmias (2). Nitric oxide counteracts thromboxane, inhibits platelet aggregation and compensates for the NSAIDs' induced reduction of prostacyclin (2). Production

From the Huntington Medical Research Institutes, Department of Experimental Cardiology, Pasadena, California. This work was supported by grants from the Charles S. and Carmen DeMora Hale Foundation, the Patron Saint Foundation and the Ann Peppers Foundation.

Manuscript received October 11, 2001; accepted November 2, 2001.

Abbreviations and Acronyms
COX = cyclo-oxygenase
iNOS = inducible form of nitric oxide-synthase
NO = nitric oxide
NSAID = nonsteroidal anti-inflammatory drug

of thromboxane and prostacyclin in the infarcted rabbit heart has been confirmed together with increased upgrading of iNOS (9). The interaction between COX and iNOS is due to an iron-heme center as the active site of COX (9). Exogenous NO, together with cytokine-induced NO, enhances both COX isoenzymes (9). Upgrading of COX-2 protein by cytokines is also accomplished by NSAIDs. This action differs from upgrading by inflammatory cytokines, which increase COX at the transcriptional levels (13).

Recently, we obtained evidence of changes in the prostacyclin/thromboxane ratio after celecoxib, which lowers myocardial prostacyclin production in infarcted heart muscle, but fails to inhibit thromboxane (14). Therefore, celecoxib (5 mg/kg) tips the balance of prostacyclin/thromboxane in favor of thromboxane, leading to increased vascular and thrombotic events (14). In contrast, the nonselective COX inhibitor aspirin (35 mg/kg/d) suppresses both prostacyclin and thromboxane (15).

Both NO and prostacyclin counteract the effect of thromboxane on platelet aggregation and, therefore, on thrombotic events (2,16). Nitric oxide is particularly important in the presence of diminished prostacyclin or unchanged and increased thromboxane. Celecoxib does not inhibit induction of iNOS, but decreases the ratio of prostacyclin/thromboxane (14). Prostacyclin and NO have an additional and different impact on the infarcted heart and tumor progression. For example, prostacyclin increases the potential for stimulating growth of new blood vessels in cancer and the infarcted heart muscle. Angiogenesis in tumors is undesirable because it may promote the spread of the tumor; it plays an important positive role in healing and remodeling of the infarcted heart (3).

How can one avoid these thrombotic events following NSAIDs? One possibility is to supplement COX-2 inhibitors with small doses of aspirin, as suggested by Mukherjee et al. (5). Another possibility is the combination of the COX-2 inhibitors with a NO donor, B-NOD; this is a newly developed NO donor that can be administered orally, its effect persisting for more than 7 h, causing no drop in blood pressure nor an increase in heart rate; it increases cyclic guanosine monophosphate and prevents platelet aggregation. In vitro, release of NO by B-NOD is augmented by the presence of blood platelets (17). We had previously suggested that a combination of aspirin with a NO donor may prevent the decline of prostacyclin after aspirin alone and celecoxib (8,13). The relative proportion of each component would have to be determined. A combination of NSAIDs and B-NOD has already been used to prevent renal depletion of prostacyclin in situ following administration of aspirin (18).

It is realized that re-evaluation of a commercially successful compound is not a desirable course. Conversely, science should not be hampered by a matter of expediency. Progress depends on re-evaluation of known facts; there are no immovable objects in either science or medicine.

Acknowledgment

The authors appreciate the excellent secretarial help of Ms. Susanna Kim.

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Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study

Wayne A Ray, C Michael Stein, Kathi Hall, James R Daugherty, Marie R Griffin

Summary

Background Non-aspirin, non-steroidal anti-inflammatory drugs (NANSAIDs) have complex effects that could either prevent or promote coronary heart disease. Comparison of the NANSAID rofexocib with naproxen showed a substantial difference in acute myocardial infarction risk, which has been interpreted as a protective effect of naproxen. We did an observational study to measure the effects of NANSAIDs, including naproxen, on risk of serious coronary heart disease.

Methods We used data from the Tennessee Medicaid programme obtained between Jan 1, 1987, and Dec 31, 1998, to identify a cohort of new NANSAID users (n=181 441) and an equal number of non-users, matched for age, sex, and date NANSAID use began. Both groups were 50–84 years of age, were not resident in a nursing home, and did not have life-threatening illness. The study endpoint was hospital admission for acute myocardial infarction or death from coronary heart disease.

Findings During 532 634 person-years of follow-up, 6362 cases of serious coronary heart disease occurred, or 11·9 per 1000 person-years. Multivariate-adjusted rate ratios for current and former use of NANSAIDs were 1·05 (95% CI 0·97–1·14) and 1·02 (0·97–1·08), respectively. Rate ratios for naproxen, ibuprofen, and other NANSAIDs were 0·95 (0·82–1·09), 1·15 (1·02–1·28), and 1·03 (0·92–1·16), respectively. There was no protection among long-term NANSAID users with uninterrupted use; the rate ratio among current users with more than 60 days of continuous use was 1·05 (0·91–1·21). When naproxen was directly compared with ibuprofen, the current-use rate ratio was 0·83 (0·69–0·98).

Interpretation Absence of a protective effect of naproxen or other NANSAIDs on risk of coronary heart disease suggests that these drugs should not be used for cardioprotection.

Lancet 2002; **359**: 118–23
See Commentary page 92

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Introduction

Non-aspirin, non-steroidal anti-inflammatory drugs (NANSAIDs)[1,2] could affect risk of acute myocardial infarction and other serious coronary heart disease. Findings of ex-vivo studies suggest that prediction of whether these effects are beneficial or harmful might be difficult because NANSAIDs have complex properties that could either prevent or promote coronary artery disease. Many NANSAIDs inhibit production of thromboxane and thus also inhibit platelet aggregation. Prevention of non-fatal myocardial infarctions by low-dose aspirin suggests that NANSAIDs could prevent coronary artery disease, an effect thought to be attributable to irreversible and almost complete inhibition of thromboxane produced by platelets.[3] Inflammation seems to have an important role in pathogenesis of atherosclerosis,[4,5] which suggests that NSAIDs in anti-inflammatory doses could reduce clinical manifestations of coronary artery disease.[6] Conversely, high doses of NSAIDs inhibit synthesis of prostacyclin, a potent endogenous platelet inhibitor,[7] which could raise risk of coronary heart disease, as could other dose-related effects of NSAIDs, such as hypertension.[8] However, up to now there have been few population-based studies of whether or not NANSAIDs affect risk of clinically important coronary heart disease in human beings.[9]

Results from a large trial of the new cyclooxygenase-2 (COX-2)-selective drug, rofecoxib,[10] have stimulated increased interest in this topic. That trial, which was designed to assess gastrointestinal safety of rofecoxib, compared patients randomly assigned to daily doses of either 50 mg rofecoxib or 1 g naproxen. The rofexocib and naproxen patients differed by occurrence of myocardial infarctions, 0·4% and 0·1%, respectively. Because there was no untreated group, we do not know whether this finding suggests a protective effect of naproxen or a harmful effect of rofexocib. Some data suggest that naproxen suppresses production of thromboxane and inhibits platelet aggregation by 88% for up to 8 h.[11] By contrast, because rofecoxib and other COX-2-selective drugs do not inhibit thromboxane synthesis,[9,11] they should not affect platelet aggregation by this mechanism. However, these drugs could increase risk of coronary heart disease because they inhibit prostacyclin formation.[7] In view of the widespread use of naproxen and other non-selective NANSAIDs, and the likelihood that such use will probably decline as that of COX-2-selective drugs rises, a differential effect of these two types of NANSAIDs on the risk of coronary heart disease has important public health ramifications.

We sought to quantify risk of myocardial infarction and fatal coronary heart disease among new users of generally prescribed NANSAIDs. We did the study before marketing of new COX-2-selective agents (celecoxib and rofecoxib) and thus did not include these drugs.

Methods

Study data

We obtained study data from Medicaid in Tennessee.[12] Medicaid computerised files allowed cohort identification, classification of cardiovascular risk factor status, and endpoint ascertainment. The files included: a central

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MRK-ABO0001016

registry of all individuals enrolled, linked with death certificates; records of prescriptions filled at the pharmacy; records of hospital admissions for people enrolled in Medicaid; records of visits to the emergency room, hospital outpatient department, outpatient surgical facility, and physician for those enrolled in Medicaid; and the nursing-home file.

Study participants

We compared new users of NANSAIDs between Jan 1, 1987, and Dec 31, 1998, with a demographically matched random sample of controls who had not used NANSAIDs. This design ensured that events early in drug use were recorded, which is important because NANSAIDs could have short-term and long-term effects on coronary heart disease. The design also allowed classification of patients' cardiovascular risk-factor status just before NANSAID use began, which avoids potential bias introduced by control for NANSAID-mediated modification of cardiovascular risk factors, such as hypertension.[8]

New use of a NANSAID was defined as prescription of a study drug, with no use of any NANSAID in the 365 days preceding the date this prescription was filled (t_0). This definition was further restricted to individuals who, at time t_0, had been enrolled for at least 365 days, were aged between 50 and 84 years, were not in a nursing home (t_0 and for the previous 365 days), and had no medical history suggesting non-cardiovascular life-threatening illness (cancer, HIV, renal failure, liver injury, respiratory failure, or other serious immunological disorders) at t_0 and for the previous 365 days. Follow-up of a new NANSAID user began at t_0 and continued until one of the following censorship times was reached: 365 days after last NANSAID use, end of the study (Dec 31, 1998), end of enrolment, death, age 85 years, entry into a nursing home, occurrence of non-cardiovascular life-threatening illness, or a study endpoint. To ensure that baseline characterisation of cardiovascular risk was not outdated, follow-up was stopped 5 years after t_0. For every new NANSAID user, we randomly selected an individual who was enrolled in Medicaid, who was not using a NANSAID at t_0 or in the past 365 days, as a control. The control was matched for sex and birth year, had to satisfy all membership criteria for NANSAID users, and furthermore, had to have at least one prescription for some other drug filled in the 365 days preceding t_0. Follow-up of controls began at t_0 and was calculated in a manner similar to that for new users, except that it would end if use of a NANSAID began subsequent to t_0.

Because the study took place over 11 years, and because use of NANSAIDs for a particular person would probably vary over this time, members of either cohort whose follow-up was stopped for any reason except death or a study endpoint could re-enter the cohort if, on that date, they met the criteria for entry. Thus, like most cohort studies, the same person could be a member of the new-user and control cohorts, but at different times, and could contribute only a single event to the analysis. To keep carryover effects to a minimum, cohort re-entry required at least 365 days without use of any NANSAID. At re-entry, baseline characteristics were updated to the new t_0. To measure the effect of cohort re-entry, we did an analysis restricted to the first period of follow-up of every person.

The study cohorts thus included 181 441 periods of new NANSAID use in 128 002 individuals and 181 441 matched control periods in 134 642 people. There were 69 314 individuals in both cohorts. In the primary analyses, these periods were the units of analysis.

Procedures

NANSAIDs and other drugs were identified from pharmacy records, which included date prescription was dispensed, drug, quantity, dose, and days of supply. For NANSAIDs, these data were checked to ensure that days of supply, from which we calculated prescription duration, were consistent with drug quantity. The most frequently used NANSAIDs were ibuprofen (38%) and naproxen (27%), for which individual analyses were done. Other NANSAIDs (grouped for analysis into a single category) were: non-acetylated salicylates (7%); fenoprofen (6%); indometacin (6%); piroxicam (3%); sulindac (3%); nabumetone (2%); meclofenamate (2%); diclofenac (1%); and phenylbutazone, tolmetin, diflunisal, ketoprofen, flurbiprofen, etodolac, ketorolac tometamol, oxaprozin, and bromfenac (all <1%). High-dose naproxen was defined as 1000 mg or greater, the dose at which platelet inhibition has been shown.[11] The cutoff points for ibuprofen (≥1800 mg) and other NANSAIDs were selected to provide comparable clinical doses.

During the study, COX-2-selective drugs were not available. Aspirin was used frequently in low doses, presumably as an antiplatelet agent, and thus was analysed separately as an indicator of cardiovascular disease.

The primary study endpoint was serious coronary heart disease, defined as acute myocardial infarction or death from coronary heart disease. Myocardial infarctions were defined as hospital admissions with a discharge diagnosis code (International Classification of Diseases, revision 9, clinical modification [ICD9-CM]) of 410.

We excluded the few inpatients who were discharged alive after a stay (including any transfers) of fewer than 3 days, because during the study, such short hospital visits were implausible for true myocardial infarctions. We also excluded patients who died from a cause other than ischaemic heart disease. Findings of validation studies of claims data[12,13] have shown that a main diagnosis code for acute myocardial infarction has a positive predictive value between 92%[12] and 95%,[13] and a sensitivity of 94%.[12]

Deaths from coronary heart disease, identified from death certificates, were defined as those with the underlying cause coded as ischaemic heart disease (ICD9 codes 410–414), not associated with hospital admission as defined above, and with no evidence of another cause (hospital admission at least 1 day before death with a main discharge diagnosis other than ischaemic heart disease). Although diagnostic coding for deaths from coronary artery disease is probably less accurate than that for myocardial infarction, inclusion is important, because coronary artery disease frequently manifests as sudden death outside of hospital. In one analysis, we broadened this definition to include out-of-hospital deaths from other vascular disease (ICD9 codes 390–459, 798, 799).

In one analysis we excluded cohort members with baseline heart failure, which was defined as one or more hospital admission or emergency-room visit for heart failure (diagnosis codes 428, 402.01, 402.11, 402.91, 404.01, 404.11, 404.13, 404.91, 404.93) in the 365 days preceding t_0, two or more outpatient visits, or concomitant prescriptions for loop diuretic and digitalis glycoside.

For periods of NANSAID use, every person-day of follow-up was classified as current (use on that day according to days of supply) or former (no use on that day) and by NANSAID dose. For both NANSAID and control periods, every day was also classified by use of prescribed aspirin, assuming that the cardioprotective effect persisted 7 days after last use.

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To control for potential differences in baseline risk of coronary artery disease, we constructed an index of risk from medical history in the 365 days preceding t_e. This index included use of prescribed drugs to treat cardiovascular disease (anti-arrhythmics, angiotensin-converting-enzyme inhibitors, anticoagulants, anti-diabetics, aspirin, β-blockers, calcium-channel blockers, digitalis, lipid-lowering agents, loop diuretics, other antihypertensives, platelet inhibitors) and hospital admissions and emergency room visits for cardiovascular and other disease. Previous myocardial infarctions also were identified (diagnosis codes 410, 412, 429.7). Serious cardiovascular disease included stroke or other cerebrovascular disease (diagnosis codes 430–438), angina or coronary artery revascularisation (prescription for nitrate or other anti-anginal drug, diagnosis of angina [codes 411 or 413], or coronary artery revascularisation procedure), and peripheral arterial disease (diagnosis codes 440.2, 443.1, 443.9, 444.22, 444.81 or prescription of cilostazol, cyclandelate, or pentoxifylline). A summary risk score was created from regression models of effect of these factors on rates of study endpoints among controls, in which regression coefficients defined weights given to every factor. This score was used in all analyses, because results thus obtained were virtually identical to those from more complex models with detailed terms for cardiovascular disease medical history.

Statistical analysis

Estimates of rate ratios adjusted for potential differences between current NANSAID users were calculated from Poisson regression models. Covariates in the model, defined at t_e, included age, sex, race, residence in Standard Metropolitan Statistical Area, calendar year of t_e, time elapsed since t_e, reason for Medicaid enrolment (aged, disabled or blind, or uninsured, a group that became eligible under a special programme initiated in Tennessee in 1994),[12] coronary-artery-disease risk score, replacement oestrogen use (in women), non-cardiovascular hospital admissions, and absence of regular physician care (fewer than two visits). Tests for differences between individual NSAIDs were done with single degree-of-freedom contrasts with the Wald method to assess statistical significance.

All analyses were done with SAS version 8.0. All p values were two-sided. The study was approved by the Vanderbilt Committee for the Protection of Human Subjects. Informed consent of participants was not needed because the study met the US criteria for consent waiver: it posed minimum risk to, and could ultimately benefit the study population.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Table 1 shows characteristics of NANSAID and control cohorts. 70% of the cohort were women, and 67% were white. Duration of follow-up and demographic factors did not differ by much between NANSAID users and controls.

Both NANSAID users and controls had high baseline risk for cardiovascular disease (table 1). A fifth of the cohort had serious cardiovascular disease in the year before cohort entry, usually obstructive coronary artery disease or heart failure. Two-thirds had previously used one or more cardiovascular drugs, suggesting raised risk of cardiovascular disease; antihypertensives, hypoglycaemics, loop diuretics, and anti-anginals were the drugs that were usually used. Among women, just under a fifth used replacement oestrogens at baseline. About a third of the cohort had previous non-cardiovascular visits to hospital or emergency-department, and just over a quarter had fewer than two physician visits in the past year. There were no material differences for these factors between NANSAID users and controls.

	NANSAID users (n=181 443)	Controls (n=181 443)
Characteristic		
Mean time entered cohort	August 1993	August 1993
Follow-up (years, mean [SD])	1·5 (1·1)	1·4 (1·1)
Age (years, mean [SD])	63·8 (9·5)	63·8 (9·5)
Men	53 862 (30%)	53 878 (30%)
White	118 126 (65%)	123 658 (68%)
Standard Metropolitan Statistical Area	86 477 (48%)	84 306 (46%)
Medicaid enrolment		
Uninsured	39 624 (22%)	42 930 (24%)
Disabled	93 825 (52%)	91 439 (50%)
Aged	47 992 (26%)	47 072 (26%)
Serious cardiovascular disease in past year	39 943 (22%)	40 289 (22%)
Myocardial infarction	2899 (2%)	3112 (2%)
Stroke or other cerebrovascular disease	6347 (4%)	7354 (4%)
Angina or revascularisation	27 965 (15%)	27 520 (15%)
Heart failure	8581 (5%)	9484 (5%)
Peripheral vascular disease	6064 (3%)	5719 (3%)
Use of any cardiovascular drug in past year	121 882 (67%)	120 502 (66%)
Antiarrhythmic	4605 (3%)	4774 (3%)
Angiotensin-converting enzyme inhibitor	33 471 (18%)	32 490 (18%)
Anticoagulant	5040 (3%)	7551 (4%)
Aspirin	11 187 (6%)	10 838 (6%)
β-blocker	23 911 (13%)	23 939 (13%)
Calcium-channel blocker	42 569 (23%)	39 524 (22%)
Digitalis glycoside	17 149 (9%)	19 043 (11%)
Hypoglycaemic agent	31 922 (18%)	30 821 (17%)
Lipid-lowering drug	17 678 (10%)	16 472 (9%)
Loop diuretic	28 546 (16%)	26 916 (15%)
Nitrate	24 920 (14%)	22 705 (13%)
Other antihypertensive	41 096 (23%)	38 608 (21%)
Platelet inhibitor	6400 (4%)	6276 (3%)
Thiazide diuretic	47 892 (26%)	43 856 (24%)
Oestrogen use among women in past year	25 293 (20%)	22 355 (17%)
Non-cardiovascular inpatient or emergency room visit in past year	58646 (32%)	50935 (28%)
Fewer than two physician visits in past year	47719 (26%)	51651 (28%)

Data are numbers of individuals (%) unless otherwise stated.

Table 1: Characteristics of the study cohorts

Table 2 shows the rates of serious coronary heart disease in the two cohorts. There were 6362 cases of serious coronary heart disease in 532 634 person-years of follow-up, or 11·9 per 1000 person-years. Of these, 4224 (66%) were hospital admissions with a discharge diagnosis for acute myocardial infarction and 2138 (34%) were deaths coded as fatal coronary heart disease.

Within the current-use and former-use groups, rate of serious coronary heart disease did not differ by much from that of controls. When we compared current use of individual NANSAIDs with controls (table 3), we noted only minor differences between drugs. The rate ratio for naproxen was significantly lower than that for ibuprofen (p=0·03), but it was not significantly different from that for other NANSAIDs (p=0·35). The rate ratio for ibuprofen ≥1800 mg was significantly greater than that for lower doses. However, there were no significant dose-response trends for naproxen or other NANSAIDs.

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	Person-years	Coronary heart disease	Rate per 1000 person-years	Adjusted rate ratio* (95% CI)
NANSAID users	275 565	3313	12·02	1·03 (0·98–1·08)
Current use	65 502	841	12·84	1·05 (0·97–1·14)
Former use	210 063	2472	11·77	1·02 (0·97–1·08)
Control cohort	257 069	3049	11·86	1·00

*Adjusted with Poisson regression.

Table 2: Rates of serious coronary heart disease by study cohort and NANSAID use

To identify subgroups most likely to benefit from NANSAID anti-inflammatory and antiplatelet effects, we classified use of NANSAIDs by duration and dose (table 4). The rate ratio for long duration of use (>60 days) was identical to that for use of shorter duration. Among long-duration users, the rate ratios for high doses did not differ by much from those for low doses. The rate ratio for high-dose naproxen use did not differ from those for ibuprofen or other individual NANSAIDs ($p \geq 0.25$).

To test the robustness of study definitions, we did several alternative analyses that altered both composition of the cohort and endpoint definition (table 5). In these analyses we also directly compared current use of naproxen with that for ibuprofen. To assess the extent to which unmeasured low-dose aspirin use might affect findings, we limited the cohort by exclusion of those with baseline history of myocardial infarction or stroke (for whom aspirin was most likely to be prescribed). All rate ratios did not differ by much from those for the original cohort (table 5).

Some data suggest NANSAIDs could worsen heart failure,[16] and thus increase risk of serious coronary heart disease, thus we did an analysis that excluded cohort members with baseline heart failure; findings did not differ from those of the original cohort. Results of several aspirin studies show a different pattern of findings for fatal and non-fatal myocardial infarctions,[17] thus we did an analysis that excluded deaths from coronary heart disease (table 5). There was a small increase in the rate ratio for all NANSAIDs but none of the rate ratios for naproxen differed significantly from 1 (reference). Classification of deaths from coronary heart disease could be affected by the few data available at time of death, thus we did an analysis that included 1746 deaths coded as attributable to vascular disease other than ischaemic heart disease (table 5); results differed little from those of the primary analysis.

We also did several alternative analyses that tested the appropriateness of the statistical methods. To assess the effects of allowing individuals to appear in the cohort more than once, we restricted the cohort to the first period of follow-up. Rate ratios for use of current naproxen, ibuprofen, and other NANSAIDs were, respectively, 0·97 (0·79–1·20), 1·17 (1·00–1·38), and 1·05 (0·89–1·23). To assess the effect of possible changes in baseline covariates, we did an analysis restricted to 1 year of follow-up; the respective rate ratios were 1·01 (0·83–1·23), 1·19 (1·02–1·40), and 1·17 (1·00–1·38). To assess the possibility of an excess of events early in NANSAID therapy, we restricted follow-up to 60 days; the respective rate ratios were 1·09 (0·80–1·49), 1·36 (1·06–1·75), and 1·35 (1·05–1·75). To assess the requirement that controls have a prescription filled before baseline, we excluded 4% of new NANSAID users who did not meet this criterion, with resulting rate ratios of 0·95 (0·82–1·10), 1·12 (0·99–1·25), and 1·02 (0·90–1·15). Finally, to ascertain whether recent discontinuation of NANSAIDs was linked to events, we assessed people in the first 30 days after cessation of the drug. The rate ratio for this category compared with controls was 0·97 (0·89–1·07).

	Person-years	Coronary heart disease	Rate per 1000 person-years	Adjusted rate ratio* (95% CI)
Other or multiple NANSAID	23 196	301	12·98	1·03 (0·92–1·16)
High dose	15 424	205	13·29	1·07 (0·93–1·24)
Low dose	7771	96	12·35	0·94 (0·77–1·16)
Naproxen	17 692	201	11·36	0·95 (0·82–1·09)
≥1000 mg	12 327	144	11·68	1·00 (0·84–1·18)
<1000 mg	5365	57	10·62	0·83 (0·64–1·09)
Ibuprofen	24 614	339	13·77	1·15 (1·02–1·28)
≥1800 mg	15 751	231	14·67	1·27 (1·11–1·45)
<1800 mg	8864	108	12·18	0·95 (0·78–1·15)
NANSAID use				
Former	210 063	2472	11·77	1·02 (0·97–1·08)
Control	257 069	3049	11·86	1·00

*Adjusted with Poisson regression.

Table 3: Rates of serious coronary heart disease by specific NANSAID

Discussion

Although effects of aspirin on coronary artery disease have been studied extensively,[1] there has been little investigation of widely used NANSAIDs. Our data suggest that, in a high-risk population of people 50 years of age or older, non-selective NANSAIDs neither increase nor decrease risk of serious coronary heart disease. Our rate ratio estimate for serious coronary heart disease is consistent with data from a case-control study of myocardial infarctions nested in a cohort of 164 769 women,[9] in which the investigators reported an odds ratio of 1·32 (0·97–1·81) for current NANSAID use.

The unexpected finding from the rofecoxib trial of a four-fold difference between this drug and naproxen in rates of myocardial infarction was interpreted as a protective effect of naproxen.[10] This hypothesis has now been discussed in both scientific[18] and lay circles,[19] in ways that might encourage the interpretation that naproxen is

	Person-years	Coronary heart disease	Rate per 1000 person-years	Adjusted rate ratio (95% CI)†
Duration >60 days	15 354	213	13·87	1·05 (0·91–1·21)
Other NANSAID				
High dose	3877	42	10·83	0·84 (0·62–1·14)
Low dose	1959	25	12·70	0·92 (0·62–1·36)
Naproxen				
≥1000 mg	3174	44	13·86	1·07 (0·80–1·45)
<1000 mg	1375	22	15·00	1·13 (0·74–1·72)
Ibuprofen				
≥1800 mg	2984	50	16·70	1·33 (1·01–1·77)
<1800 mg	1964	30	15·27	1·09 (0·76–1·57)
Duration <60 days	50 149	628	12·52	1·05 (0·96–1·15)
Former	210 063	2472	11·77	1·02 (97–1·08)
Control	257 069	3049	11·86	1·00

*Number of previous days of current NSAID use with gaps of less than 7 days allowed. †Adjusted with Poisson regression.

Table 4: Rates of serious coronary heart disease by duration of continuous NANSAID use*

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	Number of events	Rate ratio (95% CI)		
		All NANSAID current use	Naproxen vs control	Naproxen vs ibuprofen
Original cohort	6362	1·05 (0·97–1·14)	0·95 (0·82–1·09)	0·83 (0·69–0·98)
Excluding cohort members with previous myocardial infarction or stroke	5595	1·05 (0·97–1·14)	0·94 (0·80–1·09)	0·83 (0·69–1·01)
Excluding cohort members with baseline heart failure	5564	1·08 (1·00–1·18)	0·99 (0·85–1·15)	0·85 (0·71–1·02)
Excluding deaths from coronary heart disease	4224	1·22 (1·11–1·33)	1·10 (0·94–1·30)	0·87 (0·71–1·06)
Including other vascular deaths	8102	0·98 (0·92–1·05)	0·91 (0·80–1·03)	0·86 (0·74–1·01)

*All rate ratios adjusted with Poisson regression.

Table 5: **Alternative analyses***

cardioprotective.[18,19] We thus did several analyses to test the hypothesis that naproxen has a unique protective effect of a size sufficient to explain the findings of the rofecoxib trial.

We did not find consistent evidence for this hypothesis. The overall rate ratio for naproxen was not significantly different from 1 (reference). We also did not find evidence that naproxen was protective for patients in whom the benefits of an anti-platelet effect were most likely to be present: those with doses of at least 1000 mg (thought to produce substantial and sustained antiplatelet effects)[11] and with more than 60 days of uninterrupted use. In this group, the rate ratio for naproxen did not differ from that for NANSAID non-users or from the ratios for comparable users of either ibuprofen or other NANSAIDs. We also directly compared naproxen with ibuprofen. These two groups will probably be closely similar with respect to unmeasured potential confounders that might differ between NANSAID users and non-users. In our analysis, the rate ratio for naproxen was slightly lower than that for all NANSAIDs. Even if this difference is attributable to a protective effect of naproxen, the size is insufficient to explain the findings of the rofecoxib trial.

The absence of a large protective effect for naproxen in our study could be explained in part by differences in the populations studied. Most NANSAID use in the community is for acute pain and symptoms of osteoarthritis,[1,2] whereas patients in the rofecoxib study had rheumatoid arthritis diagnosed, which might affect both risk of coronary artery disease[20,21] and effects of NSAIDs. The rofecoxib protocol prohibited aspirin use, and thus such use would probably have been lower than that in our study. However, the Medicaid cohort had an approximately four-fold higher incidence of serious coronary heart disease than did the patients in the rofecoxib trial,[10] which is evidence against the hypothesis that naproxen might differentially benefit high-risk patients.

Our study had several limitations. We used a computerised database of medical histories to define exposure to NANSAIDs and to identify serious coronary heart disease. Automated pharmacy records have been found to be an excellent unbiased source of information on drug use.[22–25] Although some NANSAIDs could be obtained over the counter during the study, Medicaid paid for these NANSAIDs when prescribed, and thus patients had strong economic incentive to obtain these drugs by prescription. In studies of Medicaid patients from Tennessee admitted to hospital for peptic ulcer,[1] colon cancer,[26] and renal failure,[27] among people who had no active prescriptions for NANSAIDs at admission, only 4% had such use noted in their chart. Conversely, in a phone-interview survey with medication container review, among people with active NANSAID prescriptions,[28] more than 90% reported current use of these drugs. However, some exposure misclassification is inevitable and would probably bias towards the null.

Were the findings for NANSAID users affected by confounding from risk factors for coronary heart disease? Several lines of evidence suggest this possibility was not the case. The Medicaid database provides extensive information on medically treated risk factors such as hypertension, diabetes, angina, and previous episodes of serious cardiovascular disease. At baseline, individuals starting use of NANSAIDs and controls had virtually identical prevalence of these risk factors, suggesting absence of systematic differences in risk of cardiovascular disease between these cohorts. Furthermore, the rate ratio estimates presented were calculated from models that controlled for these factors.

Because the study database did not have information on smoking, obesity, inactivity, and diet, these lifestyle factors could be confounders. However, in other studies in this population, smoking—potentially the strongest such confounder—has not varied with NANSAID use.[1,29] Furthermore, the effect of these lifestyle factors is shown by raised prevalence of medical risk factors such as hypertension or angina; these are controlled for in our analysis. Although residual confounding by behavioural or lifestyle factors is possible, the fact that risk for former non-current users of NANSAIDs was virtually identical to that of non-users suggests that the size of such confounding is not large.

Although our study had information on prescribed aspirin use, rates of use were low, and many patients were probably using over-the-counter aspirin. This factor would introduce bias only if aspirin use differed in accordance with NANSAID status. In studies of peptic ulcer,[1,29] colon cancer,[26] and renal failure,[27] this difference did not occur. In our cohort, exclusion of members with previous myocardial infarction or stroke—the group most likely to receive aspirin—did not significantly change findings.

Absence of a protective effect of naproxen or other non-selective NANSAIDs suggests that none of these drugs should be used for cardioprotection in the absence of evidence from randomised controlled trials to lend support to such a practice.

Contributors

W A Ray wrote the initial drafts of the study protocol and the report, and did the statistical analyses. M R Griffin and C M Stein contributed to the initial design of the study and helped revise both the protocol and the report. J R Daugherty and K Hall contributed to the study protocol and did computer programming.

Conflict of interest statement

M R Griffin is a consultant for Merck Research Laboratories and W A Ray has consulted for Merck in the past year, but none of the funding for this study was provided by any pharmaceutical company.

Acknowledgments

This study was funded in part by the Agency for Healthcare Research and Quality, Centers for Education and Research in Therapeutics cooperative agreement (grant # HS1-0384), and a cooperative agreement with the Food and Drug Administration (FD-U-001641).

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MRK-ABO0001020

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MRK-ABO0001021

Relationship Between Selective Cyclooxygenase-2 Inhibitors and Acute Myocardial Infarction in Older Adults

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Background—Although cyclooxygenase-2 inhibitors (coxibs) were developed to cause less gastrointestinal hemorrhage than nonselective nonsteroidal antiinflammatory drugs (NSAIDs), there has been concern about their cardiovascular safety. We studied the relative risk of acute myocardial infarction (AMI) among users of celecoxib, rofecoxib, and NSAIDs in Medicare beneficiaries with a comprehensive drug benefit.

Methods and Results—We conducted a matched case-control study of 54 475 patients 65 years of age or older who received their medications through 2 state-sponsored pharmaceutical benefits programs in the United States. All healthcare use encounters were examined to identify hospitalizations for AMI. Each of the 10 895 cases of AMI was matched to 4 controls on the basis of age, gender, and the month of index date. We constructed matched logistic regression models including indicators for patient demographics, healthcare use, medication use, and cardiovascular risk factors to assess the relative risk of AMI in patients who used rofecoxib compared with persons taking no NSAID, taking celecoxib, or taking NSAIDs. Current use of rofecoxib was associated with an elevated relative risk of AMI compared with celecoxib (odds ratio [OR], 1.24; 95% CI, 1.05 to 1.46; $P=0.011$) and with no NSAID (OR, 1.14; 95% CI, 1.00 to 1.31; $P=0.054$). The adjusted relative risk of AMI was also elevated in dose-specific comparisons: rofecoxib ≤25 mg versus celecoxib ≤200 mg (OR, 1.21; 95% CI, 1.01 to 1.44; $P=0.036$) and rofecoxib >25 mg versus celecoxib >200 mg (OR, 1.70; 95% CI, 1.07 to 2.71; $P=0.026$). The adjusted relative risks of AMI associated with rofecoxib use of 1 to 30 days (OR, 1.40; 95% CI, 1.12 to 1.75; $P=0.005$) and 31 to 90 days (OR, 1.38; 95% CI, 1.11 to 1.72; $P=0.003$) were higher than >90 days (OR, 0.96; 95% CI, 0.72 to 1.25; $P=0.8$) compared with celecoxib use of similar duration. Celecoxib was not associated with an increased relative risk of AMI in these comparisons.

Conclusions—In this study, current rofecoxib use was associated with an elevated relative risk of AMI compared with celecoxib use and no NSAID use. Dosages of rofecoxib >25 mg were associated with a higher risk than dosages ≤25 mg. The risk was elevated in the first 90 days of use but not thereafter. (***Circulation.*** **2004;109:2068-2073.)**

Key Words: cyclooxygenase inhibitors ■ myocardial infarction ■ aging

The Vioxx and Gastrointestinal Outcomes (VIGOR) trial compared the gastrointestinal safety of rofecoxib 50 mg/d with naproxen 1000 mg/d in patients with rheumatoid arthritis who did not take aspirin regularly.[1] Although the trial found that patients taking rofecoxib had fewer serious gastrointestinal outcomes, there were more acute myocardial infarctions (AMIs) with rofecoxib than naproxen. This study could not discern the extent to which the difference in AMI could be explained by a protective effect of naproxen[2–4] and/or an increased risk associated with the selective cyclooxygenase (COX)-2 inhibitor (coxib).

Previous studies on the association between coxibs and AMI have provided conflicting results. In an analysis comparing the rates of AMI in phase III trials of rofecoxib and celecoxib with the rates in the placebo arms of several trials of aspirin, the coxibs were associated with an elevated risk.[5] Pooled analyses of rofecoxib randomized clinical trials, including VIGOR, suggested that there may be a statistically significantly increased risk of cardiovascular events in patients taking rofecoxib compared with naproxen, but this risk was not seen when rofecoxib was compared with other nonsteroidal antiinflammatory drugs (NSAIDs) or with placebo.[6,7] A reanalysis of the Celecoxib Long-term Arthritis Safety Study (CLASS), which compared celecoxib with ibuprofen or diclofenac, found no increase in the risk of AMI associated with celecoxib.[8] A large observational study suggested that rofecoxib at dosages >25 mg was associated with an approximately 2-fold increased risk of AMI compared

Received October 7, 2003; revision received January 22, 2004; accepted February 5, 2004.

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Drs Solomon, Schneeweiss, and Avorn have received salary support from an unrestricted research grant from Pfizer. No authors have direct personal financial relationships with any pharmaceutical company.

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Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000127578.21885.3E

with celecoxib or no NSAID, whereas rofecoxib ≤25 mg was not associated with an elevated risk.[9] A smaller observational study found no increased risk of AMI with either coxib, but dosage was not addressed.[10]

In 2002, more than 41 million prescriptions were filled in the United States for coxibs,[11] making any potential relationship between coxibs and AMI a substantial clinical and public health issue. We undertook an observational study examining the association between rofecoxib, celecoxib, NSAIDs, and AMI in a large population of older adults for whom complete information was available on prescription medication use and clinical encounters.

Methods

Study Participants

All persons studied were Medicare beneficiaries who received prescription medications through the Pennsylvania Pharmaceutical Assistance Contract for the Elderly or the New Jersey Pharmaceutical Assistance Program for the Aged and Disabled during 1998, 1999, and 2000. These 2 programs cover medication expenses for low-income elderly with annual household incomes between $10 000 and $17 000. To be included, participants had to be enrolled and active users of Medicare and the respective prescription drug benefit program from 1998 through their index date (defined below), as demonstrated by presence in the program eligibility files and filling at least 1 prescription as well as having at least 1 healthcare encounter in each 6-month period.

From this pool of eligible persons (n=310 229), we excluded patients who had illnesses that might have obscured any potential relationship between coxibs and AMI. These included persons with a serious life-threatening illness, including HIV/AIDS (n=114) or malignancy (n=50 973), and persons with a coagulopathy (n=5403). We also excluded persons with a hospitalization during 1998 who received a diagnosis of AMI that was not the principal discharge diagnosis (n=2441).

All patient identifiers and all traceable information were deleted from the case-control study database to protect patients' privacy. The Human Subjects Committee of Brigham and Women's Hospital and the Centers for Medicare and Medicaid Services approved this study.

Acute Myocardial Infarction

The case-defining event was a hospitalization in 1999 or 2000 with a discharge diagnosis code of AMI (ICD-9-CM 410) in the first or second position. The length of hospitalization must have been at least 3 days and no more than 180 days, unless the patient died. This was found to be an accurate algorithm for defining AMI in another study population.[12] To assess the accuracy of this algorithm in our study population, we identified a subset of patients with Medicare diagnosis codes for AMI and had their primary hospital records reviewed. We chose all patients from Pennsylvania taking a coxib or an NSAID who had a Medicare diagnosis code for AMI in 1998 (n=1525), as well as a random subset of those not taking these agents (n=675). Trained chart abstractors blinded to the study question reviewed the charts using a review form developed as part of the Cardiovascular Coordinating Project.[13] On the basis of the primary medical records, we determined whether each admission met criteria for an AMI established by the World Health Organization.[14] The Medicare ICD-9-CM diagnosis plus the length-of-stay requirements had a positive predictive value of 93% (95% CI, 92% to 94%). We identified 10 895 hospitalizations for AMI in the eligible study population on the basis of this algorithm.

Four control subjects (controls) who did not sustain an AMI during the study period were identified for each case. The date of hospitalization for AMI was the index date for cases. A randomly selected date was the index date for controls. Controls were matched to cases on the basis of age (±1 year), gender, and the month of index date.

Coxib and Nonselective NSAID Use

The study database contained information on all prescription drugs filled by eligible beneficiaries, including drug name, dosage, frequency, and days of supply. The exposures of interest were the use of celecoxib or rofecoxib on the index date. During the study period, both drugs were covered by the prescription benefit programs without restriction, and copayments were less than $10. The risk of AMI associated with these agents was compared with several reference groups: use of the other coxib, no NSAID or coxib, ibuprofen, naproxen, or other NSAIDs. Prescriptions filled on the index date were excluded in the primary analyses. Persons with prescriptions for more than one of the drug categories on the index date were included in both categories.

Two dosage and 3 duration categories were defined a priori for all relevant exposures. Dosage categories for the coxibs and NSAIDs were split at the modal daily dosage. For example, the modal dosage of celecoxib was 200 mg, so current use was categorized as ≤200 mg or >200 mg. For rofecoxib, the modal dosage was 25 mg; current use was dichotomized as ≤25 mg or >25 mg. Dosage categories were created for the NSAIDs on the basis of the same methodology. For each individual study drug, 3 duration categories were created: 1 to 30 days, 31 to 90 days, and >90 days.

Covariates

Covariates were defined on the basis of data from the year before the study period. Although information for most of these patients and covariates was available for longer than 12 months, we restricted the ascertainment to this period to reduce potential bias that might arise because of varying lengths of covariate assessment. The covariates assessed include age, gender, race, previous MI, angina, coronary artery revascularization, congestive heart failure, ischemic cerebrovascular accident, diabetes, hypertension, use of a lipid-lowering drug (statin), use of hormone replacement therapy, use of an anticoagulant (clopidogrel, dipyridamole, ticlopidine, and warfarin), use of an NSAID in 1998, rheumatoid arthritis, osteoarthritis, presence of a hospitalization, number of visits for ambulatory care, number of comorbid medical conditions,[15] and number of different medications used.

Several variables of interest were not available within the study database, including body mass index, tobacco use, aspirin use, and socioeconomic status. In theory, these variables could be differentially related to use of a coxib, use of an NSAID, and AMI.[16–18] We therefore analyzed data from the Medicare Current Beneficiary Survey,[19] a nationwide in-home survey conducted among 8785 beneficiaries ≥65 years old in 1999 with a 97% response rate. We compared patients' body mass index, tobacco use, aspirin use, annual household income, and educational attainment between patients reporting use of celecoxib (n=562), rofecoxib (n=244), and an NSAID (n=1302). In these analyses, body mass index was comparable in both groups of coxib users (celecoxib, 27.5 kg/m^2 versus rofecoxib, 27.2 kg/m^2, P=0.2) and similar to that of NSAID users (27.7 kg/m^2, P=0.5 versus coxib users). Current tobacco use was equally common in both groups of coxib users (celecoxib, 8.7% versus rofecoxib, 7.0%, P=0.5) and was more common among NSAID users (9.8%, P=0.005). Aspirin use was similar in both coxib groups (celecoxib, 8.2% versus rofecoxib, 11.5%, P=0.2) and among NSAID users (10.2%, P=0.4). The proportion of persons with an educational level of college or higher was not statistically different between coxibs (celecoxib, 29.6% versus rofecoxib, 31.8%, P=0.11) or between coxibs and NSAIDs (26.5%, P=0.2). The mean annual household income of both coxib groups was similar (P=0.7) and higher than that for NSAID users (P=0.0001).

Analyses

The distribution of covariates was assessed in each exposure category. The unadjusted odds ratio (OR) between each covariate and AMI was then examined separately for New Jersey and Pennsylvania. The CIs for the crude ORs for each state overlapped for every covariate; data from both states were combined for the multivariable analyses. All covariates were tested in multivariable conditional

TABLE 1. Baseline Characteristics of Study Population by Exposure Category

	Celecoxib (n=2140)	Rofecoxib (n=941)	Naproxen (n=331)	Ibuprofen (n=263)	Other NSAID (n=1874)	No Current Exposure (n=49 044)
Gender, female	1814 (84.8)	813 (86.4)	272 (82.2)	207 (78.7)	1531 (81.7)	37 690 (76.9)
Age, y, mean±SD	81.4±6.7	81.7±6.5	80.8±6.7	80.8±6.8	80.7±6.4	81.7±7.0
Race						
White	1967 (91.9)	877 (93.2)	288 (87.0)	227 (86.3)	1686 (90.0)	44 628 (91.0)
Black	132 (6.2)	45 (4.8)	35 (10.6)	30 (11.4)	151 (8.1)	3478 (7.1)
Other	41 (1.9)	19 (2.0)	8 (2.4)	6 (2.3)	37 (2.0)	938 (1.9)
Nursing home resident in previous year	135 (6.3)	56 (6.0)	8 (2.4)	16 (6.1)	82 (4.4)	3393 (6.9)
No. of physician visits, mean±SD	9.8±7.7	9.6±7.1	7.9±5.6	7.8±6.1	8.5±6.3	7.5±6.2
Hospitalized in previous year	617 (28.8)	266 (28.3)	70 (21.2)	72 (27.4)	429 (22.9)	13 519 (27.6)
Comorbid conditions, mean±SD	0.9±1.1	0.9±1.1	0.7±0.9	0.9±1.1	0.8±1.0	0.9±1.2
Diabetes	674 (31.5)	273 (29.0)	92 (27.8)	77 (29.3)	549 (29.3)	14 185 (28.9)
Hypertension	1367 (63.9)	609 (64.7)	202 (61.0)	156 (59.3)	1178 (62.9)	27 829 (56.7)
No. of different prescription drugs, mean±SD	7.6±5.2	7.3±5.3	6.4±4.8	6.1±4.5	7.3±4.9	5.4±4.4
History of previous myocardial infarction	170 (7.9)	84 (8.9)	19 (5.7)	17 (6.5)	132 (7.0)	4293 (8.8)
History of angina	323 (15.1)	160 (17.0)	44 (13.3)	34 (12.9)	265 (14.1)	6985 (14.2)
History of coronary revascularization	22 (1.0)	14 (1.5)	5 (1.5)	7 (2.7)	18 (1.0)	728 (1.5)
History of congestive heart failure	321 (15.0)	128 (13.6)	38 (11.5)	33 (12.6)	266 (14.2)	7166 (14.6)
History of a cerebrovascular accident	273 (12.8)	141 (15.0)	30 (9.1)	24 (9.1)	219 (11.7)	6800 (13.9)
Use of a statin	431 (20.1)	196 (20.8)	52 (15.7)	39 (14.8)	360 (19.2)	7624 (15.6)
Use of hormone replacement therapy	139 (6.5)	69 (7.3)	18 (5.4)	14 (5.3)	97 (5.2)	1756 (3.6)
Use of any anticoagulant*	311 (14.5)	145 (15.4)	25 (7.6)	19 (7.2)	189 (10.1)	7047 (14.4)
Rheumatoid arthritis	126 (5.9)	33 (3.5)	20 (6.0)	8 (3.0)	86 (4.6)	823 (1.7)
Osteoarthritis	783 (36.6)	328 (34.9)	94 (28.4)	66 (25.1)	661 (35.3)	8368 (17.1)
Previous nonselective NSAID use	319 (14.9)	105 (11.2)	238 (71.9)	187 (71.1)	190 (10.1)	3451 (7.0)

Values are n (%) unless noted. Current use refers to use on the index date. Persons who were current users of multiple agents (n=117) are counted in the appropriate column for each drug used.

*Anticoagulants include clopidogrel, dipyridamole, ticlopidine, and warfarin.

logistic regression models conditioning on all matching factors. On the basis of a backward selection routine with a threshold of $P<0.2$, anticoagulant use, previous hospitalization, osteoarthritis, and nursing home residence were dropped from all versions of the adjusted model. The remaining covariates were included in all multivariable conditional logistic regression models. The model was rerun for each reference group (the alternative coxib, no NSAID, ibuprofen, naproxen, and other NSAIDs). A secondary analysis excluded persons exposed to multiple agents on the index date (n=117). The results were virtually identical to the main analyses and are not shown.

We assessed the relationship between dosage categories and AMI for the coxibs and NSAIDs using similar multivariable regression models in which the dosage was classified as less than or equal to the modal dosage or greater than the modal dosage. For example, in analyses comparing the coxibs, the most commonly used dosages of rofecoxib (≤25 mg) were compared with the most commonly used dosages of celecoxib (≤200 mg). Users of rofecoxib >25 mg were then compared with users of celecoxib >200 mg.

Several sensitivity analyses were undertaken. On the basis of previous findings that first-time users may be at the highest risk for cardiovascular events associated with coxibs,[9] we constructed conditional regression models that considered persons exposed only if their use on the index date was their first time using a coxib. We examined the relationship between AMI and the duration of exposure to coxibs in this group of users. Assessing the effect of duration among first-time users provides a more precise estimate of the actual period of exposure, because persons with intermittent prescriptions were not considered exposed. Another set of sensitivity analyses redefined the no NSAID use reference group to only persons who had never been exposed to an NSAID during the study period. Finally, we assessed the relationship between coxibs and AMI in subgroups of persons with rheumatoid arthritis, a history of MI, or NSAID use during the baseline period.

The data and all analyses were under control of the authors. An independent review of the study protocol and statistical programming was performed by an epidemiologist external to the study sponsor and project team. All analyses were conducted using SAS statistical software (version 8.2).

Results

The baseline characteristics of patients are shown in Table 1. The study population was primarily elderly women with a mean age >80 years in all drug use groups. More than 85% of patients were white. The study population used substantial healthcare resources. Risk factors for AMI, such as diabetes and hypertension, were common, and previous cardiovascular disease was frequent. In the baseline period, more than 5% of the population had sustained a previous MI, more than 13% had angina, more than 12% had congestive heart failure, and more than 9% had a previous ischemic stroke. Statins were used by more than 15% of all patients. As seen in Table 1, patients using celecoxib or rofecoxib were similar with regard

TABLE 2. Adjusted Association Between Coxibs and Acute Myocardial Infarction

	Adjusted Odds Ratio (95% CI)	P
Exposure (reference group)		
Rofecoxib (celecoxib)	1.24 (1.05–1.46)	0.011
Celecoxib (no current use)	0.93 (0.84–1.02)	0.13
Rofecoxib (no current use)	1.14 (1.00–1.31)	0.054
Celecoxib (naproxen)	0.95 (0.74–1.21)	0.7
Rofecoxib (naproxen)	1.17 (0.90–1.52)	0.2
Celecoxib (ibuprofen)	0.98 (0.78–1.26)	0.9
Rofecoxib (ibuprofen)	1.21 (0.92–1.58)	0.2
Celecoxib (other NSAID)	0.95 (0.82–1.10)	0.4
Rofecoxib (other NSAID)	1.17 (0.99–1.38)	0.073
Covariate		
Race, white	1.20 (1.12–1.29)	<0.001
No. of physician visits		
4–6	1.11 (1.05–1.18)	<0.001
7–12	1.11 (1.05–1.17)	<0.001
13+	1.09 (1.02–1.16)	0.011
Comorbid conditions		
1–2	1.25 (1.20–1.31)	<0.001
3+	1.42 (1.33–1.52)	<0.001
No. of different drugs		
6–9	1.14 (1.08–1.19)	<0.001
10+	1.18 (1.12–1.25)	<0.001
Diabetes	1.48 (1.42–1.54)	<0.001
Hypertension	1.15 (1.11–1.20)	<0.001
Previous myocardial infarction	1.56 (1.48–1.66)	<0.001
Angina	1.31 (1.25–1.38)	<0.001
Previous coronary revascularization	0.78 (0.69–0.89)	<0.001
Congestive heart failure	1.37 (1.31–1.44)	<0.001
Cerebrovascular accident	1.07 (1.01–1.27)	0.014
Use of statin	1.00 (0.94–1.04)	0.7
Use of hormone replacement therapy	0.88 (0.79–0.98)	0.02
Rheumatoid arthritis	1.16 (1.02–1.31)	0.02
Previous nonselective NSAID use	0.97 (0.90–1.04)	0.3

Conditional logistic model matched on age, gender, and month of index date. All other variables listed were adjusted for in the multivariable models. The number of AMIs in each exposure group was as follows: celecoxib 425, rofecoxib 225, ibuprofen 49, naproxen 63, other NSAID 371, and no current use 9793.

to baseline characteristics. Compared with NSAID users, coxib users were somewhat less healthy during the baseline period, with more health service use, hypertension, previous MIs, cerebrovascular accidents, angina, and cardiovascular medication use (statins and anticoagulants).

The results of the multivariable conditional logistic regression models are shown in Table 2. After control for all available confounders, rofecoxib was associated with an elevated risk of AMI compared with persons who were taking celecoxib (OR, 1.24; 95% CI, 1.05 to 1.46). The adjusted relative risk of AMI associated with rofecoxib was elevated but did not reach statistical significance compared with no current NSAID (OR, 1.14; 95% CI, 1.00 to 1.31), naproxen (OR, 1.17; 95% CI, 0.90 to 1.52), and ibuprofen (OR, 1.21; 95% CI, 0.92 to 1.58). Relatively few patients were current users of naproxen (n=331) or ibuprofen (n=263), contributing to the wide CIs. Celecoxib was not associated with an elevated risk of AMI in these analyses.

In all comparisons related to dose, use of rofecoxib >25 mg/d was associated with a higher adjusted relative risk of AMI than rofecoxib ≤25 mg. The adjusted relative risk of rofecoxib >25 mg (OR, 1.70; 95% CI, 1.07 to 2.71) was higher than that seen for ≤25 mg (OR, 1.21; 95% CI, 1.01 to 1.44) compared with celecoxib >200 mg or ≤200 mg. The magnitude in elevation of relative risk was similar when rofecoxib was compared with no current NSAID, naproxen, ibuprofen, and other NSAIDs. Neither celecoxib dosage was associated with an elevated risk of AMI in any comparison.

Sensitivity analyses that considered only the first-time use of a coxib or NSAID during the study period provided findings very similar to those of the primary analysis. A sensitivity analysis comparing rofecoxib users with patients who had no use of either a coxib or NSAID since January 1, 1999, produced results nearly identical to those of the primary analysis (OR, 1.14; 95% CI, 0.99 to 1.31; $P=0.062$).

We also examined the relationships between duration of coxib exposure and AMI in first-time users. Compared with celecoxib use of similar duration, rofecoxib use for 1 to 30 days was associated with an elevated risk of AMI (OR, 1.43; 95% CI, 1.12 to 1.83; $P=0.005$). A similar elevation was associated with 31 to 90 days of rofecoxib use (OR, 1.46; 95% CI, 1.14 to 1.86; $P=0.003$), but no elevation in AMI risk was observed with >90 days of rofecoxib use (OR, 1.04; 95% CI, 0.77 to 1.38; $P=0.8$). The elevated relative risk of AMI seen in patients taking rofecoxib for 90 days or less was not restricted to those taking >25 mg. Compared with patients taking celecoxib ≤200 mg for 1 to 90 days, the adjusted relative risk of AMI associated with rofecoxib ≤25 mg (OR, 1.37; 95% CI, 1.15 to 1.63; $P=0.0004$) was similar to the adjusted relative risk for rofecoxib >25 mg (OR, 1.38; 95% CI, 0.80 to 2.37; $P=0.3$). No duration category for celecoxib use was associated with an elevated risk.

Subgroup analyses that focused on patients with previous AMI (n=4698) and compared persons taking rofecoxib with those taking celecoxib found no elevation in relative risk associated with rofecoxib (OR, 0.91; 95% CI, 0.60 to 1.38; $P=0.6$). Analyses restricted to patients with rheumatoid arthritis (n=1088) also found no elevation in AMI risk with either coxib. These subgroup analyses were limited by small numbers of patients.

Discussion

We studied the relationship between coxibs, NSAIDs, and hospitalization for AMI in a large population of older patients. The study database contained information on more than 50 000 older adults in 2 US states with complete prescription drug coverage. The main analyses, as well as dose- and duration-specific analyses, found an elevated risk of AMI associated with rofecoxib but not with celecoxib. The risk was higher in persons taking >25 mg of rofecoxib and

during the first 90 days of use and was observed consistently in relation to several reference groups.

It is important that these findings be considered in light of previous research. In the VIGOR trial, which compared 50 mg of rofecoxib with 1000 mg of naproxen in patients with rheumatoid arthritis, the risk of AMI was elevated in patients treated with rofecoxib.[1] Patients were not allowed to take aspirin during the trial. In an analysis that compared data from phase III randomized clinical trials of celecoxib and rofecoxib with data from the placebo groups of 4 aspirin primary prevention trials, the annualized MI rates for patients randomized to either celecoxib or rofecoxib were higher than rates for the meta-analysis of the placebo groups.[5] This analysis has been criticized because the coxib trials included osteoarthritis and rheumatoid arthritis patients, and the latter group has been observed to have an elevated baseline risk of AMI.[20] The control population was characterized by relatively low rates of AMI. A reanalysis of data from the CLASS trial, in which patients were allowed to take aspirin, found no elevation in risk of AMI associated with celecoxib.[8] An observational study conducted in the Tennessee Medicaid population found that rofecoxib at dosages >25 mg/d was associated with a nearly 2-fold increased risk of AMI compared with nonuse of any NSAID.[9] Our findings differ from the pooled analyses of rofecoxib randomized controlled trials, which showed no significant increase in cardiovascular events compared with non-naproxen NSAIDs.[6,7] In addition, a recently published observational analysis from Ontario also found no increased risk of AMI associated with any dosage of rofecoxib.[10] This analysis excluded persons who were prescribed a coxib for <30 days. The findings of our study suggest that the first 30 days of use may include a period of elevated risk. Finally, rofecoxib dosages >25 mg, which were associated with the highest relative risk of AMI in this study and the study by Ray and colleagues,[9] were not reported separately in the Ontario study.

There are important potential limitations to the present study. One is the concern about possible misclassification of end points using Medicare use data. We studied the accuracy of the AMI diagnosis codes and found that they had a positive predictive value of 93% compared with primary hospital records. However, patients who suffered an AMI and were not hospitalized because of sudden death or a silent event would not be counted in these analyses for any exposure group. In addition, it is possible that some cases sustained their AMI during the hospitalization. If so, these patients may not have been exposed to the medications of interest for a period of time before their event. This may have influenced the results if patients taking one particular medication before admission were more likely to suffer an AMI during the course of a hospitalization. However, we have no reason to believe that this was the case. Second, similar to all retrospective observational studies, these results may have been biased because of confounding by factors not observable in Medicare use data. We examined this possibility using data from the in-home Medicare Current Beneficiary Survey and found that people taking rofecoxib or celecoxib were similar with respect to 5 variables known to be independent risk factors for cardiovascular end points, including body mass index, aspirin use, tobacco use, income status, and educational attainment. A comparison of people taking coxibs with those taking NSAIDs suggests that unmeasured confounding by each of these factors may result in a small degree of bias toward the null. In addition to the potential for bias by unmeasured confounders, these results may be influenced by residual confounding by factors that were incompletely assessed in this administrative database, such as severity of cardiovascular risk factors. However, the relationship between available covariates and AMI is consistent with results from previous observational studies. Third, it is possible that some patients prescribed coxibs and/or NSAIDs used them on an as-needed basis. Thus, patients may not have been exposed to the drug on all days of the calculated prescription period, leading to potential misclassification of exposure status. If the pattern of misclassification was similar across drugs, the bias would be toward the null value. Alternatively, if it varied by drug or dose, as a function of the indication for the medication (such as acute versus chronic pain) or the efficacy of the treatment, the magnitude and direction of bias could be toward or away from the null value. We have no compelling reason to believe that this misclassification of exposure would have differed by drug. Finally, one must consider the generalizability of findings on the basis of data from an older, low-income population in 2 states, whose prescription drug use was slightly higher than the national average. Because the elderly are among the most frequent users of coxibs, the study population examined is relevant.

Several biological pathways could underlie a potential association between selective COX-2 inhibition and coronary events. Although NSAIDs inhibit both COX isoforms, selective inhibition of COX-2 results in decreased prostacyclin, a vasodilator and moderator of platelet activation, without reducing COX-1–dependent thromboxanes, contributors to platelet aggregation and vasoconstriction.[21,22] Emerging data support a varied role for COX-2 in the vascular bed, with important functions in vascular resistance,[23] late preconditioning,[24] endothelial function,[25,26] and atherogenesis.[27,28] Data from rat models of hypertension suggest that celecoxib may be associated with improvements in endothelial function and reductions in oxidative stress[29]; neutral findings have been reported for rofecoxib and diclofenac.[30] Although both rofecoxib and celecoxib, like most NSAIDs, have been associated with hypertension, several large head-to-head randomized controlled trials have reported higher rates among patients treated with rofecoxib[31]; other smaller studies in healthy adults suggest similarity between coxibs.

In conclusion, we observed an elevated risk of hospitalization for AMI among elderly Medicare enrollees treated with rofecoxib. This risk was higher in persons taking >25 mg of rofecoxib than in patients taking the most common dosages used of ≤25 mg. The risk was elevated during the first 90 days of exposure but not thereafter. We did not find an elevated risk of AMI for persons taking celecoxib. Because of the important potential public health implications, our findings should be followed up by additional clinical and mechanistic studies, several of which are ongoing.

Acknowledgments

This work was supported by Merck & Co through an unrestricted research grant to Brigham and Women's Hospital. The authors had sole responsibility for study design, data interpretation, and publication of findings. Dr Solomon was also supported by grants from the Arthritis Foundation and the National Institutes of Health (AR-48616 and AR-48264). We want to thank an epidemiologist who participated actively in the study design, statistical analysis and interpretation of the data, and preparation of the manuscript. We are also grateful to Rhonda Bohn, ScD, who performed an independent review of the study protocol and statistical programming.

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ARTHRITIS & RHEUMATISM
Vol. 43, No. 8, August 2000, pp 1891–1896
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THROMBOSIS IN PATIENTS WITH CONNECTIVE TISSUE DISEASES TREATED WITH SPECIFIC CYCLOOXYGENASE 2 INHIBITORS

A Report of Four Cases

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Specific inhibitors of cyclooxygenase 2 (COX-2) have been approved for the treatment of osteoarthritis and rheumatoid arthritis. Unlike nonsteroidal antiinflammatory drugs, specific COX-2 inhibitors do not inhibit platelet activation. However, these agents significantly reduce systemic production of prostacyclin. As a result, theoretical concerns have been raised that specific COX-2 inhibitors could shift the hemostatic balance toward a prothrombotic state. Patients with connective tissue diseases (CTD), who may be predisposed to vasculopathy and thrombosis, often have arthritis or pain syndromes requiring treatment with antiinflammatory agents. Herein we describe 4 patients with CTD who developed ischemic complications after receiving celecoxib. All patients had a history of Raynaud's phenomenon, as well as elevated anticardiolipin antibodies, lupus anticoagulant, or a history compatible with antiphospholipid syndrome. It was possible to measure a urinary metabolite of thromboxane A_2 in 2 of the patients as an indicator of in vivo platelet activation, and this was markedly elevated in both. In addition, the patients had evidence of ongoing inflammation as indicated by elevated erythrocyte sedimentation rate, hypocomplementemia, and/or elevated levels of anti-DNA antibodies. The findings in these 4 patients suggest that COX-2 inhibitor–treated patients with diseases that predispose to thrombosis should be monitored carefully for this complication.

Prostaglandins (PG) and thromboxane (TX) are regulators of platelet and endothelial cell function. Activated platelets synthesize TXA_2, which is a potent platelet aggregant and vasoconstrictor. PGI_2, which is synthesized primarily by endothelial cells, inhibits platelet activation by elevating platelet cyclic AMP and induces vasodilation. There is evidence that endogenous PGI_2 has antithrombotic properties. Infusion of PGI_2 and enhancement of endogenous PGI_2 also provide antiplatelet activity (1).

A multienzyme pathway that includes the cyclooxygenase (COX) enzymes is responsible for synthesis of prostanoids. There are 2 COX isoforms, COX-1 and COX-2. COX-1 is constitutively expressed in most tissues and is the only isoform in platelets (2). The antiplatelet effects of aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) are mediated through inhibition of COX-1–dependent TXA_2 production (3). COX-2 expression is induced by inflammation and tissue injury (4). The majority of the antiinflammatory, analgesic, and antipyretic actions of NSAIDs are due to inhibition of COX-2 (4). Specific COX-2 inhibitors developed for use in patients with osteoarthritis, rheumatoid arthritis, and pain have efficacy similar to that of nonselective NSAIDs that inhibit both COX isoforms.

Supported in part by University of Michigan Multipurpose Arthritis and Musculoskeletal Disease Center grant P60AR-20557 and by NIH grants DK-48831, GM-42056, CA-77839, HL-56415, HL-52779, HL-55907, GM-15431, and AR-01943. Dr. Oates' work was supported by a Department of Veterans Affairs Career Development Award. Dr. Morrow is the recipient of a Burroughs Wellcome Clinical Scientist Award in translational research.

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Submitted for publication February 9, 2000; accepted in revised form April 5, 2000.

MRK-ABA0002084

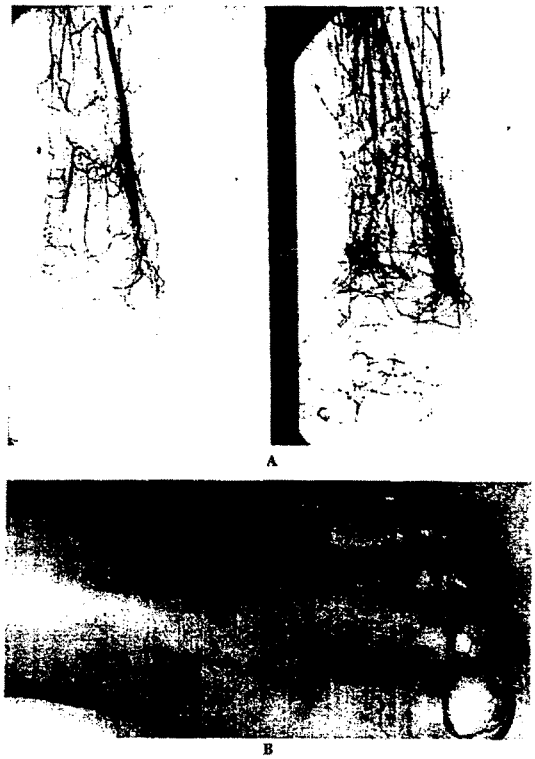

Figure 1. A, Early-phase (left panel) and late-phase (right panel) lower extremity angiography of the left lower leg of patient 1, demonstrating abrupt occlusion of the anterior tibial artery at the level of the ankle. There is little collateral flow and no perfusion distal to the metatarsals. B, Dorsal aspect of the left foot of patient 1, demonstrating ischemic change.

Inhibition of both COX-1 and COX-2 by anti-inflammatory doses of aspirin and NSAIDs leads to a simultaneous decrease in platelet TXA_2 and endothelial cell PGI_2, resulting in a balanced reduction of prostanoids with opposing actions. In contrast, specific COX-2 inhibitors have no effect on platelet TXA_2, and thus do not inhibit platelet function (5,6). Since specific COX-2 inhibitors block production of systemic PGI_2, the question has been raised as to whether these agents may be prothrombotic (7,8). Herein we report the cases of 4 patients with connective tissue diseases (CTD) in whom administration of

Table 1. Summary of the results of serologic and coagulation studies in the 4 patients*

	Patient 1	Patient 2	Patient 3	Patient 4
ANA, titer and pattern	>1:2,560, speckled†	>1:2,560, homogeneous†	1:2,560, nucleolar†	1:160, homogeneous†
Anti-dsDNA, IU/ml (normal 0.0–0.7)	52.1†	129.9†	–	17.3†
ENA	Sm+, RNP–, Ro/SSA–, La/SSB–	Sm–, RNP–, Ro/SSA+, La/SSB+	Sm–, RNP+, Ro/SSA+, La/SSB–	Sm–, RNP–, Ro/SSA–, La/SSB–
Anti-Scl-70	+†	–	ND	ND
RF, IU/ml (normal 0–30)	250†	ND	ND	<20
C3, mg/dl (normal 83–240)	66†	69†	55.6†	61†
C4, mg/dl (normal 13–60)	<10†	12†	12†	13
ESR, mm/hour (normal 0–20)	67†	17	100†	91†
CRP, mg/dl (normal 0.0–0.6)	1.6†	0.9†	ND	2.1†
IgG ACA, GPL (normal 0–22)	52†	42†	–	10
IgM ACA, MPL (normal 0–10)	25†	2	–	2
DRVVT, seconds (normal 25.9–34.7)	ND	33.9	ND	37.2†
PT, seconds (normal 9.3–10.9)	11.9†, INR 1.2 (on heparin)	9.6, INR 1.0	18.3†, INR 2.6 (on warfarin)	9.6, INR 1.0
APTT, seconds (normal 20.3–27.4)	84† (on heparin)	23.4	40†	20.1

* ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; ENA = extractable nuclear antigen; ND = not done; RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ACA = anticardiolipin antibody; DRVVT = dilute Russell viper venom time; PT = prothrombin time; INR = international normalized ratio; APTT = activated partial thromboplastin time.
† Abnormal value.

celecoxib, a specific COX-2 inhibitor, was temporally associated with thrombosis.

CASE REPORTS

Patient 1. Patient 1, a 42-year-old woman, was admitted to the University of Michigan Medical Center (UMMC) with a painful, cold, and cyanotic left foot. She had a 23-year history of arthritis, Raynaud's phenomenon (RP), and fatigue treated intermittently with prednisone and hydroxychloroquine (HCQ). She had a 45–pack-year smoking history. Two weeks prior to admission, celecoxib in 200-mg capsules had been prescribed, to be taken up to twice daily on an as-needed basis. Her symptoms had developed acutely after 2 doses of celecoxib. She presented to an outside hospital, where angiography revealed diffuse aortoiliac and common femoral atherosclerotic disease, chronic occlusion of the left posterior tibial and peroneal arteries at the level of the mid-calf, and abrupt occlusion of the anterior tibial artery at the level of the ankle, consistent with acute thromboembolic disease (Figure 1A). She was administered 1 dose of intravenous methylprednisolone (IV MP). Treatment with unfractionated heparin was begun, and she was transferred to UMMC.

On admission, the patient's left forefoot showed blue mottling (Figure 1B) and was cool to touch. The dorsalis pedis and posterior tibial pulses were diminished. Heparin and IV MP were continued, and treatment with an oral calcium channel blocker was added to alleviate vasospasm. Findings on a surface echocardiogram were normal. The results of serologic and coagulation studies are presented in Table 1. Urokinase infusion failed to reestablish blood flow, and the patient underwent an embolectomy, which resulted in partial restoration of arterial flow. Just prior to discharge, a spot urine collection was obtained for analysis of the urinary metabolites of TXA_2 (11-dehydro TXB_2) and PGI_2 (2,3-dinor-6-keto $PGF_{1\alpha}$) (Table 2). The patient was discharged on a regimen of daily warfarin, prednisone, and HCQ. At followup 1 month after discharge, arterial flow to the left forefoot remained diminished, with a pulse detectable only by doppler. She had developed gangrene of the distal half of the left great toe and an ischemic ulcer on the dorsum of the foot.

Patient 2. Patient 2 was a 37-year-old woman who was admitted to UMMC with pain and cyanosis of the toes of the right foot and interdigital ulceration. Systemic lupus erythematosus (SLE) had been diagnosed 7 years previously. Her disease was characterized by RP, arthritis, sicca symptoms, and, more recently, cerebritis necessitating monthly treatment with IV cyclophosphamide. Other medications included daily MP (16 mg) and HCQ (400 mg). She had previously undergone right upper extremity sympathectomy for refractory RP. Celecoxib (100 mg twice daily) had been prescribed 3 weeks prior to admission. Within 1 week of beginning this treatment, she developed swelling of the right foot. After an additional week of treatment, she developed

Table 2. Urinary metabolites of systemic thromboxane A_2 (TXA_2) and prostaglandin I_2 (PGI_2)*

	Patient 1	Patient 3
Urine 11-dehydro TXB_2	1.89 ng/mg creatinine (normal <1.00; matched control 0.18)†	4.11 ± 0.17 ng/mg creatinine (normal <0.65)
Urine 2,3-dinor-6-keto $PGF_{1\alpha}$	0.348 ng/mg creatinine (normal <0.200; matched control 0.025)	0.472 ± 0.032 ng/mg creatinine (normal <0.29)

* Urine 11-dehydro TXB_2 is the metabolite of extrarenal TXA_2, and urinary 2,3-dinor-6-keto $PGF_{1\alpha}$ is the metabolite of PGI_2 produced outside the kidney. Metabolites were measured by gas chromatography negative ion chemical ionization mass spectometry using authentic deuterated standards (8). Patient 2 had been treated with low-dose aspirin, and values were in the normal range (data not reported). Urine for measurement of eicosanoid metabolites was unavailable from patient 4.
† Control was matched by age and sex.

purplish discoloration of the toes of the right foot, with pain and swelling that prompted her to discontinue the celecoxib. She was admitted because of worsening pain and cyanosis.

On presentation, the dorsalis pedis pulses were strong and equal bilaterally. There was no lower extremity edema. The toes of the right foot were cyanotic, and there were ulcerations in the third and fourth interdigital spaces. Serologic and coagulation results are shown in Table 1. She was treated with IV MP, 1 gm daily for 3 consecutive days, and discharged on a regimen of oral MP 20 mg and aspirin 325 mg daily, later reduced to 80 mg daily. With aspirin treatment, measured values of urinary PGI_2 and TXA_2 metabolites were within the normal range, as expected (data not shown). After the patient failed to improve clinically, she was readmitted 2 weeks later to receive an IV bolus of cyclophosphamide. On followup 2 weeks later, the ulcerated areas had healed, but there was persistent digital ischemia with constant pain, bluish discoloration, and coolness to touch.

Patient 3. This patient, a 56-year-old woman with systemic sclerosis (SSc) and lupus anticoagulant (LAC), was admitted to the Medical University of South Carolina with shortness of breath. She was diagnosed as having SSc associated with pulmonary hypertension and RP in 1995. She developed an ulnar artery thrombosis in May 1997 and was prescribed warfarin after the LAC was detected. Her prothrombin time international normalized ratio was maintained in the 2.0–2.5 range rather than the recommended range of >3 since she had previously had excessive vaginal and gastrointestinal bleeding. In April 1999, she developed leg pain and was prescribed celecoxib (200 mg once or twice daily). After 2 days, she developed dyspnea. She presented to the emergency room 2 days after the dyspnea developed.

A V/Q scan identified at least 3 mismatched defects in the right upper lobe, right lower lobe, and left upper lobe, leading to interpretation as a high probability for pulmonary embolus. Cardiac and lower extremity ultrasound failed to reveal a thrombotic source. She was treated with heparin, and a followup V/Q scan before discharge revealed no mismatched defects. Findings of serologic and coagulation studies are shown in Table 1. After resolution of the thrombus, discontinuation of celecoxib and heparin, and reinitiation of warfarin, spot urine samples were collected for measurement of urinary metabolites of TXA_2 and PGI_2 (Table 2).

Patient 4. Patient 4, a 41-year-old woman with a history of SLE, was admitted to UMMC with a cold, painful, cyanotic right foot. The patient had an earlier history of bilateral deep venous thromboses, a miscarriage occurring at 7 months into the pregnancy, and elevated IgG anticardiolipin antibody (ACA). She had been treated with warfarin for ~7 years, but it had been discontinued 10 years prior to admission. Past manifestations of SLE also included lupus nephritis diagnosed by renal biopsy, myositis, RP, and synovitis. She had been treated with methotrexate (15 mg/week) and prednisone (10 mg/day). Her antiinflammatory drug was changed to celecoxib (200 mg twice daily) 5 months prior to admission. Approximately 2 months after the initiation of celecoxib treatment she presented to the emergency room with bluish mottling and pain in her right foot. The symptoms were attributed to vasculitis. The next month she again developed bluish discoloration of her right foot with ulcer formation on the toes. She was admitted to UMMC with a diagnosis of vasculitis.

Serologic and coagulation findings are shown in Table 1. Ankle–brachial arterial indices were normal, and a surface echocardiogram failed to reveal valvular vegetations. The patient was treated with IV MP and discharged on a regimen of prednisone in an increased dosage (60 mg/day). Her treatment with celecoxib was continued. She returned 1 week later with an ischemic, pulseless right foot. Arteriography revealed a large, elongated thrombus of the distal right common iliac artery extending to and occluding the right internal iliac

Table 3. Temporal relationship between initiation of cyclooxygenase 2 inhibition treatment and development of thrombotic symptoms

	Patient 1	Patient 2	Patient 3	Patient 4
Duration of treatment prior to symptoms	2 weeks (2 doses)	1 week	2 days (3 doses)	2–5 months*
Prescribed dosage	200 mg twice daily as needed	100 mg twice daily	200 mg once or twice daily	200 mg twice daily

* Symptoms attributed to vasculitis 2 months after initiation of treatment in this patient may, in retrospect, have been due to thrombosis.

artery. Occlusive thrombus was also present within the distal right popliteal artery above the level of the knee. Occlusive emboli involved the proximal right anterior tibial, proximal peroneal, and proximal posterior tibial arteries. There was no evidence of atherosclerotic disease. The patient was treated with thrombolytic infusion therapy that resulted in some improvement; however, surgical embolectomy was needed for restoration of blood flow to the pedal vessels. Long-term warfarin therapy was instituted prior to discharge.

DISCUSSION

This is the first report of thrombosis temporally associated with administration of a specific COX-2 inhibitor (Table 3). The findings in these patients raise the possibility that specific inhibition of COX-2 may shift the hemostatic balance toward a prothrombotic state in some patients. Specific inhibition of COX-2 decreases systemic PGI_2, a significant proportion of which is likely derived from the vascular endothelium (7,8). PGI_2 is a potent inhibitor of platelet function and vascular tone (9), and decreased PGI_2 production results in the loss of a natural inhibitor of platelet activation. Reduced PGI_2 synthesis may act in concert with other thrombotic risk factors occurring in a given patient to precipitate acute vascular occlusion. This risk is likely increased in patients whose platelet TXA_2 synthesis is already elevated.

Recent studies have shown that COX-2 is the primary isoform responsible for the systemic biosynthesis of PGI_2 under physiologic conditions in humans (7,8). This finding is consistent with in vitro data showing that laminar, but not turbulent, shear stress induces selective and sustained up-regulation of COX-2 in macrovascular endothelial cells (10). Endothelial COX-2 expression may also be increased in the presence of atherosclerotic disease or proinflammatory cytokines, both of which can be present in patients with CTD (11,12).

The influence of celecoxib on PGI_2 production in these patients occurred in the context of risk factors that collectively predispose to thrombosis. Two patients had elevated levels of ACA, 1 had LAC, and 1 had previously elevated ACA with a history of thrombosis and miscarriage typical of the antiphospholipid syndrome (APS). ACA and LAC are part of the spectrum of antiphospholipid antibodies (aPL) that predispose to arterial and venous thrombosis (13). The mechanism of vascular thrombosis in patients with APS is not completely known, but it is likely multifactorial (13). There is evidence that alterations of eicosanoid generation may be involved. Patients with aPL have increased TXA_2 levels, suggesting a role for platelet activation in the pathophysiology of thrombotic events (13,14). In fact, an imbalance of thromboxane/prostacyclin biosynthesis based on measurement of urinary metabolites has been previously proposed as being crucial to development of thrombosis in patients with LAC (15).

In a recent study of patients with SLE, enhanced excretion of urinary TXA_2 metabolites was highly associated with the presence of aPL and evidence of endothelial perturbation, as determined by elevated urinary excretion of von Willebrand factor and tissue plasminogen activator (16). Over a median followup period of 48 months, all patients who developed vascular complications of myocardial infarction, stroke, or deep venous thrombosis had elevated urinary 11-dehydro-TXB_2 excretion (16). Further evidence for the importance of eicosanoid production in patients with aPL comes from in vitro studies that demonstrate increased platelet TXA_2 production and aggregation when platelets are cultured with β_2-glycoprotein I and ACA (17).

The patients described herein had elevated urinary metabolites of systemic TXA_2 and PGI_2. This finding corroborates studies demonstrating that platelet activation is present in patients with aPL (16). The increased excretion of 2,3-dinor-6-keto $PGF_{1\alpha}$ in these patients is consistent with the concept that the production of PGI_2 is an important restraint on the excessive activation of platelets. It also suggests that patients with a known prothrombotic state and elevated platelet TXA_2 production may be at risk for thrombosis when selective COX-2 inhibitors are administered.

Three of these patients had reduced levels of free protein S antigen (patient 1 21%, patient 2 26%, patient

4 40%; normal 43–132%); this was not measured in patient 3. Protein S is a required cofactor for activated protein C to function as an anticoagulant. We suspect that in these patients, reduced free protein S resulted from the inflammatory state that elevated C4b-binding protein levels, leading to a shift of free protein S to the complexed, inactive form. Although a reduced protein S level alone may not have been sufficient to trigger thrombus formation, when combined with other risk factors it may have contributed to the clinical presentation.

Independent of the prothrombotic risk factors described above, these patients also had abnormal vascular endothelial cell function that could have interfered with the constitutive anticoagulant nature of the endothelium. The patients with SLE had active disease with hypocomplementemia and elevated levels of anti-DNA antibodies, suggesting circulating immune complexes. The patient with SSc had reduced complement levels as well. Patient 1 also smoked cigarettes and had evidence of atherosclerotic disease by arteriography and by pathologic examination after embolectomy.

A causal relationship between the initiation of treatment with a specific COX-2 inhibitor and these thrombotic events cannot be established on the basis of the available evidence, even though the temporal relationship is impressive and the pathophysiologic rationale well-founded. These findings are, however, consistent with a hypothesis that thrombosis is an adverse consequence of inhibition of prostacyclin biosynthesis in patients with a prothrombotic disorder. Additional evidence would be needed to support or refute this hypothesis. Certainly these observations, together with the knowledge that COX-2 inhibitors selectively block prostacyclin biosynthesis, suggest the need for heightened surveillance of the consequences of specific COX-2 inhibition in patients with diseases that predispose to thrombosis.

ACKNOWLEDGMENT

The authors are grateful to Dr. John A. Oates, Vanderbilt University, for manuscript review and many insightful comments.

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PERSPECTIVE

Failing the Public Health — Rofecoxib, Merck, and the FDA

Eric J. Topol, M.D.

On May 21, 1999, Merck was granted approval by the Food and Drug Administration (FDA) to market rofecoxib (Vioxx). On September 30, 2004, after more than 80 million patients had taken this medicine and annual sales had topped $2.5 billion, the company withdrew the drug because of an excess risk of myocardial infarctions and strokes. This represents the largest prescription-drug withdrawal in history, but had the many warning signs along the way been heeded, such a debacle could have been prevented.

Neither of the two major forces in this five-and-a-half-year affair — neither Merck nor the FDA — fulfilled its responsibilities to the public. The pivotal trial for rofecoxib involved 8076 patients with rheumatoid arthritis and demonstrated that this coxib had lower gastrointestinal toxicity than naproxen.[1] Even though the drug was approved in 1999 on the basis of data submitted to the FDA, the data were not submitted to a peer-reviewed journal until the following year and did not appear in print until November 23, 2000, one and a half years after commercial approval had been granted. The cardiovascular data reported in that article were incomplete, in part because of incomplete ascertainment: the design and execution of the trial had not anticipated that untoward cardiovascular events might occur.[1]

It was not until February 8, 2001, that the FDA Arthritis Advisory Committee met to discuss concern about the potential cardiovascular risks associated with rofecoxib. It remains unclear why the FDA waited two years after its review and approval of rofecoxib to conduct this meeting. My colleagues and I reviewed the data from the meeting that were made publicly accessible and published an analysis of all the available data on rofecoxib and celecoxib on August 22, 2001.[2] Our primary conclusion, based on the clear-cut excess number of myocardial infarctions associated with rofecoxib and the numerical, albeit not statistically significant, excess associated with celecoxib, was that "it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents."[2] Such a trial needed to be conducted in patients with established coronary artery disease, who frequently have coexisting osteoarthritis requiring medication and have the highest risk of further cardiovascular events. Given the very high coincidence of coronary disease and arthritis, this group may represent the largest segment of the population for whom rofecoxib was prescribed. In light of the insight that arterial inflammation is the basis for myocardial infarction and stroke and the knowledge that coxibs reduce the production of biomarkers of inflammation such as C-reactive protein and improve endothelial function, such a trial would also have been quite attractive from the standpoint of potential benefit. The trial would have prospectively determined the incidence of cardiovascular events, whose possible association with coxib treatment had not been anticipated in the early and pivotal trials of these drugs.

Unfortunately, such a trial was never done. The FDA has the authority to mandate that a trial be conducted, but it never took the initiative. Instead of conducting such a trial at any point — and especially after the FDA advisory committee meeting in 2001 — Merck issued a relentless series of publications, beginning with a press release on May 22, 2001, entitled "Merck Reconfirms Favorable Cardiovascular Safety of Vioxx" and complemented by numerous papers in peer-reviewed medical literature by Merck employees and their consultants. The company sponsored countless continuing medical "education" symposiums at national meetings in an effort to debunk the concern about adverse cardiovascular effects. The message that was duly re-

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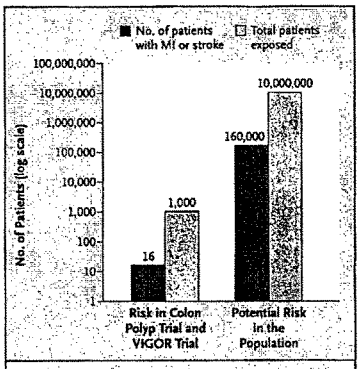

Risk of Myocardial Infarction (MI) or Stroke Associated with Rofecoxib Use.

Data are from Mukherjee et al.[2] and the Adenomatous Polyp Prevention on Vioxx (APPROVe) study.

inforced was that rofecoxib had no cardiovascular toxicity: rather, naproxen was cardioprotective. Only by happenstance, in a trial involving 2600 patients with colon polyps who could not have been enrolled if they had had any cardiovascular disease, was it discovered that 3.5 percent of the patients assigned to rofecoxib had myocardial infarction or stroke, as compared with 1.9 percent of the patients assigned to placebo ($P<0.001$), necessitating premature cessation of the trial and the decision to discontinue treatment with rofecoxib.

Over the course of the five-and-a-half-year saga, many epidemiologic studies confirmed and amplified the concern about the risk of myocardial infarction and serious cardiovascular events associated with rofecoxib.[3] These studies considered large populations, up to 1.4 million patients, tracking the use of various nonsteroidal antiinflammatory medications or coxibs to determine the risk of adverse events. Each time a study was presented or published, there was a predictable and repetitive response from Merck, which claimed that the study was flawed and that only randomized, controlled trials were suitable for determining whether there was any risk. But if Merck would not initiate an appropriate trial and the FDA did not ask them to do so, how would the truth ever be known?

Meanwhile, Merck was spending more than $100 million per year in direct-to-consumer advertising — another activity regulated by the FDA and a critical mechanism in building the "blockbuster" status of a drug with annual sales of more than $1 billion. For the past few years, every month has seen more than 10 million prescriptions for rofecoxib written in the United States alone. At any point, the FDA could have stopped Merck from using direct-to-consumer advertising, especially given the background concern that the cardiovascular toxicity was real and was receiving considerable confirmation in multiple studies conducted by investigators who were independent of Merck. The only significant action taken by the FDA occurred on April 11, 2002, when the agency instructed Merck to include certain precautions about cardiovascular risks in its package insert. The FDA also sponsored one of the large epidemiologic studies performed in a cohort of Kaiser Permanente patients.

Considering the tens of millions of patients who were taking rofecoxib, we are dealing with an enormous public health issue. Even a fraction of a percent excess in the rate of serious cardiovascular events would translate into thousands of affected people. Given the finding in the colon-polyp trial in low-risk patients without known cardiovascular disease — an excess of 16 myocardial infarctions or strokes per 1000 patients — there may be tens of thousands of patients who have had major adverse events attributable to rofecoxib (see Figure).

I believe that there should be a full Congressional review of this case. The senior executives at Merck and the leadership at the FDA share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health. Sadly, it is clear to me that Merck's commercial interest in rofecoxib sales exceeded its concern about the drug's potential cardiovascular toxicity. Had the company not valued sales over safety, a suitable trial could have been initiated rapidly at a fraction of the cost of Merck's direct-to-consumer advertising campaign. Despite the best efforts of many investigators to conduct and publish meaningful independent research concerning the cardiovascular toxicity of rofecoxib, only the FDA is given the authority to act. In my view, the FDA's passive position of waiting for data to accrue is not acceptable, given the strong signals that there was a problem and the vast number of patients who were being exposed. Furthermore, the tradeoff here involved a drug for symptoms of arthritis, for which many alternative medications are available, in the

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context of serious, life-threatening cardiovascular complications. Certainly there are many facts that we are not privy to, such as the direct communication between the FDA and Merck, but all the facts can and should be scrutinized closely in a Congressional review in order to avert such a catastrophe in the future.

From the Cleveland Clinic Foundation, Cleveland.

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Coxibs and Cardiovascular Disease

Garret A. FitzGerald, M.D.

The coxibs are a subclass of nonsteroidal anti-inflammatory drugs (NSAIDs) designed to inhibit selectively cyclooxygenase-2 (COX-2).[1] Their development was based on the hypothesis that COX-2 was the source of prostaglandins E_2 and I_2, which mediate inflammation, and that cyclooxygenase-1 (COX-1) was the source of the same prostaglandins in gastric epithelium, where they afford cytoprotection. Three coxibs — celecoxib, rofecoxib, and valdecoxib — have been approved for use by the Food and Drug Administration (FDA); a fourth, etoricoxib, has been approved by the European regulatory authority, and it and a fifth, lumiracoxib, are currently under consideration for FDA approval.

Coxibs have been aggressively marketed directly to consumers in the United States and have rapidly dominated the prescription-drug market for NSAIDs, accounting for worldwide sales of roughly $10 billion. Rofecoxib has now been withdrawn from the market by Merck, following the premature cessation, by the data and safety monitoring board, of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study, which was designed to determine the drug's effect on benign sporadic colonic adenomas. This action was taken because of a significant increase by a factor of 3.9 in the incidence of serious thromboembolic adverse events in the group receiving 25 mg of rofecoxib per day as compared with the placebo group. Blood pressure was elevated in patients in the rofecoxib group early in the course of the study, but the incidence of myocardial infarction and thrombotic stroke in the two groups began to diverge progressively after a year or more of treatment.

Coincident with the approval of rofecoxib and celecoxib in 1999, my colleagues and I reported that both drugs suppressed the formation of prostaglandin I_2 in healthy volunteers.[2] Prostaglandin I_2 had previously been shown to be the predominant cyclooxygenase product in endothelium, inhibiting platelet aggregation, causing vasodilatation, and preventing the proliferation of vascular smooth-muscle cells in vitro. However, it was assumed that prostaglandin I_2 was derived mainly from COX-1, the only cyclooxygenase species expressed constitutively in endothelial cells. This assumption later proved incorrect, since studies in mice and humans showed that COX-2 was the dominant source. The individual cardiovascular effects of prostaglandin I_2 in vitro contrast with those of thromboxane A_2, the major COX-1 product of platelets, which causes platelet aggregation, vasoconstriction, and vascular proliferation.

Whereas aspirin and traditional NSAIDs inhibit both thromboxane A_2 and prostaglandin I_2, the coxibs leave thromboxane A_2 generation unaffected, reflecting the absence of COX-2 in platelets. Increasing laminar shear stress in vitro increases the expression of the gene for COX-2, leading our group to suggest that COX-2 might be hemodynamically induced in endothelial cells in vivo. If so, suppression of the COX-2–dependent formation of prostaglandin I_2 by the coxibs might predispose patients to myocardial infarction or thrombotic stroke.

Thus, a single mechanism, depression of prostaglandin I_2 formation, might be expected to elevate blood pressure, accelerate atherogenesis, and predispose patients receiving coxibs to an exaggerated thrombotic response to the rupture of an atherosclerotic plaque. The higher a patient's intrin-

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 54

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 2 3 2004

Mathias Hukkelhoven, Ph.D.
Senior Vice President, Global Head
Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Dr. Hukkelhoven:

I am writing in response to your November 13, 2003, letter regarding the publication policies of the Food and Drug Administration (FDA's) Center for Drug Evaluation and Research (CDER). Your letter expressed concern about the Agency's submission of a letter to the editor of the New England Journal of Medicine, conveying a safety assessment of your product Zometa, without first discussing the safety issue with Novartis.

We agree with your assertion that when the FDA identifies safety concerns with a product, the sponsor should immediately be notified. We also agree that remedial actions to address safety concerns, including changes to the labeling, should first be addressed through a dialogue between FDA and the sponsor, and any necessary remedial actions should be taken promptly. Only after any concerns are discussed and addressed should publication of the agency's findings be considered. We have decided to review our internal policies and procedures to determine whether they appropriately convey this approach and will make revisions if necessary.

I thank you for bringing this issue to our attention. Please do not hesitate to contact me if you have any additional questions or concerns.

Sincerely,

Robert Temple

Robert Temple, M.D.
Director
CDER Office of Medical Policy

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 55

-----Original Message-----
From: Trontell, Anne E
Sent: Thursday, May 13, 2004 4:19 PM
To: Beitz, Julie G; Brinker, Allen D; Bonnel, Renan A
Cc: Avigan, Mark I; Seligman, Paul; Chen, Min Chu; Harvey, Brian
Subject: Merck and Drugs in Aging publication re rofecoxib

Julie, Allen, and Renan,

I was contacted by Dr. Braunstein of Merck asking why they were not informed about the submission and publication of the article in the link below. He indicated that after the Vioxx and aseptic meningitis letter was published a few years back and created a lot of press interest without Merck's prior awareness, there had been an agreement that Merck would be informed prior to any FDA publication about one of their drug products. Can any of you inform me about when this paper was submitted, who cleared it, and whether anyone attempted to inform the company? With Larry Goldkind as one of the authors, I would expect that it was submitted some time ago.

FYI, Dr. Braunstein indicated that his supervisor, Dennis Urb (sp?) might contact FDA management about tl event.

Anne

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=151327

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United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 56

Graham, David J

From: Seligman, Paul
Sent: Friday, August 13, 2004 7:21 AM
To: Graham, David J
Subject: Re: cox-2 ispe poster- more comments

David,

Please sent me the latest draft of your poster.

I would like to discuss with you and the co-authors this afternoon the one conclusory statement regarding high dose rofecoxib use that I commented on earlier.

The statement has been the one impediment in keepng me from clearing the presentation. I would like to resolve today.

Thanks foe your cooperation.

Paul

Sent from my BlackBerry Wireless Handheld (www.BlackBerry.net)

Graham, David J

From: Graham, David J
Sent: Friday, August 13, 2004 5:12 PM
To: Seligman, Paul
Subject: RE: COX2 Poster at ISPE

Paul,

Thanks for forwarding John's email. I've gone about as far as I can without compromising my deeply-held conclusions about this safety question. I've also shared with you the perspectives of my co-authors and I think it's safe to say they share these same conclusions. The *a priori* reason for our doing this study was not that we reach a conclusion consistent with FDA's handling of the issue in labeling. You know my views about the effectiveness of labeling and if Duract taught us anything, it's that you can't restrict their use to a limited duration of time. Also, physicians aren't computers that can optimize a therapeutic decision balancing pain against risk of AMI or SCD. Most of rofecoxib high dose use is for more than 5 days, and is more often measured in months. The company's RCTs show no added efficacy for the 50 mg dose above that with the 25 mg dose in treating chronic OA.

Dave

---Original Message-----
From: Seligman, Paul
Sent: Friday, August 13, 2004 4:46 PM
To: Graham, David J
Subject: FW: COX2 Poster at ISPE

I shared your revised conclusion with John and Jonca. John provided feedback below for your consideration.

Paul

-----Original Message-----
From: Jenkins, John K
Sent: Friday, August 13, 2004 1:23 PM
To: Seligman, Paul; Bull, Jonca
Subject: RE: COX2 Poster at ISPE

I still think this is pretty strong language since to my knowledge FDA is not contemplating such a warning for labeling. I think something like "This and other studies suggest an increased risk of AMI with rofecoxib use and should be considered by prescribers when making individual treatment decisions." This is more in line with what I think we have done with the labeling.

John

Graham, David J

From: Seligman, Paul
Sent: Friday, August 13, 2004 7:21 AM
To: Graham, David J
Subject: Re: cox-2 ispe poster- more comments

David,

Please sent me the latest draft of your poster.

I would like to discuss with you and the co-authors this afternoon the one conclusory statement regarding high dose rofecoxib use that I commented on earlier.

The statement has been the one impediment in keepng me from clearing the presentation. I would like to resolve today.

Thanks foe your cooperation.

Paul

Sent from my BlackBerry Wireless Handheld (www.BlackBerry.net)

Graham, David J

From: Quinn, Kathleen K.
Sent: Wednesday, August 25, 2004 4:14 PM
To: Seligman, Paul; Trontell, Anne E
Cc: Graham, David J
Subject: RE: anti-inflammatory study?

One quick thing--do we have a copy of the paper/study etc.?

Kathleen K. Quinn
Director Media Relations Staff
Office of Public Affairs (301-827-3414)

-----Original Message-----
From: Seligman, Paul
Sent: Wednesday, August 25, 2004 10:34 AM
To: Quinn, Kathleen K.; Trontell, Anne E; Seligman, Paul
Cc: Graham, David J
Subject: RE: anti-inflammatory study?

Kathleen,

Yes, I am familiar with the study. FDA provided some support for the study. It was conducted in collaboration with Kaiser Permanente of California using their data. In David's absence, I think the reporter should talk to the Kaiser folks. They are Drs. Campen, Cheetham, Hui and Spence, all of whom are with Kaiser. I believe David will be back in the office on Monday, August 30th.

Unfortunately, I don't have contact information for the Kaiser folks, but am sure the reporter can find them using a Kaiser Permanente directory.

Let me know if I can be of further assistance.

Paul

-----Original Message-----
From: Quinn, Kathleen K.
Sent: Wednesday, August 25, 2004 9:35 AM
To: Trontell, Anne E; Seligman, Paul
Subject: FW: anti-inflammatory study?
Importance: High

Paul/Anne,

I hear from the reporter that David is out of the country possibly presenting this study. Do you know anything about this study or who else may? Was it funded by FDA, what the conculsions were? if anyone else can talk on it or just David? Please let me know what you can.

Thank you.

Kathleen K. Quinn
Director Media Relations Staff
Office of Public Affairs (301-827-3414)

-----Original Message-----
From: Quinn, Kathleen K.
Sent: Wednesday, August 25, 2004 9:20 AM
To: Graham, David J
Cc: Trontell, Anne E; Seligman, Paul
Subject: anti-inflammatory study?

David,

I have a call from Reuters requesting to speak to you on a study/paper you may have authored with Kaiser Permante on anti-inflammatory issues? I don't know much about this so if this is the case can you fill me in and let me know if you are interested in speaking to the reporter?

Thank you.

Kathleen K. Quinn
Director Media Relations Staff
Office of Public Affairs (301-827-3414)

Graham, David J

From: brucev.stadel@verizon.net
Sent: Thursday, September 30, 2004 11:47 AM
To: grahamd@cder.fda.gov
Subject: NYTimes.com Article: Merck Pulls Vioxx Painkiller

From Market, and Stock Plunges
Content-Type: text/plain; charset=US-ASCII
MIME-Version: 1.0

The article below from NYTimes.com
has been sent to you by brucev.stadel@verizon.net.

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Bruce

brucev.stadel@verizon.net

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\----------/

Merck Pulls Vioxx Painkiller
From Market, and Stock Plunges

September 30, 2004
By TERENCE NEILAN

Merck & Company announced today that it was immediately pulling its arthritis and acute pain medication Vioxx from the worldwide market after data from a clinical trial showed that the drug produced an increased risk for heart attacks and strokes.

"We are taking this action because we believe it best serves the interests of patients," the chairman, president and chief executive officer of Merck, Raymond V. Gilmartin, said in a statement on the New Jersey company's Web site.

"Although we believe it would have been possible to continue to market Vioxx with labeling that would ncorporate these new data, given the availability of lternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take."

Merck's shares plunged by more than $12 to as low as $32.46 when trading opened on the New York Stock Exchange this morning, and the stock remained down by about 25 percent in early trading - reducing the company's market capitalization by about $26 billion.

Shares of Pfizer, maker of Celebrex, Vioxx's main competitor, were up $1.24 to $31.50, at the opening, but fell back to $30.50 in early trading..

The Vioxx risk came to light during a three-year trial designed to evaluate the efficacy of taking the drug in preventing a recurrence of colorectal polyps in patients with a history of benign colorectal tumors, the company said.

Merck found that after 18 months of treatment, patients taking Vioxx were at greater risk for heart attacks compared with those taking a placebo.

At a news conference in New York this morning, Merck officials said they received the data last friday and examined it over the weekend, holding meetings with various medical experts.Officials informed the board of directors Tuesday morning and later that day met with the F.D.A. to inform it of their intentions. The company then informed other regulatory agencies around the world.

Mr. Gilmartin asserted that Merck remained "very strong financially." He said there would be no need to close any plants based on this action. "We had anticipated expanding the sales forces," he said. "This will allow us to redeploy our sales force instead of hiring new employees, and researchers and scientists associated with Vioxx will be able to deployed elsewhere."

But he acknowledged that he expected some people to leave the company. In reply to a question, he said he would not resign.

Mr. Gilmartin said he expected earnings per share to be "negatively affected by 50 to 60 cents" a share, and as a results they were pulling back on its third-quarter earnings estimate.

Merck officials declined to speculate on potential litigation against the company or the impact it might have.

Mr. Gilmartin said Merck would undertake "many pro-active steps" to inform patients of the recall, including placing advertisements in newspapers. Information can be found on the Web sites merck.com and vioxx.com.

The Merck clinical trial confirmed the findings of a Food and Drug Administration investigator who reported similar risks with the drug in August.

The difference in heart risk was statistically significant between a recommended dose of Vioxx, 25 milligrams a day or less, and Celebrex, according to results the investigator, Dr. David Graham, presented Aug. 25 at a conference in France of the International Society for Pharmacoepidemiology.

The study also found that Vioxx doses in excess of 25 milligrams a day more than tripled the risk, compared with

patients who had not taken painkillers within the past two months.

He said his findings did not reflect the F.D.A.'s official position.

At that time, Merck disagreed with the results of the study, a spokeswoman, Mary Elizabeth Blake, said. Conclusions from that type of examination do not carry as much weight as results from a study comparing two groups of patients actually taking the medicines for a set period, she said. Vioxx was launched in the United States in 1999 and has been marketed in more than 80 countries, Merck said. In some countries, the product is marketed under the trademark Ceoxx. Worldwide sales of Vioxx in 2003 amounted to $2.5 billion, the company statement said.

"While the cause of these results is uncertain at this time, they suggest an increased risk of confirmed cardiovascular events beginning after 18 months of continuous therapy," Peter S. Kim, Ph.D., president of Merck Research Laboratories, said in the Web site statement. "While we recognize that Vioxx benefited many patients, we believe this action is appropriate."

http://www.nytimes.com/2004/09/30/business/30CND-MERCK.html?ex=1097559232&ei=1&en=6cda4d00ed12bf31

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Graham, David J

From: Felix M Arellano [arellanofm@msn.com]
Sent: Thursday, September 30, 2004 10:57 AM
To: David J Graham
Subject: More on Vioxx

Quite a bit of CYA in the Q&A... not a mention of the fact that there were three studies before, including yours, showing the same. By the way, in order to justify the results of VIGOR by naproxen cardioprotection it would have to be way better than aspirin, clopidogrel and dipyridamole together.

Regards,
http://www.fda.gov/bbs/topics/news/2004/NEW01122.html

Felix

Graham, David J

From: Bruce M. Psaty [psaty@u.washington.edu]
Sent: Friday, October 01, 2004 9:45 AM
To: David J Graham

David,

Strong work on Vioxx!

Bruce

==========

Bruce M. Psaty, MD, PhD
Professor, Medicine & Epidemiology
University of Washington
Cardiovascular Health Research Unit
1730 Minor Avenue, Suite #1360
Seattle, WA 98101-1448
Phone: 206/287-2777
Fax: 206/287-2662
Email: psaty@u.washington.edu

==========

Graham, David J

From: Dr. Gurkirpal Singh [gsingh@stanford.edu]
Sent: Monday, October 04, 2004 11:24 AM
To: Graham, David J
Subject: RE: Vioxx

I can't believe it! And this is when you were proved right! What if you were wrong?

Thanks for speaking with David Campen. I look forward to hearing from him.

Gurkirpal

At 04:48 AM 10/4/2004, you wrote:

> Believe it or not, I'm being treated as if I was Benedict Arnold-with antagonism, hostility and a strong dose of ostracism.
>
> Dave
>
> ----Original Message----
> From: Gurkirpal S Sehgal [mailto:gsingh@stanford.edu]
> Sent: Thursday, September 30, 2004 11:22 PM
> To: GRAHAMD@cder.fda.gov
> Subject: Vioxx
>
> Dave,
>
> Now, you are a hero ! Is the White House inviting you yet for the Commissioner job?
>
> On another note, did you get a chance to speak with David Campen?
>
> Gurkirpal

Graham, David J

From: Stadel, Bruce V
Sent: Friday, October 01, 2004 6:19 AM
To: Trontell, Anne E
Cc: Graham, David J
Subject: RE: Request for your help for internal FDA peer review

I was involved as a Cosultant in the early part of the study and think it would therefore be inappropriate for me to act as a reviewer.

Sincerely,

Bruce V. Stadel, MD, MPH
Medical Officer
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation 2
Center for Drug Evaluation & Research
Food & Drug Administration
Parklawn Building, Room 14B45, HFD-510
5600 Fishers Lane
Rockville, Maryland 20857-0002
Phone: (301) 827-6417
Email: stadel@cder.fda.gov

—Original Message—
From: Trontell, Anne E
Sent: Thursday, September 30, 2004 6:50 PM
Cc: Seligman, Paul; Trontell, Anne E
Subject: Request for your help for internal FDA peer review

Colleagues,

Paul Seligman and I request your help and advanced epidemiologic expertise to help us review the methods employed in a case control study using propensity score matching for controls and also using a composite cardiovascular risk score based on 30 variables. There are 2 papers: one a methods paper and the other a results paper. The latter deals with the risk of AMI and sudden cardiac death with NSAIDs. We are especially interested in a close evaluation of this study done in Kaiser Permanente because of today's market withdrawal of Vioxx.

We do not have a fixed timeframe to complete the review, but are seeking as timely feedback as possible on this public health issue. Would you be able to review these papers by the end of October?

Thanks for considering this invitiation. If you have others in FDA who you would recommend as a reviewer, or if you can recommend an outside SGE who would be as well qualified as yourselves, we would very much appreciate it.

Thank you.

Anne Trontell

Anne Trontell, M.D., M.P.H.
Deputy Director
Office of Drug Safety
Center for Drug Evaluation and Research
15B-33 Parklawn
HFD-400
5600 Fishers Lane
Rockville MD 20857
301-827-3219
301-443-5161 (fax)
trontella@cder.fda.gov

Graham, David J

From: Galson, Steven
Sent: Friday, October 08, 2004 12:56 PM
To: Graham, David J
Subject: RE: your comments in today's washington post

David,
I hear you. I have non-stopped mtgs until 5. Will call you as soon as I can after that.
S

-----Original Message-----
From: Graham, David J
Sent: Friday, October 08, 2004 12:08 PM
To: Galson, Steven
Cc: Seligman, Paul; Trontell, Anne E; Graham, David J
Subject: FW: your comments in today's washington post

Steve,

I've thought more about your comments in today's Post. If you were misquoted by the Post, I request that you contact the Post today to issue a retraction of your misquoted remarks about my having missed deadlines. If you were not misquoted, I request that you write a letter to the editor of the Post for publication there, in which you set the record straight with regard to the deadline for my report, stating clearly that I did indeed meet the deadline I was given. As it stands, your published remarks have defamed my name and reputation. If there are any other media outlets to which you have made similar remarks that have been published or aired on radio, television, cable or internet outlets, I request that you similarly correct the public record.

Thank-you,

Dave

-----Original Message-----
From: Graham, David J
Sent: Friday, October 08, 2004 10:19 AM
To: Galson, Steven
Cc: Seligman, Paul; Trontell, Anne E; Graham, David J
Subject: your comments in today's washington post

Steve,

I read your remarks in this morning's Post. To set the record straight, and so you have the correct facts, there was only one deadline related to our COX-2 AMI/SCD study that was ever discussed or conveyed to me. That deadline was September 30, 2004 for the completion of a study report. I met that deadline. I spoke with Paul Seligman about this this morning and he told me that he knew I had met (not missed) the deadline and would convey that to you. He suggested that you may have been mis-quoted by the press which, we all know, can happen.

I think it is also important for you to know that when Paul discussed this deadline with me, I told him that it was too short a time-frame in which to produce a report that would meet my personal standards (especially as regards an adequate literature review and well-framed discussion), and used as an example, our statin/rhabdo paper, which took me 2 months to get into the proper shape after all the analyses had been completed. As it is, I worked many 12 hour days and weekends after I was informed of the September 30 deadline in order to meet it. Finally, I learned this morning from Dr. Rennie at JAMA that our statin paper has been accepted for publication.

Thank-you,

Dave

Graham, David J

From: Seligman, Paul
Sent: Monday, August 30, 2004 6:13 PM
Lemley, Lee; Trontell, Anne E
Cc: Graham, David J
Subject: RE: Vioxx Question

Lee,

There is no study report and it has not been published. The only information I have is what was presented on the poster a ISPE.

The authors will be producing such a report for publication forthwith.

Thanks.

Paul

-----Original Message-----
From: Lemley, Lee
Sent: Monday, August 30, 2004 6:00 PM
To: Seligman, Paul; Trontell, Anne E
Subject: Vioxx Question

Is the study actually public or did we just present from the study. OTCOM is getting flooded with calls and that is one of the questions they are asking - is the study published?

Lee

Lee Lemley
Policy Analyst
Executive Operations Staff
Office of Executive Programs
(301) 443-5575

Graham, David J

From: Galson, Steven
Sent: Friday, October 08, 2004 3:11 PM
To: Graham, David J
Cc: Seligman, Paul; Trontell, Anne E
Subject: RE: your comments in today's washington post

David,
I just had another interview with the same reporter and I corrected the misimpression. I will memorialize this in an email to him and send you copy. I didn't discuss deadlines with any other reporters. When I spoke to him yesterday I was responding to the allegation he said you were making that you had been suppressed by your management and I was trying to convey that since we didn't have a full study report (at the time) there wasn't anything for us to suppress.
Steven

-----Original Message-----
From: Graham, David J
Sent: Friday, October 08, 2004 12:08 PM
To: Galson, Steven
Cc: Seligman, Paul; Trontell, Anne E; Graham, David J
Subject: FW: your comments in today's washington post

Steve,

I've thought more about your comments in today's Post. If you were misquoted by the Post, I request that you contact the Post today to issue a retraction of your misquoted remarks about my having missed deadlines. If you were not misquoted, I request that you write a letter to the editor of the Post for publication there, in which you set the record straight with regard to the deadline for my report, stating clearly that I did indeed meet the deadline I was given. As it stands, your published remarks have defamed my name and reputation. If there are any other media outlets to which you have made similar remarks that have been published or aired on radio, television, cable or internet outlets, I request that you similarly correct the public record.

Thank-you,

Dave

-----Original Message-----
From: Graham, David J
Sent: Friday, October 08, 2004 10:19 AM
To: Galson, Steven
Cc: Seligman, Paul; Trontell, Anne E; Graham, David J
Subject: your comments in today's washington post

Steve,

I read your remarks in this morning's Post. To set the record straight, and so you have the correct facts, there was only one deadline related to our COX-2 AMI/SCD study that was ever discussed or conveyed to me. That deadline was September 30, 2004 for the completion of a study report. I met that deadline. I spoke with Paul Seligman about this this morning and he told me that he knew I had met (not missed) the deadline and would convey that to you. He suggested that you may have been mis-quoted by the press which, we all know, can happen.

I think it is also important for you to know that when Paul discussed this deadline with me, I told him that it was too short a time-frame in which to produce a report that would meet my personal standards (especially as regards an adequate literature review and well-framed discussion), and used as an example, our statin/rhabdo paper, which took me 2 months to get into the proper shape after all the analyses had been completed. As it is, I worked many 12 hour days and weekends after I was informed of the September 30 deadline in order to meet it. Finally, I learned this morning from Dr. Rennie at JAMA that our statin paper has been accepted for publication.

Thank-you,

Dave

Graham, David J

From: Graham, David J
Sent: Friday, October 08, 2004 3:54 PM
To: Galson, Steven
Subject: RE: Yesterday's interview

Steve,

Thanks for the email. I think I would feel better if the corrected facts could be included in an article or if a correction could be printed in the paper in some fashion.

Just so you have the full story, I presented preliminary results to Paul and Anne in early May. Additional work was done during June and July because we discovered that our variables for cardiovascular hospitalizations and emergency room visits include some double-counting (patients seen in the ER and then hospitalized were counted in both categories when they should have been coded only as hospitalized because we wanted to count the most serious aspect of a given encounter). This was causing colinearity in the regression models, resulting in expected predictors of cardiovascular disease actually appearing to be protective (such as past AMI). Paul and Anne were kept informed about these problems and my progress in completing the study. After Kaiser recoded the variables (around August 5), we were able to proceed with the analysis. The analysis was completed on August 10. On August 11, I sent a poster presentation to Paul for the ISPE meeting that began on August 20. Of note, if you were to format the poster as a manuscript, you'd see that it runs about 8 pages. While it is not a full study report, it is a very detailed poster with nearly enough content for a manuscript. And most of that additional content would be in the discussion. At ISPE, those who visited the poster were impressed by its completeness. What I'm saying is that while you always want to have a study report, this poster is detailed enough for a reasonably trained epidemiologist to understand exactly what we did, how we did it and what we found. It certainly wasn't as sketchy, telgraphic or incomplete as a manuscript abstract is. This is another misconception that has been promoted by some FDA spokespersons to the media.

Dave

-----Original Message-----
From: Galson, Steven
Sent: Friday, October 08, 2004 3:22 PM
To: Graham, David J
Subject: FW: Yesterday's interview

David
As promised. I should still be able to talk at 5 if you still want to.
S

-----Original Message-----
From: Galson, Steven
Sent: Friday, October 08, 2004 3:18 PM
To: 'kaufmannm@washpost.com'
Subject: Yesterday's interview

Mark,
I wanted to memorialize what I said to you at the beginning of today's interview. I clarified that Dr. Graham had been given only one formal deadline of September 30th and that he had met it. In yesterday's interview I was referring to the fact that we didn't have a full study report from him during the time period between when he first made his findings known to his supervisor (Dr. Seligman thought this was in May) and when he turned in the full study report on September 30th.
Steven Galson

Graham, David J

From: Graham, David J
Sent: Friday, October 15, 2004 10:37 AM
To: Axelrad, Jane A
Cc: David Campen (E-mail)
Subject: RE: Posting of Report

Jane,,

The report belongs to FDA so it's FDA's decision regarding whether to post it on the web. As I stated before, the greatest concern on the part of my co-authors and myself is that such posting may jeopardize publication in a major medical journal, which is in my opinion, the appropriate forum for peer review and medical-scientific discourse. In the event that posting on the web resulted in its not being accepted by a major journal, this would represent a great loss to the medical community and to the science of postmarketing drug safety.

The "2000" number for the size of the NDTI physician panel was given to me by one of our drug-use analysts within ODS. During the IMS clearance process after I completed the report, I learned that this number is actually 3200.
Dave

-----Original Message-----
From: Axelrad, Jane A
Sent: Friday, October 15, 2004 10:02 AM
To: Graham, David J
Subject: Posting of Report

I have had discussions with Dr. Campen and as indicated below, he has agreed that we may post your report with a disclaimer. IMS also identified an error that we need to identify in the document. I have added the disclaimer to the report as shown in the attached document. Please confirm that you do not object to posting the report with this disclaimer. I need to know by noon today. Thanks.

Jane

<< File: vioxxgraham.doc >> << Message: Vioxx Study Report >>

Graham, David J

From: Trontell, Anne E
Sent: Thursday, October 28, 2004 6:37 PM
To: Graham, David J
Cc: Seligman, Paul; Trontell, Anne E

David,
I have meetings and commitments out of the office taking up most of my day this Friday. It may well happen that I will have to send out my comments on your manuscript etc. relatively late in the day. Did you already send it to the Lancet? If you have, please share the email or other address that it went to. That way I can share my comments directly with them at the same time I send them to you. Thanks!
Anne

Anne Trontell, M.D., M.P.H.
Deputy Director
Office of Drug Safety
Center for Drug Evaluation and Research
15B-33 Parklawn
HFD-400
5600 Fishers Lane
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301-827-3219
301-443-5161 (fax)
trontella@cder.fda.gov

17Sep04.

In terms of roll-out of data, the Agency prefers to receive interim safety data before efficacy data. The Agency also requested all of the open and closed ESMB sessions minutes.

ACR Meeting Presentation
The APPROVe data will be presented on 18Oct04 (Monday) evening in a half-hour plenary-type session, with 10 minutes for the presentation and 20 minutes for discussion. The Agency has been invited to participate in the session by the meeting organizers.

Graham Paper
The Agency invites our critical appraisal of the recently published paper by Graham. Specifically, the Agency would like to hear our comments on the regression model and the risk factors. MRL accepted the invitation for a Teleconference and will contact the appropriate individuals in Epidemiology.

AD CV data
We reminded the Agency that the CV data from the Alzheimer's Disease studies were provided in the labeling supplement submitted at the end of March, 2004.

Other submissions
We informed the Agency that we would be providing them with a list of the ViP study events and a copy of the Ingenix epidemiology paper.

Conclusion
The tone of the Teleconference was cordial throughout. We agreed that we would meet again next week for another update. The Teleconference concluded with a review of the action items.

Action Items

1. MRL will provide a list of investigators for non-Merck sponsored studies.
2. MRL will evaluate making the Year-4 colonoscopy optional.
3. MRL will discuss the duration of the off-drug period in APPROVe (1 yr vs. longer) with the ESMB.
4. The Agency will be provided with all of the ESMB sessions (open and closed) minutes.
5. MRL will provide the Agency with an update on the pharmacy withdrawal.
6. MRL will critique the Graham paper in a Teleconference with the Agency.
7. MRL will provide a list of CV adjudicated events from ViP.
8. MRL will provide a timeline for the submission of additional APPROVe reports.

Diane C. Louie, M.D., M.P.H.
Director
Regulatory Affairs-Domestic
Merck & Co., Inc.
RY32-605
P.O. Box 2000
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E-mail: diane_louie@merck.com

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 57

To: Weiner, Jan D.; Frazier, Kenneth C.; Reicin, Alise S.; Wainwright, Joan; Reaves, Gregory E; Dixon, Wendy L.; Beauchard, Lucine E.; Basaman, Mary Elizabeth
From: Greene, Douglas Dr.
Cc
Bcc:
Date: 2001-01-27 17:06:39
Subject: RE: Timeline on VIGOR Communications

Thanks for the timeline summary.
Do we have written responses to the VA questions? They would be helpful in discussing the issue with Dr. Fries.
Doug

Douglas A. Greene, M.D.
Executive Vice President, Clinical Sciences and Product Development
Merck Research Laboratories
Merck & Co., Inc.
RY33-628
P.O. Box 2000
Rahway NJ 07065
voicemail: 732-594-7271
office: 732-594-7272
fax: 732-594-4069
doug_greene@merck.com

-----Original Message-----
From: Weiner, Jan D.
Sent: Friday, January 26, 2001 11:34 PM
To: Frazier, Kenneth C.; Greene, Douglas Dr.; Reicin, Alise S.; Wainwright, Joan; Reaves, Gregory E; Dixon, Wendy L.; Beauchard, Lucine E.; Basaman, Mary Elizabeth
Subject: Timeline on VIGOR Communications

I did the best I could to assemble the timeline and events regarding the communications of the VIGOR data with a particular focus on the thrombotic and renal issues referenced in Dr. Fries letter. There are holes in the timeline and it lacks some specifics, and I apologize for that, but the people with specific information were not available late on Friday afternoon. If there are specific questions, please let me know what they are and we can have others fill in the missing holes. Thanks to Dr. Reicin for her mastery of this information.

Please read the first document because it contains a reference that explains the second one.

Jan Weiner

<< File: vigor timeline.doc >>

<< File: VA Questions for Merck.doc >>

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 58

CONFIDENTIAL

MEMO

January 23, 2001

TO: MR. D. W. ANSTICE

FROM: L. M. Sherwood

SUBJECT: Academic Interactions

As you know well, I have spent more than 21 years in academia and now more than 13 at Merck. As an academic chairman, I always felt responsibility for the actions (good and bad) of faculty members in my department. I believe this is generally the view held by academic department chairmen and division heads. Even though faculty members operate as independent entrepreneurs, they also represent the university or medical school when they are out doing things or speaking in the world at large. As such, they are expected to be credible, honest and fair representatives of their institutions. In this light, I have felt it appropriate in highly selected instances (fortunately, not often) to intervene with individuals and/or their division head, chair or dean, depending on the circumstance. Without trying to appear immodest, I believe I am the most respected physician in the pharmaceutical industry among academic chairs and deans. Therefore, when I call them on a matter of urgent concern, they generally take it seriously. This has been a source of strength for USHH, as I have been able to exert balanced leverage in some difficult situations.

I am obviously a strong supporter of Merck and passionate about its science, credibility and stature in the pharmaceutical world. We make our mistakes, as does everybody, but, in general, taking the high road the way Merck does, leads us to be more often right than wrong.

During the past three years, as the COX-2 wars have been waged, there have been several instances in which I have heard repeated messages from the field and headquarters about problem individuals. There is certainly no orchestrated campaign or specific program for dealing with these kinds of issues. They come up purely on an ad hoc basis. I will only get involved when our representatives, HSAs, Regional Medical Directors, MRL physicians, Senior Business Director or key individuals in the TBG have felt frustrated by their inability to reach out to or "balance" selected individuals. At such points, I have been willing to intervene either with the individual or with their superior. It is in this context that I have tried to help resolve challenges for Merck. I found the letter from Fries disappointing, with many inaccuracies and misquotes. As we discussed, it is much better for me not to get into the issues with him and let you and others deal with the situation. I did want, however, to indicate to you what my involvement has or has not been with the individuals mentioned in his letter, as follows:

1. Dr. Peter Lipsky – Dr. Lipsky was the former Chief of Rheumatology at the University of Texas Southwestern in Dallas and is currently at the National Institute of Arthritis and Musculoskeletal Diseases as Research Director. I have known Dr. Lipsky for 20 years; I once tried to recruit him to Einstein as Chief of Rheumatology. Dr. Lipsky has a checkered record with Merck. He was previously a member of the Board of Scientific Advisors for MRL. His contract was not renewed, because MRL felt that he had leaked confidential information to competitors. I was not involved in any of those discussions, and heard about it second hand, enough to know that Dr. Lipsky was not trusted by MRL.

My primary interaction with Dr. Lipsky occurred around a CME symposium that he chaired for Searle at the American College of Rheumatology 2+ years ago. The concern had to do with a symposium that was attended by a number of Merck physicians including Greg Bell, Beth Seidenberg, Ben Shapiro, etc. It was felt to be very unbalanced and highly selective in emphasizing Searle data as opposed to Merck data. We discussed the matter extensively with the TBG, MRL and the lawyers. It was decided that I would write a letter expressing our concern to the American College of Continuing Medical Education, which I did. The matter was reviewed extensively by the ACCME with the University of Texas. In the final analysis, they determined that the program was not unbalanced, although all of the Merck personnel felt differently. The matter was closed and resolved, and we have excellent relationships with the rheumatologists as the University of Texas Southwestern and with the medical school in general. Dr. Lipsky left more than a year ago for NIH, and the matter is closed. I have seen him on occasion at scientific meetings and exchanged pleasantries.

2. Dr. Andrew Whelton at John Hopkins – Dr. Whelton was a former full-time nephrologist at Johns Hopkins Medical School. He has now left the full-time faculty and works as a private consultant. He spends the major portion of his time involved with Pharmacia/Pfizer speaking about the renal and hypertensive adverse experiences of COX-2 inhibitors and emphasizing the unique safety aspects of Celebrex as opposed to VIOXX. He has published several articles on the subject. Experts in the field like Craig Brater, Dean at the University of Indiana, are in strong disagreement with Dr. Whelton on the issues and have a different view. A number of Merck personnel, including HSAs, Regional Medical Directors and members of MRL (Beth Seidenberg and Brian Daniels before they left) have talked with Dr. Whelton, tried to provide him with balancing data, etc. Dr. Whelton continues to speak regularly at symposia and talks sponsored by our competitors and to highlight differences between VIOXX and Celebrex in terms of safety. I have never met Dr. Whelton, talked with him or discussed with anyone at Johns Hopkins his activities. I have heard lots about him, but have felt others at Merck have talked extensively to him). Furthermore, since he is no longer on the full-time faculty at Johns Hopkins, there is little leverage available.

3. Dr. Michele Petri – Dr. Michele Petri is a faculty member at Johns Hopkins in Rheumatology. I have never met Dr. Petri or spoken to her. She has been known to say some "outrageous" things about Merck and VIOXX, such as Merck stealing VIOXX from Searle, etc. Others such as HSAs and Regional Medical Directors have met with Dr. Petri and had little success in helping her achieve balance. On one occasion, when Dr. Edward Benz (then Chairman of Medicine at Johns Hopkins) was visiting Merck as part of the Hopkins proposal, I mentioned to Dr. Benz confidentially that we had some concerns about some of Dr. Petri's comments in her talks. Dr. Benz threw up his hands and indicated a certain level of frustration himself with Dr. Petri. That is where the matter ended, and I have had no further information. As far as a speaking engagement being canceled, that would have been done in the field.

4. Dr. David Yocum – Dr. David Yocum is a rheumatologist at the University of Tucson whom I do not know. Whether he is currently head of the FDA Advisory Panel or not, I do not know. Dr. Pamela Davis, our Regional Medical Director in Arizona, knows Dr. David Yocum as they are both members of faculty at the University of Arizona. She has interacted with him in a very positive and friendly way. He has done a great number of clinical studies and an observational study for Searle, but he has also been involved to a limited degree in studies for Merck. According to Dr. Davis, about one year ago, some of the representatives expressed concern to the HSA in Tucson about Dr. Yocum's talks. As far as I know, nothing further happened, and my knowledge of this is strictly third hand. Dr. Yocum may have been involved with Dr. Fries' ARAMIS database (speculation from me).

5. Dr. Lee Simon – Dr. Lee Simon is an Associate Professor of Medicine at Harvard at the Beth Israel-Deaconess Hospital. He is fairly well known to me and to Merck. Dr. Simon has been extensively involved with Searle and Pfizer for many years, is widely viewed not only at Merck, but also in the academic world as an individual in the competitors camp. He is said to receive very large amounts of consulting and other grant monies from our competitors. Dr. Simon is not respected (according to our Boston team) in the Harvard community. For example, Dr. Michael Weinblatt at Brigham & Women's, current President of the ACR, has no respect for Dr. Simon. In the past, Dr. Simon has been described as giving a number of unbalanced presentations on Celebrex versus VIOXX, despite our giving him data. I have talked to Dr. Simon on a couple of occasions myself about these issues, and his talks at times have been balanced (particularly if they are in an academic institution), and at other times not. At the time of the CLASS presentation and the press release on VIGOR, Dr. Simon made the following statements to our HSA in Boston with whom I spoke: "These data will allow us to bury Merck and put the nails in Merck's coffin. VIOXX is a dangerous drug. Beth Seidenberg left Merck because she would have been fired and Charlotte McKines and Lou Sherwood will also be fired because of the VIGOR study." Dr. Simon was apparently quite vociferous, enthusiastic about the prospects of burying Merck. I thought his statements were pretty unusual for an academic. On a subsequent occasion when I had opportunity to speak to Dr. Michael Rosenblatt, President of the Beth Israel Deaconess Hospital and a former Merck employee, I mentioned to him my concern about Dr. Simon making unbalanced presentations and being so anti-Merck and aggressive in pursuing that agenda. I indicated to Dr. Rosenblatt that I felt academics should be more balanced and data-driven. On a subsequent occasion, Dr. Rosenblatt had the Chairman or Vice Chairman of the Department of Medicine talk with Dr. Simon. That is the only interaction of which I am aware. I have had subsequent casual interactions with Dr. Simon and exchanged pleasantries.

6. Dr. James McMillen – Dr. McMillen is a "rheumatologist" in Harrisburg, PA. Dr. McMillen was never trained in rheumatology, but somehow was grandfathered. Although he is in the practice of medicine in Harrisburg, he spends a major portion of his time traveling the country for Pharmacia/Pfizer, boosting Celebrex and blasting VIOXX. For example, Dr. McMillen presents a list of top 10 reasons why VIOXX should not be prescribed, a presentation that was the basis for a complaint filed by Ellen Westrick at FDA. Numerous Merck personnel, HSAs, RMDs, Business personnel have met with Dr. McMillen without success. For at least a year after he was terminated from the Penn State Medical School faculty (not because of Merck, but because he no longer did anything there) our competitors continued to list his faculty title on flyers. I heard numerous concerns for the field (Senior Business Directors, etc.) and Headquarters. I contacted the Chair of Medicine at Penn State to indicate that he was still using the title even though he was no longer on the faculty. I have never met Dr. McMillen or spoken with him on the telephone.

7. Dr. Thomas Stillman is a well-known senior rheumatologist on the faculty of the Hennepin County Hospital at the University of Minnesota. Dr. Stillman has been used by Merck in the past as a speaker, but has not been used for the last couple of years. He is passionate in his view that Celebrex is a much safer drug, and despite regular visits from the HSA (who doesn't trust him), Greg Bell, other Regional Medical Directors, Spencer Kubo, etc., Dr. Stillman continues to be a passionate advocate for our competitors. Unfortunately, a number of talks that Stillman was supposed to give were canceled abruptly by individuals in the field. This led to hard feelings, and finally at my urging, Paul Fonteyne actually met with Stillman and smoothed over the situation.

   My principal interaction with Dr. Stillman had to do with a video that he prepared for the Veterans Administration which was widely distributed. He was on the videotape, presenting

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Exhibit 59

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

NOV 16 2004

The Honorable Charles E. Grassley
Chairman, Committee on Finance
United States Senate
Washington, D.C. 20510-6200

Dear Mr. Chairman:

This is in response to your letter dated November 15, 2004, requesting that the Office of Inspector General provide available data showing total Medicaid reimbursement of Vioxx from calendar year 1999 to the present. According to data the States reported to the Centers for Medicare & Medicaid Services (CMS), Medicaid has paid in excess of $1 billion for Vioxx. The period of these expenditures was from the second quarter of 1999 (the first quarter that Vioxx was reimbursed by Medicaid) through the second quarter of 2004 (the most recent quarter available). We obtained the Medicaid reimbursed amounts from CMS's Medicaid Drug Rebate System. We cannot attest to the accuracy of these data because we have not audited the data collection system. Given this, the Committee may want to confirm the data with CMS.

The enclosed schedule provides the reimbursement amounts by calendar quarter for each of the five forms of Vioxx. We appreciate your interest in this matter. If you would like to discuss it, please contact me or have your staff call Stuart Wright, Director of External Affairs, at (202) 205-9523.

Sincerely,

Daniel R. Levinson

Daniel R. Levinson
Acting Inspector General

Enclosure

Total Medicaid Reimbursement for Merck's Vioxx Drug[1]

Calendar Year Qtr.	National Drug Codes (NDC) 00006-0074	00006-0110	00006-0114	00006-3784	00006-3785	Totals By Quarter
1999-2	$ 106,562.36	$ 81,473.98	$ -	$ 281.81	$ 129.35	$ 188,447.50
1999-3	4,391,228.19	5,358,273.29	-	9,175.33	8,992.70	9,767,669.51
1999-4	8,792,541.12	15,793,523.73	-	20,684.83	19,144.20	24,625,893.88
2000-1	9,596,239.46	22,845,182.03	3,937.39	26,133.60	30,640.00	32,502,132.48
2000-2	10,552,068.04	31,891,990.63	1,090,956.77	33,142.15	36,591.57	43,604,749.16
2000-3	11,248,322.66	40,559,821.32	2,436,763.94	38,485.22	54,055.61	54,337,448.75
2000-4	11,231,948.81	45,929,964.79	3,461,139.37	58,100.86	64,284.35	60,745,438.18
2001-1	10,688,720.27	50,487,609.37	4,492,695.04	71,114.78	79,004.75	65,819,144.21
2001-2	10,224,999.02	53,722,609.35	5,476,896.01	87,812.60	86,172.29	69,598,489.27
2001-3	10,366,469.32	53,625,957.06	5,570,843.46	91,395.11	77,157.24	69,731,822.19
2001-4	10,473,409.22	55,103,217.88	5,987,305.42	96,113.03	83,446.30	71,743,491.85
2002-1	9,619,970.18	52,900,255.55	6,027,192.54	99,563.06	80,639.96	68,727,621.29
2002-2	8,574,961.50	48,792,806.98	5,378,186.77	103,907.45	80,793.52	62,930,656.22
2002-3	7,921,280.23	45,116,659.60	4,874,375.00	103,230.29	81,810.50	58,097,355.62
2002-4	7,656,324.74	44,520,303.15	4,769,326.64	93,933.93	84,631.66	57,124,520.12
2003-1	7,361,479.86	43,544,429.98	4,220,524.50	92,857.27	100,912.52	55,320,204.13
2003-2	7,242,480.67	43,437,795.74	4,006,155.14	100,426.56	106,153.42	54,893,011.53
2003-3	7,716,081.02	45,325,316.13	4,130,150.49	120,382.76	116,322.23	57,408,252.63
2003-4	7,530,177.07	45,260,844.98	3,843,845.31	127,747.70	114,200.37	56,876,815.43
2004-1	7,151,394.95	43,276,759.96	3,574,060.78	101,625.85	101,345.12	54,205,186.66
2004-2	7,525,395.35	48,050,959.63	3,802,502.71	128,507.77	127,837.99	59,635,203.45
Totals	$ 175,972,054.04	$ 835,625,755.13	$ 73,146,857.28	$ 1,604,621.96	$ 1,534,265.65	$ 1,087,883,554.06

NDCs for Merck's Vioxx drugs were identified from the "2003 Red Book."
Reimbursement data was obtained from CMS's Medicaid Drug Rebate System.

00006-0074 = 12.5 milligram tablet
00006-0110 = 25 milligram tablet
00006-0114 = 50 milligram tablet
00006-3784 = 12.5 milligram/5 milliliter suspension
00006-3785 = 25 milligram/5 milliliter suspension

[1]Source of the data is from unaudited States' submissions to CMS.

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Exhibit 60

Braunstein, Ned S.

From: Louie, Diane
Sent: Thursday, October 07, 2004 12:55 PM
To: Braunstein, Ned S.
Subject: 07Oct04: FDA T-con IND 46,894/59,222

Importance: High

Follow Up Flag: Follow up
Flag Status: Completed

Categories: VIOXX

Ned, please review.

- A Teleconference was held at the Agency's request on Thursday, October 07, 2004, to discuss the status of the Vioxx withdrawal and the timeline of providing the APPROVe data to the Agency.

FDA attendees included: Drs. Jonca Bull, Brian Harvey, Sharon Hertz, Rumble; and Project Management staff: Gould, DeBellas, and Rodgers.

Merck attendees: Drs. Ned Braunstein, Diane Louie, Janet van Adelsberg, Sean Curtis.

Withdrawal Activities
The Agency requested an update on the withdrawal activities, per 21CFR 312.56(d). The active trials include APPROVe, ViP, VICTOR (Oxford-sponsored), and PN269 (ODT formulation pilot). We informed the Agency that letters had been sent to all investigators notifying them that Vioxx has been withdrawn from the market and that dosing is terminated in all Vioxx trials. The investigators were provided with a patient notification letter that the patients are to be asked to sign. Investigators of non-Merck studies, including MSG-funded ones, were also sent the notification letters. Oxford will be maintaining a patient contact log for VICTOR. Copies of the notification letters to the investigators and patients were submitted to the Agency under the INDs and NDAs.

The Philadelphia field office is coordinating the pharmacy withdrawal activities. We will ask that office to provide details on the status of the pharmacy withdrawal for our next week's Teleconference with the Agency.

Follow up of patients in APPROVe
We explained to the Agency that a 1-yr off drug follow-up was already specified as part of APPROVe. Protocol-specific letters were issued to the APPROVe investigators and patients asking them to participate in the off-drug follow-up. Copies of these letters are being sent to the Agency.

The only change in the APPROVe protocol is that the Year 4 colonscopy has been made optional. MRL believes that this Year 4 colonoscopy may disincentivize patients from participating in the extension. Dr. Harvey challenged this amendment, because he believes that the Year 4 assessment may provide useful information with respect to the question of rebound of neoplasms. MRL agreed to bring this issue back to our GI group and management.

The Agency also questioned whether a one year off drug follow up was adequate with regard to CV risk assessment. MRL agreed to discuss this issue with the ESMB.

meline of Providing APPROVe Data to the Agency
ne Agency has the slide deck from MRL's presentation on September 28, 2004.
omorrow, MRL will provide the Agency with the 13Sep04 APPROVe safety update report at was provided to the ESMB and the ESMB closed session minutes from

8. MRL will provide a timeline for the submission of additional APPROVe reports.

Diane C. Louie, M.D., M.P.H.
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Regulatory Affairs-Domestic
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Rahway, NJ 07065
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Chronology

Final Study Proposal Submitted	10-8-01
Contract signed	4-18-02 (Merck)
Meeting at Merck at which final agreement given to protocol (?find confirm)	7-15-02
Interim Study Report sent to Merck	10-17-02
Contract amended to add ACS charts	12-17-02
Conference call with Merck to review analytic plan for draft final report, decision to add secondary claims based MI endpoint and periods of new continuous treatment made	6-12-03
Original planned delivery date for draft final report	9-15-03
Draft final report submitted, dose analyses held pending agreement	11-25-03
Conference call between Merck and Ingenix following draft final report submission, minutes in contract folder, discussion of dose analyses agreed to	12-18-03
Carolyn Cannuscio on early maternity leave, has a baby boy	1-31-04
Final report, including dose-analyses (first submission of any dose analyses to Merck) submitted	2-16-04
PV on maternity leave	2-20-04
Draft manuscript (final contract deliverable) submitted (by JL who integrated final comments from WW and AW while PV was on maternity leave)	3-?-04
Note from Doug Watson citing Nancy Santanello's approval of payment processing for final report, with comments for our consideration attached, including request regarding multiple reviews issue	3-16-04
PV returns from maternity leave	5-11-04
First revisions made to final report (re multiple reviews and other minor comments), sent to DW	6-23-04
Further discussion of multiple reviews issue by e-mails and phone ensues	July/August 04
Meeting during ICPE conference in Bordeaux, France, AW, PV, Nancy Santanello and Harry Guess, DW by telephone-to resolve remaining disagreement on multiple reviews issue	8-?-04
Last agreed revisions made to final report (re multiple reviews), sent to DW	9-20-04
Revised manuscript inclusive of revisions similar to those on report, plus responding to other comments received, sent to DW	9-27-04
Vioxx withdrawal from US market announced-con call with Doug Watson, AW, PV. Ingenix gives two weeks for Merck approval of authorship of current manuscript before manuscript is submitted to journal under Ingenix authorship	9-30-04
Submission of manuscript to JAMA following Merck approval	10-21-04
Manuscript reportedly under review at JAMA	11-16-04

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Exhibit 62

Graham, David J

From: Graham, David J
Sent: Friday, August 13, 2004 5:12 PM
To: Seligman, Paul
Subject: RE: COX2 Poster at ISPE

Paul,

Thanks for forwarding John's email. I've gone about as far as I can without compromising my deeply-held conclusions about this safety question. I've also shared with you the perspectives of my co-authors and I think it's safe to say they share these same conclusions. The *a priori* reason for our doing this study was not that we reach a conclusion consistent with FDA's handling of the issue in labeling. You know my views about the effectiveness of labeling and if Duract taught us anything, it's that you can't restrict their use to a limited duration of time. Also, physicians aren't computers that can optimize a therapeutic decision balancing pain against risk of AMI or SCD. Most of rofecoxib high dose use is for more than 5 days, and is more often measured in months. The company's RCTs show no added efficacy for the 50 mg dose above that with the 25 mg dose in treating chronic OA.

Dave

-----Original Message-----
From: Seligman, Paul
Sent: Friday, August 13, 2004 4:46 PM
To: Graham, David J
Subject: FW: COX2 Poster at ISPE

I shared your revised conclusion with John and Jonca. John provided feedback below for your consideration.

Paul

-----Original Message-----
From: Jenkins, John K
Sent: Friday, August 13, 2004 1:23 PM
To: Seligman, Paul; Bull, Jonca
Subject: RE: COX2 Poster at ISPE

I still think this is pretty strong language since to my knowledge FDA is not contemplating such a warning for labeling. I think something like "This and other studies suggest an increased risk of AMI with rofecoxib use and should be considered by prescribers when making individual treatment decisions." This is more in line with what I think we have done with the labeling.

John

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Terms to Know

- **Adverse Events** – A toxic reaction to a medical therapy
- **APPROVe Study** – Adenomatous Polyp Prevention on Vioxx study, which resulted in Vioxx being removed from the market
- **Celecoxib** – drug name for brand Celebrex
- **Clinical Study** – A study pertaining to or founded on actual observation and treatment of patients, as distinguished from theoretical sciences
- **COX-1 (Cyclooxygenase- 1)** – an enzyme normally present in a variety of areas of the body, including sites of inflammation and the stomach. The COX-1 enzyme ensures natural mucus lining which protects the inner stomach.
- **COX-2** – Similar to COX-1 in that it regulates mucus, but is located only in areas of the body responsible for inflammation. Blocking these and not COX-1 should help protect the stomach while reducing inflammation in the joints.
- **COX-2 Inhibitor** – NSAID drugs, such as Vioxx and Celebrex, that work by stopping the body's production of a substance that causes pain and inflammation, the COX-2 enzyme, with less stomach irritations than other NSAIDs because they do not impede the COX-1 enzyme as some other NSAIDs do; Vioxx is a more potent COX-2 inhibitor than Celebrex
- **Coxibs** – similar efficacy to NSAIDs but safer in terms of ulcers; compounds that would retain the NSAID effect of relieving pain and inflammation (inhibition of COX-2) but would not cause gastrointestinal disease (weak inhibitors of COX-1); prostaglandin synthesis has two pathways, both of which use the intermediate enzyme cyclooxygenase (COX)
- **CV Event – Cardiovascular Event**:
  - **myocardial infarction** – heart attack (irreversible injury to heart muscle)
  - **unstable angina** – chest pain as a result of lack of oxygen to the heart
  - **cardiac thrombus** – blood clot within the heart
  - **resuscitated cardiac arrest** – revival from complete stoppage of the heart
  - **ischemic stroke** – a condition due to lack of oxygen to the brain leading to reversible or irreversible paralysis

- **Drug Inserts** - give physicians information on prescription drugs. Product labeling represents a primary way to share critical drug information with physicians.
  - **Warnings** - written by pharmaceutical companies, and approved by federal regulators, to give doctors the fine print about prescription drugs: their approved uses, dosages and possible side effects, including potentially dangerous interactions with other medications.
  - **Contraindications** – lists any conditions, especially any condition of disease, which renders some particular line of treatment improper or undesirable
  - **Possible Adverse Effects** – lists any undesirable or unwanted consequence of a preventative, diagnostic, or therapeutic procedure or regimen.

- **Epidemiological Study** – A study that that deals with the incidence, distribution, and control of disease in a population. Not done in a clinical setting.

- **GI Issue – Gastrointestinal Issue**: issues pertaining to or communicating with the stomach and intestines.

- **IND – Investigational New Drug**: An IND application containing laboratory study results of the drug candidate is submitted to the FDA to request permission to conduct studies in humans

- **Naproxen** – An anti-inflammatory agent used in the treatment of rheumatoid arthritis.

- **NSAID** – Non-Steroidal Anti-Inflammatory Drug: a large group of anti-inflammatory agents that work by inhibiting the production of prostaglandins (naturally occurring pain-producing substances). Example: ibuprofen, and aspirin.

- **PDUFA** – Prescription Drug User Free Act: provided FDA with additional revenue to hire more reviewers and support staff and upgrade its information technology systems to speed up the application review process for new drugs and biological products without compromising FDA's traditionally high standards for approval

- **Prostacyclin** – type of prostaglandin that counterbalances activity of thromboxane; causes relaxation of blood vessels and inhibits platelet activation; usually synthesized by the COX-2 path way

- **Prostaglandins** – compounds derived from lipids that mediate the body's response to pain and inflammations; promote edema, blood flow, and increased sensitivity to an injured area.

- **Prothrombotic** – clot forming

- **PUBs** – Perforations, Ulcers, Bleeds:
  - Perforation – The act of boring or piercing through a part
  - Ulcer – A local defect of the surface of an organ or tissue
  - Bleed – To lose blood from the body
  - Strokes – the damage to a group of nerve cells in the brain due to interrupted blood flow (blood clot, or blood vessel bursting), resulting in coma, paralysis, speech problems, dementia (depending on location of the interruption).
- **Thromboxane** – a specific type of prostaglandin which constricts blood vessels and promotes clotting (aggregation) of platelets (aspirin synthesizes this to prevent clotting); predominately synthesized in platelets by the COX-1 pathway.

- **VIGOR study** – Vioxx Gastrointestinal Outcomes Research Study: clinical trial using patients with rheumatoid arthritis, commissioned to remove the gastrointestinal warning label from Vioxx and to get approval for use for rheumatoid arthritis; study showed that Vioxx more than doubled the risk of adverse cardiovascular events – results known in December 1999.

Vioxx (rofecoxib) – used to relieve the pain, tenderness, inflammation (swelling), and stiffness caused by arthritis. In a class of nonsteroidal anti-inflammatory medications (NSAIDs) called COX-2 inhibitors.

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anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS - Anaphylactoid Reactions, and PRECAUTIONS - Preexisting Asthma).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation:
Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

It is unclear, at the present time, how the above rates apply to VIOXX (see CLINICAL STUDIES, Special Studies, *Upper Endoscopy in Patients with Osteoarthritis*). Among 3357 patients who received VIOXX in controlled clinical trials of 6 weeks to one year duration (most were enrolled in six month or longer studies) at a daily dose of 12.5 mg to 50 mg, a total of 4 patients experienced a serious upper GI event, using protocol derived criteria. Two patients experienced an upper GI bleed within three months (at day 62 and

that required them to be free of ulcers at study entry. It is unclear if this study population is representative of the general population. Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIOXX vs comparator NSAID products have not been performed.

disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in

elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

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For relief of the signs and symptoms of osteoarthritis.
For relief of the signs and symptoms of rheumatoid arthritis in adults.
For the management of acute pain in adults.
For the treatment of primary dysmenorrhea.

CONTRAINDICATIONS

VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX.
VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, *Anaphylactoid Reactions* and PRECAUTIONS, *Preexisting Asthma*).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Although the risk of GI toxicity is not completely eliminated with VIOXX, the results of the VIOXX GI outcomes research (VIGOR) study demonstrate that in patients treated with VIOXX, the risk of GI toxicity with VIOXX 50 mg once daily is significantly less than with naproxen 500 mg twice daily. (See CLINICAL STUDIES, *Special Studies, VIGOR.*)

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

severe, potentially fatal bronchospasm in those taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, *Preexisting Asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

Treatment with VIOXX is not recommended in patients with advanced renal disease. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, *Renal Effects*).

Pregnancy

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

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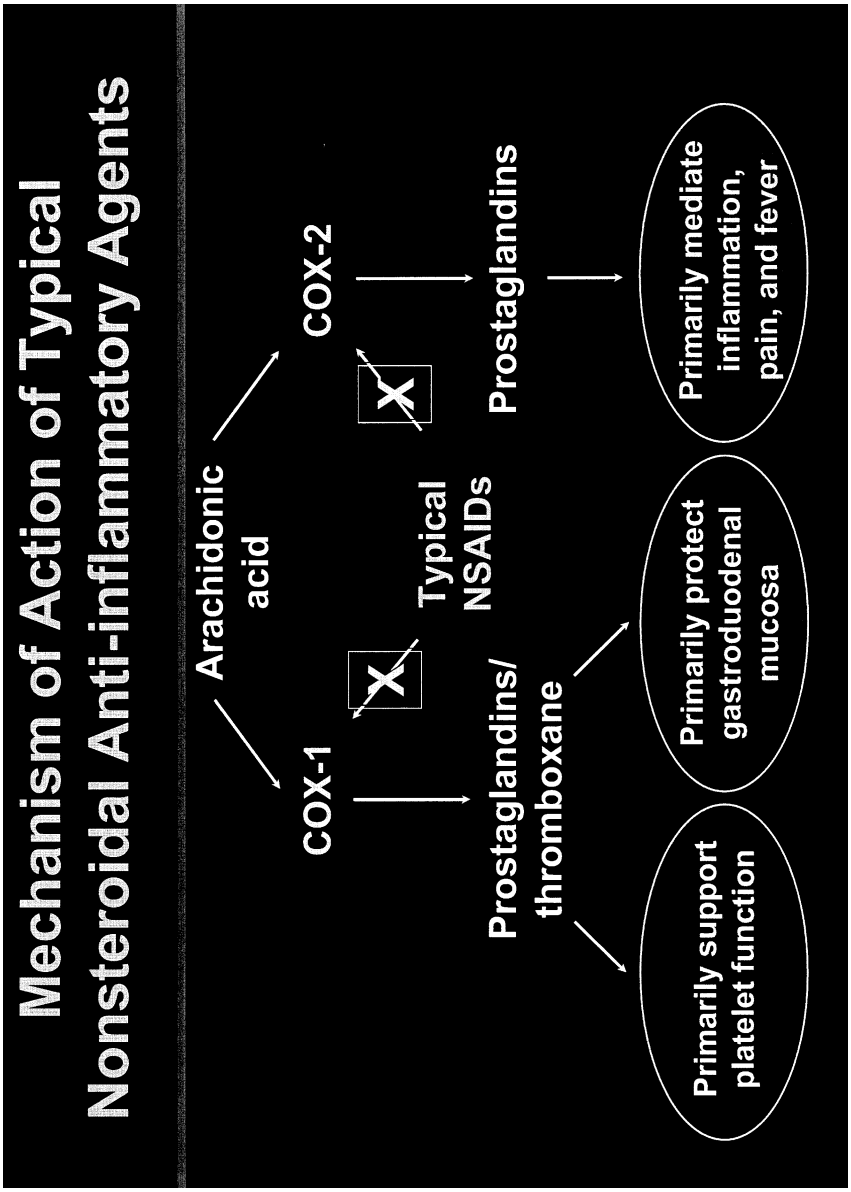
Mechanism of Action of Typical Nonsteroidal Anti-inflammatory Agents
Arachidonic acid
COX-1
COX-2
Typical NSAIDs
Prostaglandins
Prostaglandins/ thromboxane
Primarily support platelet function
Primarily protect gastroduodenal mucosa
Primarily mediate inflammation, pain, and fever

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Exhibit 67

The Process of Thrombosis

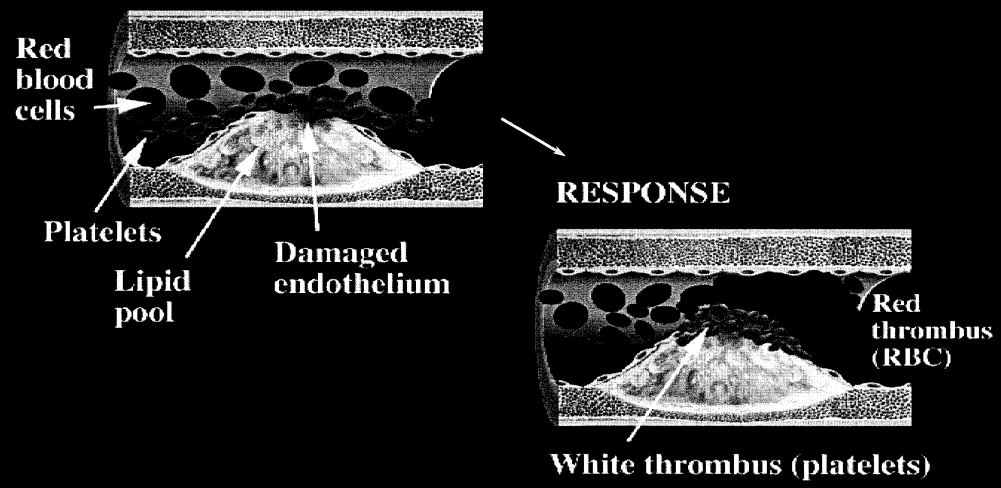

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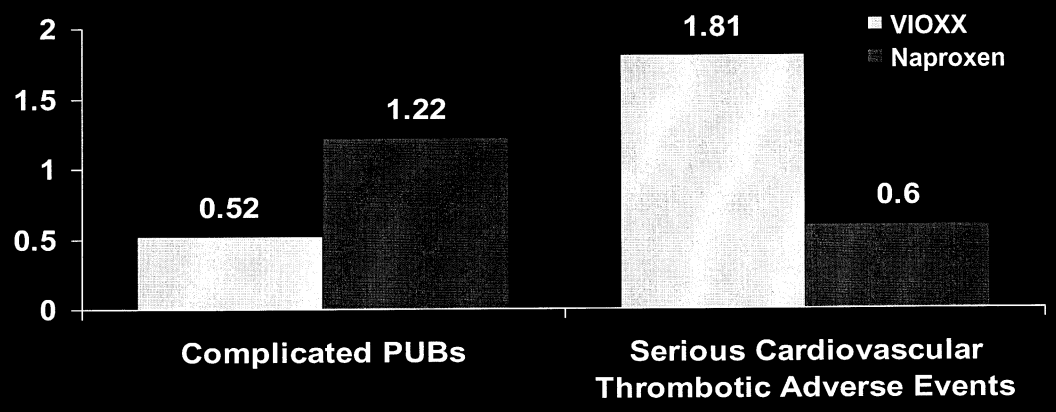
Exhibit 68

Risk-Benefit Comparison of Complicated PUBs and CV Events

Kaplan-Meier Cumulative Rate of complicated PUBs and CV Thrombotic Adverse Events



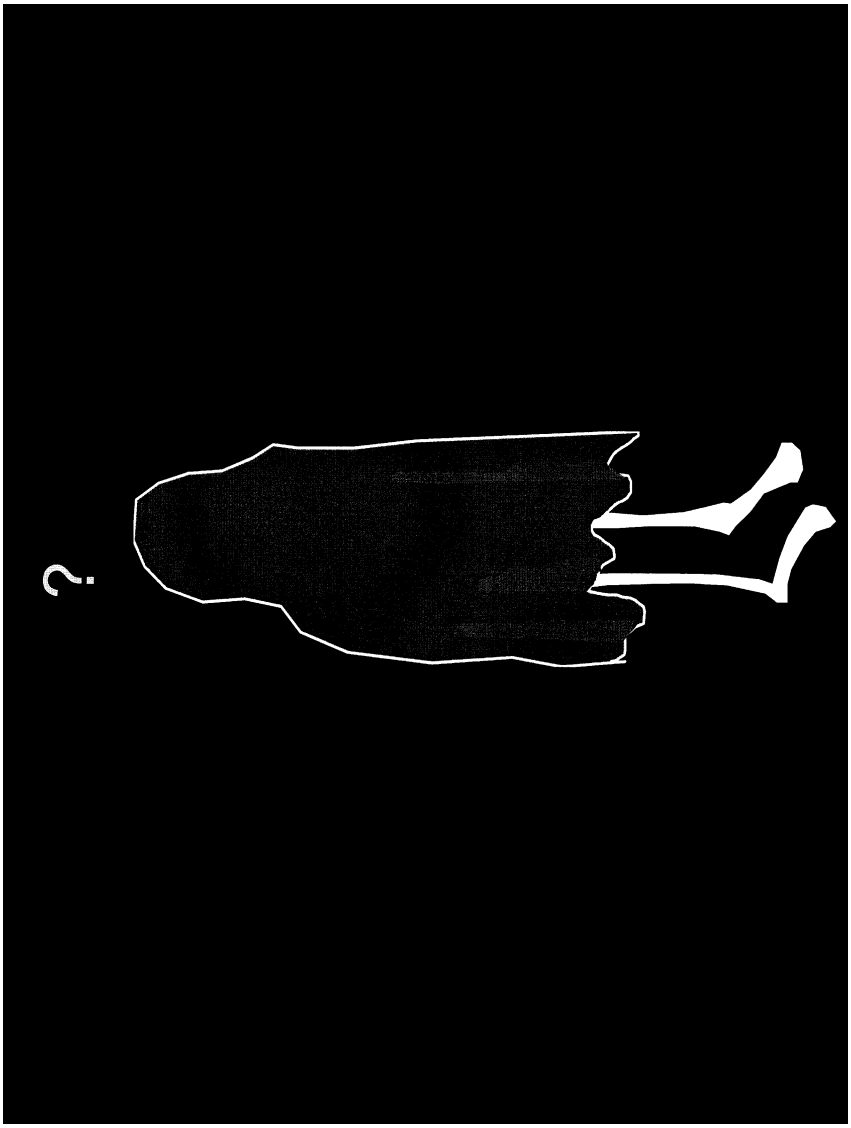
[1]Kaplan-Meier cumulative rate at end of study when at least 500 patients remained (approximately 10 ½ months)
[2]Confirmed by blinded adjudication committee
VIOXX Prescribing Information (http://www.merck.com/product/usa/vioxx/product_info/pi/9183810.pdf) accessed April 19,2002

United States Senate
Committee on Finance

"FDA, Merck, and Vioxx:
Putting Patient Safety First?"

November 18, 2004

Exhibit 69



Poster Exhibits

Committee on Finance
Hearing: FDA, Merck and Vioxx: Putting Patient Safety First?
November 18, 2004
Chairman Charles E. Grassley

Exhibit	Date	Exhibit Subject Matter
5 (a&b)	June 9, 1998	Pemrick memorandum, VIOXX Project Team Minutes for May 12, 1998
8 (a&b)	April 20, 1999	FDA approved VIOXX for acute pain, dysmenorrheal and OA
9	April 22, 1999	FDA approved VIOXX for acute pain, dysmenorrheal and OA
10 (a&b)	May 17, 1999	NDA 21-042/21-052 (VIOXX) – tables containing data on adverse events observed and overall conclusions of the rofecoxib program, including the safety of the drug
17	March 28, 2000	Email regarding Merck regarding Carol Patrono on VIGOR
21 (a-c)	May 17, 2001	HHPAC, "Key Marketing Messages"
29 (a-d)	February 1, 2001	According to Dr. Targum's memorandum, dated February 1, 2001, despite the lower dose of rofecoxib (12.5mg), the smaller sample size, and aspirin use in 085 and 090, studies to evaluate the efficacy and safety of MK-0966 (rofecoxib) at 12.5mg compared to nabumetone at 1000mg in patients with osteoarthritis of the knee, "the trend [with respect to adverse experiences] is against rofecoxib." Dr. Targum states in his comments on 085 that the results did not convince him that "there is no safety issue with rofecoxib....An increase in cardiovascular events at higher doses of rofecoxib cannot be excluded." He notes in his comments on 090 that there are numerically more myocardial infarctions in the rofecoxib group compared with nabumetone and placebo.
30	February 8, 2001	Dr. Villalba VIGOR presentation MVX for Vioxx: "Remember you do not initiate or respond to questions on the FDA Advisory Committee review of the study
38 (a-c)	September 17, 2001	FDA sent Merck warning letter relating to false and misleading promotional activities and materials for the marketing of VIOXX.
40	December 11, 2001	USA Today article, "Spotlight Falls on Drug Sales, referencing a November 2001 report released by the National

		Institute for Health Care Management, "Prescription Drugs and Mass Media Advertising, 2000"
46 (a-d)	October 12, 2004	Diane Louie, Director of Regulatory Affairs at Merck, submits a September 20, 2004 Ingenix Epidemiology report to Brian Harvey, Acting Director of FDA/CDER; report shows that the relative risk of the combined endpoint of acute myocardial infarction, acute coronary syndrome or sudden cardiac death was increased in patients taking rofecoxib compared to patients taking ibuprofen or diclofenac (RR 1.35).
51 (a-c)	NA	Merck Jeopardxx (LEH0127238)
52 (a- c)	NA	Merck Top Ten Obstacle Handlers
54	February 23, 2004	FDA letter to Novartis, "We also agree that remedial actions to address safety concerns, including labeling changes, should first be addressed through a dialogue between FDA and sponsor.
56	August 11, 2004-November 8, 2004	Series of e-mails between Dr. David Graham and FDA staff and others regarding publication of Dr. Graham's study on rofecoxib use and increased risk of acute myocardial infarction and sudden cardiac death.
61		
64		Vioxx Label 1999
65		Vioxx Label 2002
66		Dr. Singh
67		Dr. Singh
68		Dr. Singh
69		Dr. Singh
		Vioxx Double Jeopardy

COMMUNICATION

From: Topol, MD, Eric

Sent: Friday, November 19, 2004 11:54 AM

To:

Subject: The Senate Hearing yesterday

Dear

I would like the corrections for major inaccuracies to be duly noted as part of the hearings yesterday and that these 2 attachments be part of the materials added before the 10 day period of closure. I would appreciate confirmation that my request will be honored.

Best regards,
Eric

Eric J. Topol, MD
Provost, Cleveland Clinic Lerner College of Medicine
Chief Academic Officer, Cleveland Clinic Foundation
Chairman, Department of Cardiovascular Medicine
Professor of Medicine and Genetics, CWRU

Major Inaccuracies in Senate Vioxx Hearings

1. Topol estimated the number of heart attacks and strokes in the US at 160,000

I never gave this estimate. In the New England Journal of Medicine editorial, I stated there may be "tens of thousands" of heart attacks and strokes induced by Vioxx and the Figure showed how 16/1000 events in VIGOR and APPROVE has a very large potential impact as population exposure soars

2. Merck states that all trials are published and it discloses all results to the scientific and medical community

Study 090, a randomized trial of Vioxx compared with Relafen or Placebo in 978 patients, conducted in 1998-9, was never published. This 6 week trial in knee osteoarthritis showed a 760% excess of heart attacks and strokes, statistically significant (P=0.03). It was available to Merck and submitted to the FDA in 2000 for review with the VIGOR trial. It is an extremely important trial because it serves as independent replication of Vioxx's cardiovascular risk in a second randomized, controlled trial—against NSAID or placebo, which Merck claims had not been demonstrated except in APPROVE.

3. FDA states there was no difference in deaths in VIGOR

There was a 47% excess of death in VIGOR (22 in the Vioxx group and 15 in the Naproxen group) and despite this the authors of the New England Journal Med paper wrote three times in the manuscript that "the overall mortality was similar." However, they never provided the actual numbers of death in the manuscript. The New England Journal editors went back to review the original submitted paper in May 2000 and the numbers for death were never submitted. Furthermore, they provided erroneous numbers for heart attacks, reporting a 4-fold which was actually a 5-fold risk. More than half of the thrombotic events that occurred in VIGOR were not reported in the manuscript. These are very serious errors of omission, erroneous data, and incomplete data.

4. It takes 18 months before Vioxx carries a risk for heart attack and stroke

This is not true based on VIGOR, which showed divergence of the event curves of heart attack by 30 days, and in Study 090 the excess was present within 6 weeks.

PERSPECTIVE

Failing the Public Health — Rofecoxib, Merck, and the FDA

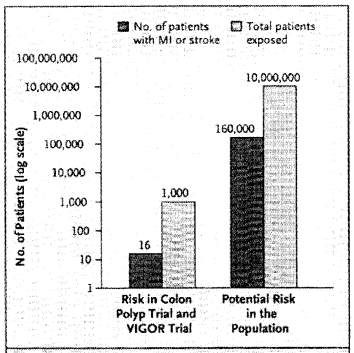
Eric J. Topol, M.D.

On May 21, 1999, Merck was granted approval by the Food and Drug Administration (FDA) to market rofecoxib (Vioxx). On September 30, 2004, after more than 80 million patients had taken this medicine and annual sales had topped $2.5 billion, the company withdrew the drug because of an excess risk of myocardial infarctions and strokes. This represents the largest prescription-drug withdrawal in history, but had the many warning signs along the way been heeded, such a debacle could have been prevented.

Neither of the two major forces in this five-and-a-half-year affair — neither Merck nor the FDA — fulfilled its responsibilities to the public. The pivotal trial for rofecoxib involved 8076 patients with rheumatoid arthritis and demonstrated that this coxib had lower gastrointestinal toxicity than naproxen.[1] Even though the drug was approved in 1999 on the basis of data submitted to the FDA, the data were not submitted to a peer-reviewed journal until the following year and did not appear in print until November 23, 2000, one and a half years after commercial approval had been granted. The cardiovascular data reported in that article were incomplete, in part because of incomplete ascertainment: the design and execution of the trial had not anticipated that untoward cardiovascular events might occur.[1]

It was not until February 8, 2001, that the FDA Arthritis Advisory Committee met to discuss concern about the potential cardiovascular risks associated with rofecoxib. It remains unclear why the FDA waited two years after its review and approval of rofecoxib to conduct this meeting. My colleagues and I reviewed the data from the meeting that were made publicly accessible and published an analysis of all the available data on rofecoxib and celecoxib on August 22, 2001.[2] Our primary conclusion, based on the clear-cut excess number of myocardial infarctions associated with rofecoxib and the numerical, albeit not statistically significant, excess associated with celecoxib, was that "it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents."[2] Such a trial needed to be conducted in patients with established coronary artery disease, who frequently have coexisting osteoarthritis requiring medication and have the highest risk of further cardiovascular events. Given the very high coincidence of coronary disease and arthritis, this group may represent the largest segment of the population for whom rofecoxib was prescribed. In light of the insight that arterial inflammation is the basis for myocardial infarction and stroke and the knowledge that coxibs reduce the production of biomarkers of inflammation such as C-reactive protein and improve endothelial function, such a trial would also have been quite attractive from the standpoint of potential benefit. The trial would have prospectively determined the incidence of cardiovascular events, whose possible association with coxib treatment had not been anticipated in the early and pivotal trials of these drugs.

Unfortunately, such a trial was never done. The FDA has the authority to mandate that a trial be conducted, but it never took the initiative. Instead of conducting such a trial at any point — and especially after the FDA advisory committee meeting in 2001 — Merck issued a relentless series of publications, beginning with a press release on May 22, 2001, entitled "Merck Reconfirms Favorable Cardiovascular Safety of Vioxx" and complemented by numerous papers in peer-reviewed medical literature by Merck employees and their consultants. The company sponsored countless continuing medical "education" symposiums at national meetings in an effort to debunk the concern about adverse cardiovascular effects. The message that was duly re-



Risk of Myocardial Infarction (MI) or Stroke Associated with Rofecoxib Use.

Data are from Mukherjee et al.[2] and the Adenomatous Polyp Prevention on Vioxx (APPROVe) study.

inforced was that rofecoxib had no cardiovascular toxicity: rather, naproxen was cardioprotective. Only by happenstance, in a trial involving 2600 patients with colon polyps who could not have been enrolled if they had had any cardiovascular disease, was it discovered that 3.5 percent of the patients assigned to rofecoxib had myocardial infarction or stroke, as compared with 1.9 percent of the patients assigned to placebo ($P<0.001$), necessitating premature cessation of the trial and the decision to discontinue treatment with rofecoxib.

Over the course of the five-and-a-half-year saga, many epidemiologic studies confirmed and amplified the concern about the risk of myocardial infarction and serious cardiovascular events associated with rofecoxib.[3] These studies considered large populations, up to 1.4 million patients, tracking the use of various nonsteroidal antiinflammatory medications or coxibs to determine the risk of adverse events. Each time a study was presented or published, there was a predictable and repetitive response from Merck, which claimed that the study was flawed and that only randomized, controlled trials were suitable for determining whether there was any risk. But if Merck would not initiate an appropriate trial and the FDA did not ask them to do so, how would the truth ever be known?

Meanwhile, Merck was spending more than $100 million per year in direct-to-consumer advertising — another activity regulated by the FDA and a critical mechanism in building the "blockbuster" status of a drug with annual sales of more than $1 billion. For the past few years, every month has seen more than 10 million prescriptions for rofecoxib written in the United States alone. At any point, the FDA could have stopped Merck from using direct-to-consumer advertising, especially given the background concern that the cardiovascular toxicity was real and was receiving considerable confirmation in multiple studies conducted by investigators who were independent of Merck. The only significant action taken by the FDA occurred on April 11, 2002, when the agency instructed Merck to include certain precautions about cardiovascular risks in its package insert. The FDA also sponsored one of the large epidemiologic studies performed in a cohort of Kaiser Permanente patients.

Considering the tens of millions of patients who were taking rofecoxib, we are dealing with an enormous public health issue. Even a fraction of a percent excess in the rate of serious cardiovascular events would translate into thousands of affected people. Given the finding in the colon-polyp trial in low-risk patients without known cardiovascular disease — an excess of 16 myocardial infarctions or strokes per 1000 patients — there may be tens of thousands of patients who have had major adverse events attributable to rofecoxib (see Figure).

I believe that there should be a full Congressional review of this case. The senior executives at Merck and the leadership at the FDA share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health. Sadly, it is clear to me that Merck's commercial interest in rofecoxib sales exceeded its concern about the drug's potential cardiovascular toxicity. Had the company not valued sales over safety, a suitable trial could have been initiated rapidly at a fraction of the cost of Merck's direct-to-consumer advertising campaign. Despite the best efforts of many investigators to conduct and publish meaningful independent research concerning the cardiovascular toxicity of rofecoxib, only the FDA is given the authority to act. In my view, the FDA's passive position of waiting for data to accrue is not acceptable, given the strong signals that there was a problem and the vast number of patients who were being exposed. Furthermore, the tradeoff here involved a drug for symptoms of arthritis, for which many alternative medications are available, in the

context of serious, life-threatening cardiovascular complications. Certainly there are many facts that we are not privy to, such as the direct communication between the FDA and Merck, but all the facts can and should be scrutinized closely in a Congressional review in order to avert such a catastrophe in the future.

From the Cleveland Clinic Foundation, Cleveland.

1. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520-8.
2. Mukherjee DM, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286:954-9.
3. Topol EJ, Falk GW. A coxib a day won't keep the doctor away. Lancet 2004;364:639-40.