**Testimony of David J. Graham, MD, MPH, November 18, 2004**

Mr. Chairman and members of the Committee,

**Introduction**. 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 three-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 US 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 US. 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 US**. Another way to fully comprehend the enormity of the Vioxx debacle is to look briefly at recent US and FDA history. The attached figure shows a graph depicting 3 historical time-points of importance to the development of drug safety in the US. 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 email 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 1970's, 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 1980's and early 1990's, 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 US 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.

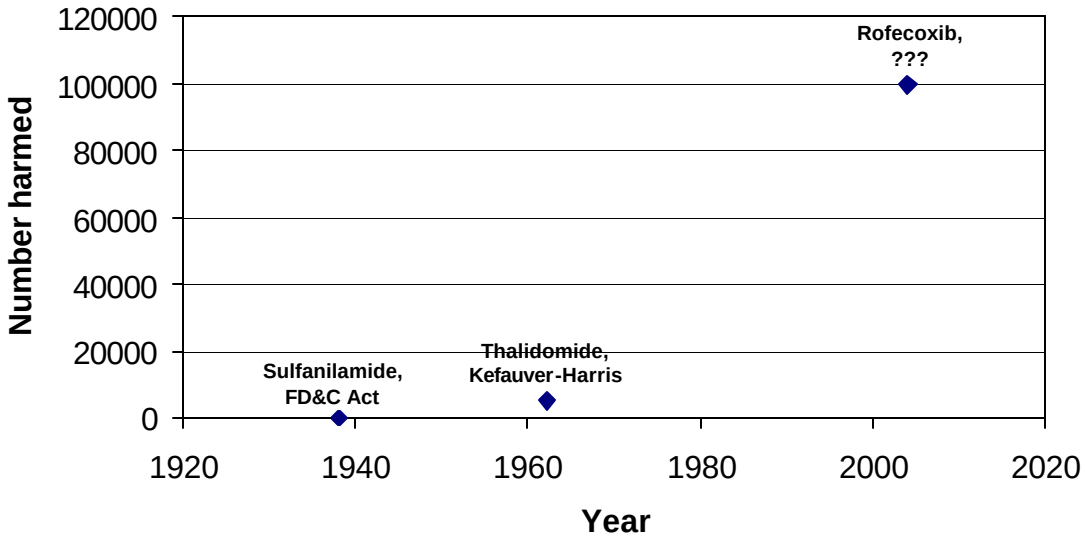
Table 1. The percentage of each State's population age 18 years or older that would be affected if an estimated 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx had all occurred in that State. The States are presented alphabetically. These are the States represented by members 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 US 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. A brief history of drug safety disasters in the US.



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