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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 4 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 scientist 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 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 issue 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 5771 patients, 3629 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 one 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, "thomboembolic 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 1631 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 COX2 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 4047 patients to VIOXX 50 mg daily and

4029 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 five times higher in VIOXX patients than in naproxen patients (0.74 vs 0.15 per 100 person years). In 1000 patients followed for one 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 seven 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 effect 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, lacking 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 vs 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 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 attacks. 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 one-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 US 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 US 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 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 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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References

1. Berwick D, Davidoff F, Hiatt H, Smith R. Refining and implementing the Tavistock principles for everybody in health care. BMJ 2001;323:616-620.
2. US Preventative Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. Ann Intern Med 2002;136:157-160.
3. Hayden M, Pignone M, Phillips C, Mulrow C. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the US Preventive Services Task Force. Ann Intern Med 2002;136:161-172.
4. Muliner T. Anticipated consequences of NSAID antiplatelet effects on cardiovascular events and effects of excluding low-dose aspirin use in the Cox-2 GI Outcomes Megatrial. Letter of November 21, 1996 to B Friedman, A Nies, and R Spector.
5. McAdams BF, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci 1999;96:272-277.
6. Buerkle MA, Lehrer S, Sohn HY, Conzen P, Pohl U, Krotz F. Selective inhibition of cyclooxygenase-2 enhances platelet adhesion in hamster arterioles in vivo. Circulation 2004;110:2053-9.
7. FitzGerald GA. Coxibs and cardiovascular disease. N Engl J Med 2004;351:1709-11.
8. Villalba ML. FDA Medical Officer Review of VIOXX (rofecoxib), NDA 21-042 (capsules) and NDA 21-052 (oral solution). Http://www.fda.gov/cder/drug/infopage/vioxx/default.htm.
9. Bombardier C, Laine L, Reicin A, et alia for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of Rofecoxib and Naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520-1528.
10. Targum SL. Consultation on NDA 21-042, S-007; Review of cardiovascular safety database [on Vioxx or rofecoxib). FDA Memorandum, Feb 1, 2001.
Http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.doc; last accessed on June 5, 2001.
11. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofexocib: cumulative meta-analysis. Lancet 2004; epud.
12. Report from the Committee of Principal Investigators. A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. Br Heart J 1978;40:1069-1118.
13. Solomon DH, Glynn RJ, Levin R, Avron J. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. Arch Intern Med 2002;162:1099-1104.
14. Ray WA, Stein CM, Hall K, Daugherty JR, Griffin MR. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. Lancet 2002;359:118-123.
15. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-flammatory drugs and risk of serious coronary heart disease. Lancet 2002;360:1071-1073.
16. Schnitzer TJ, Burnester GR, Mysler E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestingal Event Trail (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 2004;364:665-674.
17. Farkauh ME, Kirshner H, Harrington RA, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic ARthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 2004;364:675-684.

18. Louie D. Revised Confidential Information Brochure for IND 55,269 VIOXX (rofecoxib). Accompanied letter of May 12, 2004 from Diane Louie to Brian E Harvey.
19. Topol EJ. Failing the public health--rofecoxib, Merck, and the FDA. N Engl J Med 2004;351:1707-1709.
20. Writing group for the Women's Health Iniative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-333.
21. Kessler DA. Introducing MEDWatch: a new approach to reporting medication and device adverse effects and product problems. JAMA 1993;269:2765-2767.
22. Mamdani M, Rochon P, Juurlink DN, et al. Effect of selective cyclooxygenase-2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly. Arch Intern Med 2003;163:1481-1486.
23. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004;109:2068-2073.
24. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with COX-2 selective and non-selective NSAIDs. Lancet 2004; in press.
25. 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.
26. 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.
27. Ray WA, MacDonald TM, Solomon DH, Graham DJ, Avorn J. COX-2 selective non-steroidal anti-inflammatory drugs and cardiovascular disease. Pharmacoepidemiol Drug Saf 2003;12:67-70.