



Hearings

FDA, Merck and Vioxx: Putting Patient Safety First?

November 18 , 2004, at 10:00 a.m. in 216 Hart Senate Office Building

Member Statements:

[Charles Grassley, IA](#)

[Max Baucus, MT](#)

Witness Statements:

Panel I

[Dr. David J. Graham](#), 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

Panel II

[Dr. Gurkirpal Singh](#), Adjunct Clinical Professor of Medicine, Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University School of Medicine, Stanford, CA

[Dr. Bruce M. Psaty](#), PhD, Professor, Medicine & Epidemiology, University of Washington, Cardiovascular Health Research Unit, Seattle, WA

Panel III

[Dr. Sandra L. Kweder](#), 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

Panel IV

[Mr. Raymond V. Gilmartin](#), Chairman, President & Chief Executive Officer, Merck & Co., Whitehouse Station, NJ

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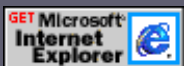
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U.S. SENATE COMMITTEE ON

Finance

SENATOR CHUCK GRASSLEY, OF IOWA - CHAIRMAN

<http://finance.senate.gov>

Opening Statement of U.S. Senator Chuck Grassley of Iowa
Chairman, Senate Committee on Finance
Hearing – FDA Merck and Vioxx: Putting Patient Safety First?
Thursday, November 18, 2004

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. Drug makers 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 to 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 five times higher for Vioxx patients than for patients on another drug. Even so, nearly two 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 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 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 monitoring the effect of a drug once it's on the market.

Our next witness is Dr. Gurkupal 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 will 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 "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 said." Dr. Graham completed an FDA-sponsored three-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 intimidate a witness on the eve of hearing. I want to hear about Dr. Graham's study today. In fact, just seven 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 develop(ing) 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.



Committee On Finance

Max Baucus, Ranking Member

NEWS RELEASE

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For Immediate Release

Thursday, November 18, 2004

Contact: Liz Fowler

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Statement of U.S. Senator Max Baucus “FDA, Merck and Vioxx: Putting Patient Safety First?”

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?
- And 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 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 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.

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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 arrhythmias 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. Overseas, 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.

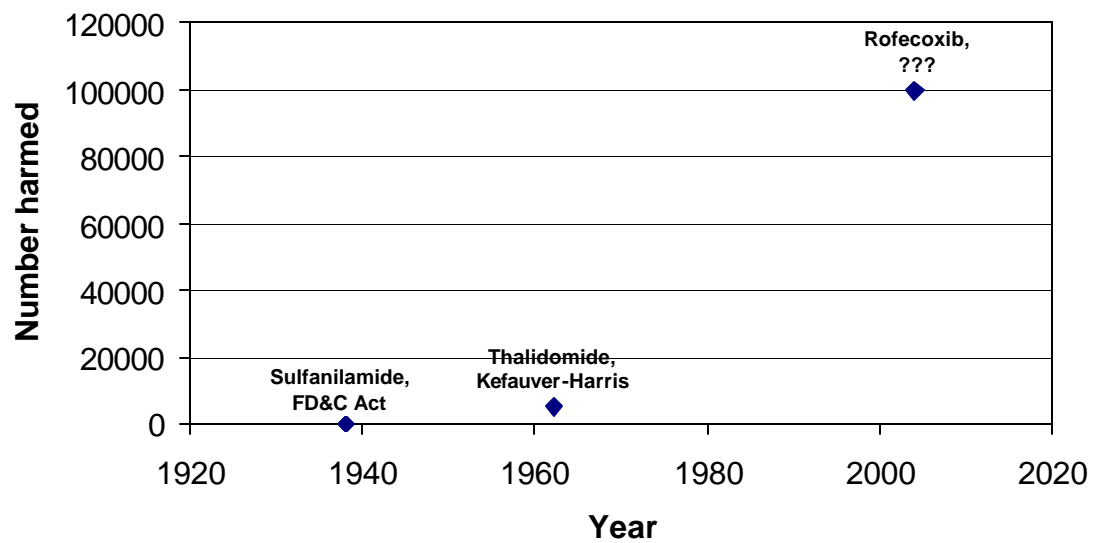
Table 1. The percentage of each State's population age 18 years or older that would be affected if an estimated 100,000 excess cases of heart attack and sudden cardiac death due to Vioxx had all occurred in that State. The States are presented alphabetically. These are the States represented by members 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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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 two 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 learnings 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 (attachment 1). 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 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 US 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 (attachment 2), 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 platelet 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 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 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 (attachment 3). At that time, it was not known that Vioxx may 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 older 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 (attachment 4), that in early 1997, Merck scientists were exploring study designs that would exclude people who may have 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 a kill a patient.

According to documents provided to me by the Senate 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 (attachment 5) 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 a careful FDA review of Merck’s new drug application for Vioxx, Dr. Villalba (attachment 6) 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 1631 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 US. 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 (attachment 7). 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 the 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 (attachment 8). Subsequently, I learnt 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 (attachment 9). 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 was published in the New England Journal of Medicine in November, 2000. A few weeks ago, Merck announced that the published VIGOR data was “preliminary” and that the “final” data was presented to the FDA. In my view, and all of 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 hear 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).

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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 was 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 was added. Even the Alzheimer's disease studies data was 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). Attachment 9 is self-explanatory.

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, 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 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 US.

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 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. 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 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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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 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 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, “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 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 \geq 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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Nov 15, 2004

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STATEMENT
OF
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U.S. FOOD AND DRUG ADMINISTRATION
BEFORE THE
COMMITTEE ON FINANCE
UNITED STATES SENATE

November 18, 2004

Release Only Upon Delivery

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 do 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 six-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 confound 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

risk in cardiovascular risk and stroke starting at the eighteen 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 non-selective 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 the five 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 two 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 and transparent in its 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 post-marketing 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 and 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.

Summary of Prepared Testimony

Raymond V. Gilmartin,
President, Chairman and Chief Executive Officer,
Merck and Co., Inc.

before the
United States Senate Committee on Finance

November 18, 2004

- The Food and Drug Administration approved Vioxx only after Merck had extensively studied the medicine.
- Merck continued to extensively study Vioxx after it was approved for marketing to gain more clinical information about the medicine.
- Merck has 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.
- Until data from the APPROVe clinical trial became available in September, 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.
- 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.
- As soon as the data from the APPROVe study became available, Merck acted quickly to withdraw the medicine from the market.

Prepared Testimony

Raymond V. Gilmartin,
President, Chairman and Chief Executive Officer,
Merck and Co., Inc.

before the
United States Senate Committee on Finance

November 18, 2004

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 four 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 one hundred 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 six 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 one 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 two 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 has 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.



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.
- Nov 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 Research¹ (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 VIOXX² (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 Therapy³ (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.

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* infection or 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

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.



Timeline of Epidemiological Studies Involving VIOXX or NSAIDs¹

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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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.

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