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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 saving 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 heart attacks – could not explain the 500% difference between Vioxx and naproxen. The reviewers also highlighted data from many other studies showing that this was not an isolated finding in VIGOR. However, Merck continued to claim “favorable cardiovascular safety profile” of Vioxx in multiple press releases and Company-sponsored lectures and conferences. In September 2001, in a Warning Letter to Merck, the FDA Division of Drug Marketing, Advertising, and Communications (DDMAC) called the press releases claiming a “favorable cardiovascular safety profile” for VIOXX “simply incomprehensible”, and pointed out that the naproxen explanation was merely “hypothetical” rather than factual. These facts had previously been discussed by FDA reviewers as well (7).

## **Post-VIGOR Label Change**

The VIGOR data were first made public in May 2000. However it was not until almost 2 years later that the FDA requested Merck to revise Vioxx's product label to reflect the heart attack risks observed in the VIGOR trial. These revisions were added to the "Precautions" section, under "Cardiovascular Effects", instead of being prominently displayed as a "Warning". While the stomach bleed safety data 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 as 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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