THE VIOXX STORY [1]

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On September 30, 2004, the blockbuster drug VIOXX was withdrawn from the worldwide market. This prescription painkiller had generated sales in excess of $2 billion annually and had been prescribed to more than 20 million Americans. After five years on the market, VIOXX - which had been touted as a "miracle drug" and was the object of the biggest launch in Merck's history - was withdrawn because of serious safety issues. This is the VIOXX story.

A. Traditional Pain Relievers and the Development of VIOXX

VIOXX is in a class of pain relievers called nonsteroidal anti-inflammatory drugs ("NSAIDs"). Traditional pain relievers in this class include but are not limited to aspirin, Tylenol, ibuprofen, and naproxen. NSAIDs provide pain relief by reducing the production of certain enzymes, called prostaglandins, which are produced at the site of injury and inflammation. However, prostaglandins are not only mediators of inflammation, but also help protect the stomach lining from digestive acids. Thus, traditional NSAIDs have long been associated with an increased risk of gastrointestinal perforations, ulcers and bleeds ("PUBs").

In 1991, it was discovered that there are two forms of enzyme responsible for the production of prostaglandins: cyclooxygenase-1 ("COX-1") and cycloxygenase-2 ("COX-2"). At that time, it was believed that COX-1 was involved in providing

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gastrointestinal tract protection and was also involved with platelet aggregation (blood clotting) in the blood stream, while COX-2 was expressed at sites of inflammation and injury. Merck began to develop selective COX-2 inhibitors in hopes of creating a new breed of NSAID. In a theory dubbed by Merck as the "COX-2 hypothesis," Merck postulated that by selectively blocking COX-2, these new NSAIDs would provide relief from pain and inflammation but would not interfere with production of the COX-1 enzyme that protected the stomach. One of several COX-2 inhibitor compounds developed by Merck - MRK-966 - eventually became known as rofecoxib and was marketed to consumers, physicians, and third-party payors under the brand-name, VIOXX.

B. VIOXX's Mechanism of Action Carried Potential Cardiovascular Risks

While the COX-2 hypothesis was very appealing from a marketing perspective, with respect to overall safety (not just GI safety), it failed to account for the additional, and significant role of the COX-2 enzyme in the cardiovascular, pulmonary, neurological, and renal systems.

The COX-1 enzyme produces thromboxane, which is a vasoconstrictor (constricts the blood vessels) and platelet aggregator. On the other hand, the COX-2 enzyme produces prostacyclin which is not only an anti-aggregatory agent but also a *vasodilator* (expands the blood vessels), an important defense mechanism for the human body when faced with the onset of a cardiovascular event. Selectively inhibiting the COX-2 enzyme disables this defense. Moreover, it tips the homeostatic balance in favor of platelet aggregation and vasoconstriction and may cause blood clots that lead to heart attacks and strokes. In simple terms, COX-1 production in the absence of COX-2 makes the blood

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thicken and also narrows the pathways through which blood must flow. Additionally, studies have demonstrated that prostacyclin plays a role in the development of arteriosclerosis and in a shearing (or thinning) of plaque along the walls of blood vessels. When plaque ruptures, particles of plaque are released into the blood stream and can cause thrombosis. One or all of these potential effects will significantly increase the likelihood of an adverse cardiovascular event—particularly in those individuals who may already have a heightened risk for such events (e.g., cigarette smokers). In addition to the circulatory system, prostacyclin is produced in the lungs, intestines, kidney, bone tissue, and the brain.

Plaintiffs assert that as early as 1996, Merck knew of the role and function of prostacyclin in the human body. Moreover, as early as 1997, Merck knew that VIOXX ingestion had resulted in a significant decrease of a urinary metabolite of prostacyclin called PGI-M in its clinical trial patients. These results generated concern that COX-2 inhibition might suppress prostacyclin in the vasculature and negatively effect cardiovascular health. For the purposes of this paper, we will refer to this theory as the "prostacyclin hypothesis." Before the FDA's approval of VIOXX, Merck conducted animal studies to assess the relationship between COX-2 inhibition and prostacyclin production and adverse cardiovascular events. Merck later conceded to the FDA that these results were inconclusive. Rather than testing the prostacyclin hypothesis in actual patients, Merck tabled the issue. At the time of the drug's approval, Merck was in a highly competitive race with another pharmaceutical company to get a selective COX-2 inhibitor to market. Thus, Merck ignored the prostacyclin theory and the dangers it represented.

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C. VIOXX Could Not Demonstrate Superior GI Safety in "Real World" Use

Even absent the potential cardiovascular risks inherent in COX-2 inhibition, Merck knew that in "real world" use, VIOXX would be unable to demonstrate superior GI safety than traditional NSAIDs. This was largely because of the characteristics of its target patient population - arthritis sufferers - who, due to their advanced age, would likely also be using antiplatelet therapies, such as aspirin, for cardioprotection. Long before the drug was approved by the FDA and marketed to the public, Merck knew that if patients taking VIOXX (a selective COX-2 inhibitor) were also taking aspirin (a non-selective inhibitor of both COX-1 and COX-2), they would lose the purported GI safety benefit of the drug.

In a 1996 memo discussing the design of a study to demonstrate the superior GI safety profile of VIOXX, one Merck scientist noted that allowing low dose aspirin use during the trial would likely increase the risk of PUBs. Moreover, the scientist observed that by prohibiting aspirin use there would be a substantial chance that significantly higher rates of serious adverse events in elderly patients, such as heart attacks and strokes, would be seen among VIOXX users. Indeed, in a 1997 series of emails between Merck employees, one scientist plainly states that without allowing the group of patients taking VIOXX to also take aspirin, "you will get more thrombotic events and kill drug." Another scientist responded that for the company it was a "no-win situation," because of the potential increase in either adverse GI or cardiovascular events. To avoid drawing attention to this risk, Merck excluded aspirin users from virtually every clinical trial of VIOXX prior to 2000.

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D. Merck's Dire Need for Speedy FDA Approval and "Blockbuster" Sales for VIOXX

Merck first publicly announced that it was developing a COX-2 specific inhibitor in May 1996, touting it as a miracle drug for arthritis sufferers. At the time it began advance promotion of the drug, Merck faced patent expirations on some of its most successful drugs - including Mevacor, Pepcid, and Prilosec - which had represented more than $4 billion in U.S. drug sales. Moreover, financial analysts asserted that Merck could resolve its financial problems only by merging with another pharmaceutical company. Merck was in dire need of a "blockbuster" drug to offset the loss of revenue streams because of imminent patent expirations and to ward off speculation about the company's stability. Similarly, Merck faced a significant competitive threat from Monsanto and Pfizer, two other pharmaceutical companies that together were developing another COX-2 inhibitor, Celebrex, which was slated to go to market months ahead of VIOXX.

E. The Marketing of VIOXX

In pursuit of VIOXX as a "blockbuster" drug, Merck (1) ignored early warning signs, (2) employed an aggressive promotional campaign of intimidation and misrepresentation, and (3) caused serious injury and death to tens of thousands of people. These are serious charges. Serious, yet sadly true in light of the clear evidence that Merck repeatedly chose to ignore and minimize significant safety issues that placed its franchise in jeopardy, in order to promote and protect a drug that was generating annual sales in excess of a billion dollars.

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1. Merck Ignored Potential Cardiovascular Risks and Early Warning Signs

Prior to Merck's submission of the VIOXX New Drug Application to the FDA in late 1998 and subsequent marketing of the drug beginning in May 1999, there were warning signs of cardiovascular risk from use of VIOXX.

For example, from late 1996 to 1998, Merck had reports of unstable angina, myocardial infarction, and transient ischemic events in small clinical trials. As discussed above, Merck saw evidence that VIOXX reduced systemic prostacyclin production as early as 1996. Indeed, Merck's Board of Scientific Advisors warned Merck that the inhibition of prostacyclin could result in an increased risk for cardiovascular events, and in May 1998, the Board instructed Merck to begin monitoring and analyzing cardiovascular events in all VIOXX clinical trials.

As part of its 1998 NDA submission to the FDA, Merck included a pooled analysis of cardiovascular events in a number of small clinical trials held from 1996-1998. Although Merck asserted that its analysis demonstrated that the cardiovascular risks associated with VIOXX were similar to that of a placebo, one FDA medical officer thought otherwise. In her review of this data, the officer noted that it was difficult to reach meaningful conclusions because Merck had combined trials with varying dosage and duration of VIOXX and different comparator drugs. More importantly, the officer expressed concern because patients taking low-dose aspirin or anti-platelet therapies were excluded from the studies. In evaluating the pre-NDA data, the medical officer concluded:

> 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

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> and other safety comparison questions. Patients who need aspirin for cardiovascular reasons should not stop aspirin when taking rofecoxib.

Merck neither conducted trials to test the prostacyclin hypothesis in humans, nor did it heed the FDA's advice regarding concomitant use of VIOXX and low-dose aspirin. In March 2000, Merck learned that its large-scale GI Outcomes trial, called VIGOR, had demonstrated a five-time greater risk of myocardial infarctions among VIOXX users than users of the comparator drug in the trial, Naproxen. The VIGOR trial did not allow patients to take aspirin with VIOXX.

When the results of the VIGOR trial were shared with the President of Merck Research Laboratories, Ed Scolnick, he concluded that the cardiovascular events were "clearly there" and lamented that the effect was "mechanism-based as we worried it was." Publicly, however, Merck refused to acknowledge a mechanism-based cardiovascular risk for VIOXX. Instead, Merck issued a press release entitled, "Merck Confirms Favorable Cardiovascular Safety Profile of VIOXX," and took the position that the differences in cardiovascular events in VIGOR were due to the cardioprotective effect of naproxen. In a subsequent warning letter to Merck, the FDA characterized this position as "simply incomprehensible."

It was disingenuous to suggest that the difference between two drugs in a clinical trial was explained entirely by a previously undiscovered benefit of the comparator drug. Naproxen had been on the market for 20 years and the subject of scores of clinical studies. The purported cardioprotective effect of naproxen asserted by Merck had never been observed before. Merck executives simply were unwilling to apportion *any* of the cardiovascular risk to VIOXX despite knowing beyond question that VIOXX increased

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the risk of severe and malignant hypertension and congestive heart failure. The difference in the incidence of cardiovascular events between VIOXX and Naproxen seen in the VIGOR trial were several times larger than what would have been observed if the comparator drug had been aspirin - a known cardioprotective agent. Merck's own internal summaries showed just that. Further, outside experts told Merck that it was unlikely that an effect of Naproxen could explain the VIGOR results.

In August 2001, the Journal of the American Medical Association (JAMA) published a study by Drs. Mukherjee, Nissen and Topol. This study also showed an increased rate of cardiovascular events among VIOXX users. The author urged caution and further study, stating:

> Given the remarkable popularity of this new class of medications, we believe that it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of their agents.

Merck undertook no such study. Indeed, despite increasing concern about the potential risks of heart attacks and strokes for VIOXX users, no study was ever conducted that had cardiovascular safety as its primary endpoint or focus. Even Merck's APPROVe trial, which ultimately led to withdrawal of the drug from market after the study demonstrated an increased cardiovascular risk for VIOXX, was primarily designed to test whether VIOXX helped reduce polyps in the colon.

2. Merck's Campaign of Intimidation and Misrepresentation

In the months following the VIGOR study, Merck vigorously defended the cardiovascular safety of VIOXX. Through its direct-to-physician detailing and "medical education" programs, Merck assured physicians that VIOXX had a favorable

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cardiovascular profile. Notably, Merck did not advise doctors to avoid giving VIOXX to patients with cardiovascular risk factors or that concomitant use of aspirin would eviscerate the superior GI safety of the drug. To the contrary, Merck developed a sales training piece called "Dodge Ball" designed to deflect physician inquiries concerning cardiovascular safety. The training document contains potential questions or statements from physicians concerning cardiovascular safety, such as, "I am concerned about the cardiovascular effects of VIOXX?" Each question is identified as an "obstacle." Merck's recommended response to such questions: **"DODGE!"**

Merck also responded aggressively when academic researchers questioned the safety of VIOXX. When Eric Topol, M.D., Chief of Cardiovascular Medicine at the Cleveland Clinic, was preparing to publish an article critical of VIOXX's safety in the August 2001 edition of JAMA, Merck employees paid him a visit in an effort to dissuade publication, or at least soften the article's conclusion. When Topol refused, Merck attempted to persuade JAMA to publish a rebuttal piece.

Indeed, internal Merck documents detail a campaign to surveil and "neutralize" physicians who publicly questioned the safety of VIOXX - either by offering financial or academic rewards or by intimidating or discrediting physicians. For example, when Dr. Gurkipal Singh of Stanford University - a frequent lecturer on behalf of Merck - expressed concern that he was not getting important cardiovascular safety data pertaining to VIOXX, Merck canceled several scheduled presentations by Dr. Singh. On another occasion, a Merck official called Dr. Singh's superiors and complained that his presentations were "anti-VIOXX." Merck warned that "if this continued, Dr. Singh would 'flame out' and there would be serious consequences for [] Stanford." A

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representative from Stanford investigated and found "a consistent pattern of intimidation of investigators by Merck" regarding VIOXX.

Merck's representations regarding the safety of VIOXX were misleading. To sell VIOXX to doctors, Merck fielded a sales force of 4,500 sales representatives and spent millions of dollars recruiting "opinion leaders" to give medical lectures at lavish dinners for physicians and in other forums. For example, in June 1999, Merck hired Dr. Peter Holt to speak at ten audio conferences for physicians in 2000. The FDA found that the content of these conferences was:

> False or misleading in that they minimized the MI results of the VIGOR study, minimized the VIOXX/Coumadin drug interaction, omitted important risk information, made unsubstantiated superiority claims, and promoted VIOXX for unapproved uses and an unapproved dosing regimen.

Additionally, the FDA warned Merck that certain VIOXX promotional pieces were "false and misleading because they contain misrepresentations of VIOXX's safety profile, unsubstantiated comparative claims, and are lacking in fair balance."

In addition to its efforts to mislead physicians regarding the drug's safety, Merck engaged in an unprecedented direct-to-consumer ("DTC") advertising campaign. For example, in 2000, Merck spent approximately $161 million on DTC advertising for VIOXX. That is more money spent on DTC advertising that year than PepsiCo spent promoting Pepsi Cola, Coca-Cola spent on Coke, and Anheuser Busch spent on Budweiser.

3. VIOXX Caused Serious Injury or Death in Tens of Thousands of Cases

A senior FDA safety expert, Dr. David Graham, recently testified that VIOXX likely caused more than 100,000 heart attacks and strokes, including an estimated 40,000

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deaths. Dr. Graham proclaimed that VIOXX could be "the single greatest drug catastrophe in the history of this country." Dr. Graham, Associate Director for Science in the FDA's Office of Drug Safety and a twenty-year FDA veteran. Similarly, Dr. Eric Topol of the highly regarded Cleveland Clinic has estimated that anywhere from 20,000 to 160,000 people suffered heart attacks and strokes as a result of taking VIOXX.

F. Conclusion

Merck insists that it acted as a responsible pharmaceutical company in the handling of VIOXX. Further, according to Merck, their actions regarding VIOXX were all about putting patients first. Clearly the liability issues involving corporate conduct will be hotly contested, but no issue is expected to draw as much attention from Merck as the issue of specific causation. With the prevalence of heart attacks and strokes in today's society, Merck will challenge plaintiffs to prove that their injury or death was caused by VIOXX as opposed to a myriad of other potential causes.

Trials are scheduled as early as May 2005. Stay tuned.

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