Clear Thinking About Vioxx - The risk is not what you think

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(by David R. Henderson and Charles L. Hooper)

If you read the news, pay attention to TV commercials for personal injury lawyers, or just get a lot of spam in your inbox, you know that many, many people are in a panic about Vioxx, the drug that was used by patients with arthritis until Merck & Co., Inc. voluntarily withdrew it in September. Some pundits have done the trial lawyers' heavy lifting for them by portraying Merck as an evil corporation concerned only with making money and not at all worried about killing innocent customers in the process. Arianna Huffington, for example, writes that Merck "sacrifice[s] the health of the public on the altar of higher and higher profits."

But before we jump on board the anti-Merck bandwagon, we should realize the stakes involved. If the courts, the FDA, and Congress do not handle the Merck case judiciously, there is great danger that the real victims of this case will include many people reading this article. And they will be victims, not of Merck, but of an overly zealous and out-of-control legal and political system.

The facts are these: (1) Vioxx, like almost all drugs, carries it own risks but also has substantial benefits for many patients, (2) some members of the media, in particular, CBS, have distorted the facts about Vioxx and about Merck, and (3) there is no evidence that Merck broke any law or even that it acted in any way irresponsibly. Let's take these points in turn:

Risks and Tradeoffs

In an October 5, 2004 Wall Street Journal, article entitled "Despite Vioxx Withdrawal, The Benefits of Medicines Can Outweigh the Risks," Andrea Petersen writes:

Even in the case of Vioxx, the likelihood that an individual taking the drug would have a heart attack or stroke is relatively small. In a study of 2,600 patients, there were 15 heart attacks or stroke per 1,000 patients among those who took Vioxx for longer than 18 months. Among those who took a placebo,

there were 7.5 heart attacks or strokes per 1,000 patients. And those who took Vioxx for less than 18 months had no increased cardiovascular risk.

In other words, the increased risk of heart attack or stroke from taking Vioxx rather than a placebo was only an additional 7.5 per 1000, or less than 1 in 100. Incidentally, the study cited by Petersen was the so-called APPROVe study, designed to test whether VIOXX could help prevent the recurrence of colon polyps. This study, incidentally, was what led Merck to withdraw Vioxx from the market.

You might argue, contrary to Petersen, that an almost one in 100 increased risk of a heart attack or stroke is fairly substantial. However, we're not talking only about the worst kind of stroke or heart attack. Most strokes and heart attacks do not cause death. Consider the results of Merck's early VIGOR study of Vioxx. VIGOR is the acronym for Vioxx Gastrointestinal Outcomes Research. In June 2000, Merck submitted the findings of this research to the Food and Drug Administration. It was a comparison of results for 4,047 patients given Vioxx and 4,029 given naproxen (Aleve). The results: five patients on Vioxx died of heart attacks and four on naproxen died of heart attacks. In other words, there was one extra death from a heart attack out of 4,000 people on Vioxx. This does seem like a small risk. Making the risk of actual usage even smaller is the fact that all the results were at double the maximum recommended daily dose for Vioxx.

Of course, some people might judge the extra 1 in 4,000 chance of a fatal heart attack as being too big a risk to take. That's fine. No one is forcing people who make that judgment to take Vioxx. The great virtue of freedom to choose is that it allows people to make their own tradeoffs between risk and other things. And one of those other things is pain from arthritis. Which brings us to the tradeoff between risk and pain reduction.

Consider Dave Ellis, a 66-year-old retired pharmacist from Edmond, Oklahoma. For 30 years, he has had degenerative arthritis in his spine. By about mid-February, he will have run through his supply of Vioxx and will not be able to buy more. He tells The Wall Street Journal he "dreads" that day. As Hayes Wilson, a rheumatologist in Atlanta, put it in a December 21 Journal

article, "If you live with intractable pain every day of your life, would you take a chance that you would have a heart attack? A lot of my patients would."

So here we have a number of patients who regret that they weren't simply told of the risks and allowed to choose for themselves. And who will argue plausibly that a pharmacist is uninformed about pharmaceuticals?

It's true that no government agency has taken Vioxx off the market. Merck chose to do that. But they made that choice under pressure. Given the huge benefits of Vioxx to a substantial subset of the people taking it, a company unconcerned about lawsuits would have continued to sell it, along with the warning. In this country at this time, however, companies have to be concerned about lawsuits, even from those who have been amply warned. So the danger of lawsuits from people who are warned about the risks is preventing people willing to take those risks from having a drug that would make their lives much better.

Let's not forget why there was a demand for a drug like Vioxx in the first place. It's true that drugs like Aleve and aspirin can reduce the pain from arthritis. But these drugs come with their own side effects: aspirin, Advil, and Aleve, all of which are non-steroidal anti-inflammatory drugs (NSAIDs), can cause gastrointestinal (GI) bleeding. The rate of major GI problems typically seen in clinical trials for NSAIDs like aspirin is two to four percent of patients treated for a year. One researcher reported that at least 6,000 U.S. deaths per year result from NSAID-induced GI bleeding. Other experts have estimated that NSAID-induced GI complications result in 16,500 deaths and more than 100,000 hospitalizations per year in the U.S.

Vioxx, which is certified by the FDA to have GI-protective effects, has produced fantastic results for those most vulnerable to the side effects of NSAIDs. Vioxx was approved by the FDA for the treatment of osteoarthritis, rheumatoid arthritis, acute pain, dysmenorrhea, and migraines. Even at twice the maximum recommended daily dose, Vioxx showed a 57 percent lower rate of serious GI bleeding than the rate for NSAIDs.

Misleading Media

CBS' 60 Minutes starts its November 14 segment on Vioxx with the story of a healthy, beautiful 39-year old, Janet Huggins, who died within a month of starting to take Vioxx. CBS goes on to say:

Instead, Merck found something potentially worse: Patients taking Vioxx for longer than 18 months were twice as likely to suffer a heart attack or stroke than those taking a placebo.

CBS then shows Huggins' husband saying that he's sure that Vioxx killed his wife. But 18 months is not one month. Merck has solid evidence that Vioxx shows no additional cardiovascular risk until after 18 months of therapy. The odds that Mrs. Huggins died from Vioxx are slim indeed. But that didn't stop CBS from exploiting her death to make a point.

Merck's Responsibility

Of course, our view of Merck might change if we had reason to think that Merck withheld evidence of Vioxx's harmful side effects. But so far we have no basis for thinking Merck did withhold evidence and, in fact, we have a strong basis for believing that it didn't.

First, let's consider the easy case. No one seems to think that Merck moved too slowly in withdrawing Vioxx within four days of getting the results from the aforementioned APPROVe study. So the issue comes down to whether Merck withheld information from earlier studies.

The closest anyone has come to a "smoking gun" is an email about the VIGOR study that Merck's chief of research, Edward Scolnick, sent to his colleagues. Here's how The Wall Street Journal put it:

On March 9, 2000, the company's powerful research chief, Edward Scolnick, e-mailed colleagues that the cardiovascular events "are clearly there" and called it a "shame." He compared Vioxx to other drugs with known side

effects and wrote, "there is always a hazard." (Anna Wilde Mathews and Barbara Martinez, "E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage," Wall Street Journal, November 1, 2004.)

In that same e-mail, Scolnick lamented, "it is a shame but it is a low incidence and it is mechanism based as we worried it was." In other words, Scolnick was saying that, contrary to what Merck researchers had believed, the higher incidence of heart attacks was due not to the fact that people taking Vioxx weren't taking NSAIDs but rather to something within Vioxx itself. This does sound like a cover-up. But notice something interesting in the time line that some anti-Vioxx lawyers put together. The next event they note after the March 9 email is that on March 17, only eight days after Scolnick's speculation, Merck updated its label by adding, in the "adverse events" section, "cardiovascular" reports. Some cover-up.

60 Minutes breathlessly added:

However, according to internal Merck documents 60 Minutes has seen, and interviews with outside scientists, Merck had concerns that Vioxx could possibly cause cardiovascular risks long before it was pulled off the market.

Of course they had these concerns. Those risks were known from the VIGOR trial, which was completed in March 2000, and whose results were reported to the FDA in June 2000.

Beginning in September, 2002, this new information was printed on the Vioxx package insert. It was reprinted, shortly after that, in the widely used 2003 version of the Physicians' Desk Reference. The package insert devotes two full tables and a number of paragraphs to the risk of cardiovascular problems. The package insert shows that 45 of 4,047 patients on Vioxx experienced a cardiovascular thrombotic event, compared to only 19 of 4,029 patients on naproxen. The package insert goes on to say that Vioxx is not a substitute for aspirin and that patients who need cardiovascular protection should continue taking aspirin. It also notes the additional one in 4,000 risk of a fatal heart attack.

The real test of whether Merck was responsible is a market test: after this information was revealed to the public in September 2002, did the demand for Vioxx decline? If it didn't decline substantially, that suggests that people taking Vioxx were not very concerned about this small additional risk. You might argue that people are not informed enough to know about this risk. But their doctors are, and doctors, in the U.S. at least, write all the prescriptions for Vioxx. Doctors regularly page through the Physicians' Desk reference and word on Vioxx would

have been out by early 2003. Yet the worldwide demand for Vioxx grew slightly while the U.S. demand declined slightly. The U.S. decline of five percent between the second quarter of 2003 and the second quarter of 2004, was so small that it could have been due to a number of other factors, including competition from similar drugs such as Celebrex. (Celebrex has also been linked to an increased risk of cardiovascular problems, but the drug's manufacturer, Pfizer Inc. has chosen not to withdraw it from the market.)

There's another test of Merck's responsibility or lack of same: look at the behavior of Merck employees, especially those intimately involved with the VIGOR study. After learning of the VIGOR results, did those employees who took Vioxx stop taking it? We don't know, but those data are relevant and, in fact, Merck would do well to gather them for its legal defense. And we do know one sample point. Merck's CEO, Ray Gilmartin, told a congressional committee that his wife took Vioxx until the day the company withdrew the drug. Unless we speculate that he was out to kill his wife slowly, and was willing to accept a low probability of succeeding, his and her behavior are powerful evidence that Merck was selling a drug it considered relatively safe.

Two final pieces of evidence come from the behavior of the FDA itself. First, the FDA is exceptionally conservative. It is acutely aware that of the two ways it can fail, approving a bad drug is significantly worse for its employees than failing to approve a good drug. Approving a bad drug may kill or otherwise harm patients, and an investigation of the approval process will lead to finger pointing. As one former FDA employee, Henry Miller, put it, "This kind of mistake is highly visible and has immediate consequences—the media pounces, the public denounces, and Congress pronounces." Given this, it seems highly unlikely that the FDA suspected any serious cardiovascular problems with Vioxx, even after it studied the VIGOR results.

The second piece of evidence is the current behavior of the FDA. No one likes to be accused of screwing up, especially if the accusation is false. If Merck had withheld important information about Vioxx from the FDA, then officials in the FDA would now have a strong incentive to lay the blame on Merck. But they aren't doing so. And it's presumably because they can't, because they were fully informed and saw the risks as being fairly small.

Why does this matter to anyone other than Vioxx patients, Merck stockholders, and trial lawyers? For two main reasons. First is the issue of simple justice. Merck is one of the most cautious and benevolent drug companies in the business. Merck has a long history of innovative discoveries that have improved human health around the world. In a huge breakthrough in 1989, Merck researchers determined the three-dimensional structure of HIV protease at a time when AIDS was much scarier. They could have used this tremendous competitive advantage, but they chose to make it publicly available. Every day that this information was withheld, they reasoned, was one more day for the AIDS epidemic to spread.

The second reason for caring about the Vioxx case is the issue of long-term consequences. The FDA already has incentives to turn down drugs that are beneficial if they have reason to expect any negative side effects. And the greatest scandal of all, even if people's worst fears about Vioxx are true, is not Vioxx but the dozens of new drugs that will never be developed because the cost of clearing the FDA's super-conservative hurdles make those drugs not worth developing. One of the authors of this article already informs drug companies that some of the medicines they are developing don't make economic sense. Add a few years and a few hundred million dollars to the development timeline and the economics become that much worse. Emory University economist Paul Rubin reports an estimate that FDA regulation saves between 500 and 1,000 injuries (not deaths) per year but costs between 2,100 and 12,000 lives annually. That's not a good tradeoff. The last thing we need is further hurdles to new drug development.