The Vioxx recall: cover-up of health risks may have resulted in thousands of deaths

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There is mounting evidence that the drug giant Merck was aware of the safety risks associated with use of its arthritis drug Vioxx years before it announced a recall on September 30. The company's attempts to cover up these risks may have resulted in the unnecessary deaths of thousands of patients around the world.

Evidence of a cover-up was documented in a November 1 article in the *Wall Street Journal*, citing internal company e-mails and marketing materials. This material has been supplemented by a paper posted November 5 on the Internet site of the British medical journal, *The Lancet*. The paper found that by 2000, scientific evidence existed of an increased risk of heart attacks and strokes due to use of Vioxx.

The record indicates that the actions of both Merck and the US Food and Drug Administration (FDA) contributed to the nearly 30,000 excess cases of heart attacks and sudden cardiac deaths that resulted from the use of the drug between 1999 and 2003. While Merck sought to cover up the danger of its own drug to protect its bottom line, the US government aided the company by approving sale of the drug without conducting any serious investigation into potential harmful consequences of its use.

During the late 1990s, Merck was in desperate need of a major drug to boost its sagging revenues. It turned to Vioxx, a type of anti-inflammatory drug known as a COX-2 inhibitor. COX-2 inhibitors have been promoted by the claim that unlike other non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen (Aleve), aspirin or ibuprofen, they do not cause gastrointestinal problems. Some 80 million prescriptions of Vioxx have been filled since the FDA approved it in 1999.

The *Journal* article notes, however, that the number of patients who suffer from the stomach problems caused by traditional NSAIDs is relatively small. "The real bonanza lay with the general mass of pain patients. In the late 1990s Merck was facing the loss of patent protection on several top drugs and needed a big hit." Vioxx could not be this big hit if patients and doctors felt that the risks associated with taking the drug were too high.

This presented a problem for Merck. As early as November 1996, a Merck official noted, "There is a substantial chance that significantly higher rates" of cardiovascular problems would be seen in any study comparing Vioxx with naproxen or other NSAIDs. However, the company needed to carry out a study comparing Vioxx with these other drugs to demonstrate Vioxx's benefit for gastrointestinal patients.

To place the drug in the best light possible, the company sought to manipulate the results of its main study carried out in 1999 known as VIGOR (Vioxx Gastrointestinal Outcomes Research). Any increase in relative heart conditions was attributed to the supposed heart benefit of naproxen rather than the adverse effects of Vioxx.

As expected, when the results of the VIGOR study came out in March 2000, they showed a significantly higher rate of heart attacks for those taking Vioxx as compared to naproxen. A patient taking Vioxx was reported to be four times more likely to suffer from a heart attack, and later analysis revealed that the actual figure was five times more likely.

The *Journal* reports, "The difference was so wide that Dr. [Edward] Scolnick, the Merck research chief, appeared to recognize it couldn't come solely from naproxen's protective effect but must involve some sort of risk inherent to Vioxx. In a March 9, 2000, e-mail with the subject line 'Vigor' Dr. Scolnick said the results showed that the cardiovascular events 'are clearly there.' In an apparent acknowledgement that Vioxx's own mechanism was at least partially at fault for the heart data, he wrote: 'it is a shame but is a low incidence and it is mechanism based as we worried it was.'"

However, when it announced the results of the trial, Merck suggested that any difference in heart incidents was due to the protective benefits of naproxen, not the negative effects of Vioxx. According to an FDA memo dated September 30, 2004, and released by the FDA after the *Wall Street Journal* article, "To explain a 5-fold difference, naproxen would have had to be one of the most potent and effective cardio-protectants known," and there was no evidence that this was the case.

Despite Merck's attempts to spin the results, the VIGOR trial raised questions within the medical community about the safety of Vioxx. The company spent hundreds of millions of dollars a year in marketing the drug, in part to counteract any questions raised.

The *Journal* reports that an internal company marketing guide directed to "all field personnel with responsibility for Vioxx" provided an "obstacle handling guide" that advised marketers to avoid direct answers on the health consequences of Vioxx. According to the *Journal*, "One training document is titled 'Dodge Ball Vioxx' and consists of 16 pages. Each of the first 12 pages lists one 'obstacle,' apparently representing statements that might be made by a doctor. Among them are, 'I am concerned about the cardiovascular effects of Vioxx' and 'The competition has been in my office telling me that the incidence of heart attacks is greater with Vioxx than Celebrex.' The final four pages each contain a single word in capital letters: 'Dodge!' "

The *Journal* article further notes that Merck sought to pressure and intimidate doctors and medical professors who raised questions about the safety of Vioxx. One Stanford professor, Gurkirpal Singh, criticized Merck for not providing more data on the cardiovascular safety of Vioxx in 2000.

The *Journal* reports, "In October 2000, a Merck official, Sherwood, called James Fries, a Stanford University Medical School professor, to complain that Dr. Singh's lectures were 'irresponsibly anti-Merck and specifically anti-Vioxx,' as Dr. Fries described the call in a January 2001 letter to Mr. [Raymond] Gilmartern, the Merck chief executive. The Merck official 'suggested that if this continued, Dr. Singh would "flame out" and there would be consequences for myself and for Stanford,' Dr. Fries wrote." Fries wrote that researchers at other schools had also reported "a consistent pattern of intimidation of investigators by Merck."

These efforts continued throughout the lifetime of Vioxx. In 2002, A Spanish institute found its funding from Merck eliminated after it refused to censor criticisms directed at Merck from one of its scientists.

Merck also sought to suppress further analysis of the consequences of Vioxx, including one study funded by the company itself, eventually published in May 2004. That study found Vioxx to be "associated with an elevated relative risk" of heart attacks when compared with Celebrex (the other major COX-2 inhibitor) or with a placebo. When the head of the team conducting the study refused to tone down its conclusions, Merck attempted to distance itself from the results by removing the name of one of its researchers from the list of authors.

Eventually, evidence demonstrating the harmful effects of Vioxx became so overwhelming—including another study carried out by Merck and one by the FDA—that further suppression was impossible. This led to the drug's recall five weeks ago.

The documents reported by the *Journal* are supported by a recent paper in *The Lancet* published by a group of researchers led by Peter Juni. That paper performed an analysis of trials and studies previously carried out that compared the cardiovascular affects of Vioxx to other NSAIDs or placebos. According to the authors, evidence was available by 2000 that patients taking Vioxx suffered from a significantly higher risk of heart attack than those taking naproxen, non-naproxen NSAID or placebo. Since the increase in heart attacks did not exist only relative to naproxen, it could not be attributed to the benefits of naproxen. The only explanation could be that Vioxx itself caused an increase in heart attacks.

An editorial in *The Lancet* notes that the paper demonstrates "The unacceptable cardiovascular risks of Vioxx (rofecoxib) were evident as early as 2000—a full 4 years before the drug was finally withdrawn from the market by its manufacturer, Merck."

In addition to indicting Merck, the editorial also notes that the FDA did nothing to ensure the safety of Vioxx before approving it for general use. "The public expects national drug regulators to complete research, such as that published by Juni and colleagues, in their ongoing efforts to protect patients from undue harm. But, too often, the FDA saw and continues to see the pharmaceutical industry as its customer—a vital source of funding for its activities—and not as a sector of society in need of strong regulation."

The editorial noted that in the FDA, the part of the agency responsible for drug safety is subordinate to the part that is responsible for approving new drugs. It also notes, "In the case of Vioxx, FDA was urged to mandate further clinical safety testing after a 2001 analysis suggested a 'clear-cut excess number of myocardial infarctions.' It did not do so.... With Vioxx, Merck and the FDA acted out of ruthless, short-sighted, and irresponsible self-interest."

According to a preliminary memo written by FDA researcher David Graham and posted on the FDA web site last week, "From 1999 to 2003, there were an estimated 92,791,000 prescriptions for rofecoxib [the medical name for Vioxx], of which 17.6% were high-dose. Combing this with data on mean prescription length, we estimate that the increased rofecoxib risk observed in this study would yield an excess of 27,785 cases of AMI [acute myocardial infarction or heart attacks] and SCD [sudden cardiac death] in the US over the years 1999-2003."

According to Graham, the fatality rate from these incidents is approximately 27 percent. This would indicate that Vioxx use was responsible for an estimated 7,500 deaths between 1999 and 2004. Since Graham found that the increased risk of heart attacks was not general to all COX-2 inhibitors, but specific to Vioxx, his study suggests that all of these deaths could have been prevented through the use of any other NSAID, including Celebrex.

Graham also found that Vioxx use results in a 90 percent increase in hospitalization rate for gastrointestinal bleeding compared to Celebrex. If this is true, than it means that there are no important health benefits associated with Vioxx use relative to other drugs on the market.

These developments are a stunning indictment of the state of health care and pharmaceutical production in the United States. Every consideration, including the safety of the drugs produced, is subordinated to the profit considerations of a handful of giant drug companies. These companies spend billions of dollars on advertising and marketing, at the expense of research and testing. Over the past 25 years, regulations on drug production have been systematically gutted in order to allow companies to quickly get their products to the market.

As a consequence, drugs reach a mass market before there is any real understanding of their effects. The interests of companies producing the drugs lies in direct contradiction to the interests of consumers and doctors in receiving complete and unadulterated knowledge of the nature of the drugs they are using and prescribing.

The case of Vioxx demonstrates quite concretely the necessity for transforming the giant drug companies into public utilities, run in the interests of social need. Only by removing the profit motive from the system of drug production can future incidents like the Vioxx debacle be prevented.