The Vioxx scandal: damning Senate testimony reveals drug company, government complicity

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Several scientists testifying before the Senate Finance Committee on November 17 provided substantial evidence that the drug company Merck and the US Food and Drug Administration (FDA) knew of safety problems years before the drug Vioxx was withdrawn from the market.

Vioxx, which was used to treat arthritis and severe pain, was withdrawn by Merck on September 30 after conclusive evidence emerged that it greatly increased the risk of heart attacks and strokes. Some 80 million prescriptions of the drug have been filled around the world, most of them in the US, since it was approved in May 1999.

The principal testimony was given by Dr. David Graham, the associate director for science and medicine at the FDA's own Office of Drug Safety. The ODS, responsible for monitoring the safety of drugs already on the market, is part of the Center for Drug Evaluation and Research (CDER), which also includes the Office of New Drugs (OND), responsible for approving new drugs for the market. Graham explained how he came into repeated conflict with the OND as he sought to raise concerns about the safety of Vioxx.

The OND is one of the branches of the FDA that is most closely tied to the giant drug companies it is nominally responsible for regulating. Since passage of the 1992 Prescription Drug User Fee Act, the office gets much of its funding directly from drug companies, in the form of new drug application fees of more than $500,000 per application. Most of this money goes toward speeding up the approval of new drugs.

Graham explained that the OND, which has a higher position in the FDA hierarchy than his ODS, is generally very reluctant to issue new regulations for drugs already on the market or order mandatory withdrawals of unsafe drugs that the office has approved. In the case of Vioxx, the drug was pulled from the market only after its producer, Merck, decided that the evidence of harmful consequences was overwhelming. It was not withdrawn as a result of any regulatory action by the FDA.

A study led by Graham that was concluded in the summer of 2004 found that Vioxx was responsible for an estimated 38,000 excess heart attacks and sudden cardiac deaths. In his testimony, Graham stated that this was a conservative estimate. He said that "a more realistic and likely range of estimates for the number of excess cases in the US" was between 88,000 and 139,000. "Of these," he added, "30-40 percent probably died. For the survivors, their lives were changed forever."

To dramatize the number of people affected, Graham noted that "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 five years."

Graham testified that as his team concluded its study and prepared to present its results, it was attacked by the Office of New Drugs and other sections of the FDA. "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 reporting his study's conclusions. "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."

Up to a week before the drug was pulled from the market by Merck, FDA management, according to Graham, was attempting to undermine Graham's conclusions.

Graham said, "[W]e are virtually defenseless" against another catastrophe on the scale of Vioxx. "The organization 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.... 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."

The prevailing sentiment at the FDA, said Graham, is one that views "the pharmaceutical industry it is supposed to regulate as its client, over-values the benefits of the dugs it approves, and seriously under-values, disregards and disrespects drug safety." When it comes to drug safety, he said, the operating principle is that the drug is safe unless it is proven to be unsafe beyond a shadow of a doubt. New drugs, including Vioxx, are pushed through the approval phase in a matter of months, before sufficient tests are done to ensure their safety. Independent clinical testing is rarely carried out by the FDA, and indications of safety problems are ignored or deliberately undermined.

Later, Graham pointed to five drugs currently on the market that he felt were potentially dangerous: Acutane, which is used to treat acne; Bextra, a painkiller; Crestor, used to lower cholesterol; Meridia, used to treat weight loss; and Serevent, used to treat asthma. All of these can cause dangerous side effects and have not been adequately tested for their safety, Graham asserted.

Others providing testimony included Gurkirpal Singh, from the Stanford University School of Medicine, and Bruce Psaty, co-director of the Cardiovascular Health Research Unit at the University of Washington. The two scientists reviewed some of the history of the testing of Vioxx and concluded that, even with the limited data available, the drug should have been pulled from the market well before it was eventually withdrawn.

Singh noted that there was evidence of serious heart problems associated with Vioxx before it was approved in 1999. "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 concluded that men taking Vioxx had a 28 percent greater risk (not statistically significant), but in women, the risk was more than double (216 percent, 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."

Merck has continually asserted that at the time of Vioxx's approval, no evidence existed indicating that the drug caused additional heart attacks. The main study carried out by Merck, known as VIGOR, showed a fivefold increase in serious heart conditions relative to another drug, naproxen (the generic form of Aleve). Merck explained these results as a consequence of naproxen's beneficial effects, rather than Vioxx's harmful ones. However, in 1999 a scientist at the FDA remarked that "thromboembolic events [such as heart attack and stroke] are more frequent in patients receiving Vioxx than placebo." Singh noted, "This meant that not only did Vioxx not [have the benefits of naproxen], but for some reason, it was likely to promote heart attacks directly."

The evidence was still limited, Singh said. "There were not adequate data to make a firm conclusion one way or another. In fact, the FDA reviewer went on to point out that '[w]ith 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 [Vioxx]. A large database will be needed to answer this and other safety comparison questions.' "

Instead of carrying out a larger study, the FDA quickly approved the drug for use. This was in spite of the fact that the drug served no pressing necessity. There were already drugs on the market that performed the same function as Vioxx: to relieve inflammation without causing stomach problems. The FDA did not even require a caution on the drug's label about the increased risk of hear attacks until April 2002.

Nor did Merck attempt a larger study. The *New York Times* reported on November 14 that such a study was contemplated in May 2000, but management rejected the idea. According to the *Times*,a slide prepared for an executives' meeting stated, "At present, there is no compelling marketing need for such a study.... The implied message is not favorable."

In their defense, Sandra Kweder, the deputy director of the Office of New Drugs, and Raymond Gilmartin, chairman and CEO of Merck, simply repeated the claim that everything was done to determine the safety of Vioxx as quickly as possible, and that the drug was immediately withdrawn as soon as safety problems became evident. The overwhelming evidence indicates the opposite: that tens of thousands of deaths likely caused by use of Vioxx were entirely preventable.