# US: new questions about safety of anti-inflammatory drugs

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Last week, the drug company Pfizer announced that it had found evidence of a connection between Celebrex, an anti-inflammatory drug that it manufactures, and an increased risk of heart attacks and strokes. The announcement calls into question the safety of a whole class of drugs commonly used to treat arthritis in millions of people in the US and internationally.

In late September, the drug company Merck withdrew its blockbuster drug Vioxx from the market after discovering a similar tendency to increase serious heart conditions. Both Vioxx and Celebrex are part of the class of anti-inflammatory drugs known as COX-2 inhibitors. They had been massively promoted and advertised during the past five years before problems with the drugs were publicized.

While Pfizer has said it is not withdrawing Celebrex, it has ceased all direct-to-consumer advertising. An eventual complete withdrawal of the drug appears likely. Some scientists have also raised concerns about another COX-2 inhibitor manufactured by Pfizer known as Bextra.

The National Cancer Institute sponsored the study that produced the results on Celebrex. It was part of an attempt by Pfizer to demonstrate a beneficial effect of Celebrex in preventing certain types of cancer. However, during the study researchers discovered that patients taking high doses of Celebrex were 2.4 times more likely to develop heart disease than patients on placebo.

Pfizer has stated that other studies do not find a connection between Celebrex and heart disease, and that the drug is just as safe as other anti-inflammatories. Nevertheless, the US Food and Drug Administration (FDA) issued a statement on Friday urging patients on Celebrex to seek an "alternative therapy" and left the door open to forcing a withdrawal of the drug.

On Monday, the FDA issued a warning on another drug used to treat inflammation, naproxen. Naproxen is most commonly manufactured by the German company Bayer under the brand name Aleve. Preliminary findings in a study carried out by the National Institute on Aging suggest that patients over the age of 70 are 1.5 times more likely to develop a serious heart condition than patients on placebo. In the study, no noticeable increase was evident in patients taking Celebrex, i.e., the heart problems associated with the drug found in the National Cancer Institute study were not repeated in the National Institute on Aging study.

The lead investigator in the study, John Breitner of the Veterans Administration Puget Sound Health Care System, cautioned that the findings were only a "weak signal" of potential problems with naproxen. He pointed out that the data, which has yet to be fully analyzed or vetted by other scientists, was not necessarily even statistically significant, meaning that the increased risk may be merely a result of chance rather than an effect of the drug.

Naproxen is not a COX-2 inhibitor, and scientists had long believed that it actually helped reduce the chance of heart attacks and strokes. Dr. Garret FitzGerald, chairman of the University Of Pennsylvania's pharmacology department, stated, "It's much too early from the information provided to know if this is a meaningful result or not."

At the same time, Breitner noted that the problems found in Vioxx and Celebrex may be general to a broader class of anti-inflammatory drugs. "It may be a problem for all nonsteroidal anti-inflammatory drugs [including COX-2 and naproxen], because we've never had an opportunity to examine this question," he said.

Given the very preliminary character of the results on naproxen, why were they heavily promoted on Monday? The FDA went so far as to issue a statement urging patients to limit use of the drug and hinted at possible future regulatory action. The story was the main item in many of the evening news programs in the US on Monday.

The concerns raised about naproxen do have the effect of relieving pressure on both the drug companies and the FDA for the scandal involving COX-2 inhibitors. In its article on Tuesday, the*New York Times* noted that the results on naproxen "could prove beneficial for Pfizer, which has been arguing that last week's findings about Celebrex should be placed in the context that similar pills may be just as hurtful to the heart and that other studies of Celebrex have shown no such worries. Indeed, if there is one message from these studies it is that nothing is certain in this science."

The paper quoted Sandra Kweder, deputy director of the FDA's Office of New Drugs, as stating, "This is a very confusing situation. Every doctor and patient is going to have to have a conversation about their unique risks." The Office of New Drugs is the branch of the FDA that is most closely tied to the interests of the pharmaceutical industry. Her comments were echoed by Pfizer's Chairman and CEO Hank McKinnell, who stated that "physicians and patients are understandably confused" at the different results of the studies.

However, while the exact side effects of the different drugs may be unclear, there is nothing confusing about the history of COX-2

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inhibitors. Many scientists have warned of potential problems with this class of drug for years, without provoking any response from the FDA to seriously investigate potential health problems. Evidence indicates that the drug companies, particularly Merck, worked assiduously to cover up damaging results in order to keep sales at extraordinarily high levels. [See "The Vioxx recall: cover-up of health risks may have resulted in thousands of deaths" http://www.wsws.org/articles/2004/nov2004/viox-n10.shtml]

COX-2 inhibitors were originally developed as a class of drugs that would treat arthritis and inflammation without causing gastrointestinal bleeding, a side effect some patients experience with the use of other anti-inflammatory drugs, including ibuprofen and naproxen. They are supposed to work by blocking one enzyme, COX-2, that is thought to cause inflammation, without blocking another enzyme, COX-1, thought to protect the stomach lining.

However, the number of patients that suffer serious side effects from the use of the other drugs is fairly small, numbering in the tens of thousands. The drug companies wanted to—and did—turn the drugs into blockbusters, used by tens of millions of people around the world.

An article in the *New York Times* on December 19 by Barry Meier ("Medicine Fueled by Marketing Intensified Trouble for Pain Pills") notes, "Having spent hundreds of millions of dollars to develop their drugs, the makers of Celebrex and Vioxx, cheered on by Wall Street, had every motivation to expand their markets beyond the older people most at risk of ulcers to encourage the drugs' use by millions more people of all ages."

The advertising campaign—directed both at patients and doctors—obscured the fact that the medications were not proven to be any more effective in relieving pain than traditional medications such as ibuprofen. Pfizer has never been able to even conclusively demonstrate that Celebrex reduces the risk of stomach problems as compared to ibuprofen.

As Meier reports, "Since the drugs' release, the companies have spent hundreds of millions of dollars on television, newspaper and magazine advertising for them and, by some estimates, at least as much on marketing and promoting the drugs to doctors. As a result, many medical experts now say that Celebrex and Vioxx, selling for $2 or $3 a pill, have been too widely prescribed to patients who could safely obtain the same pain benefits from over-the-counter drugs costing pennies apiece."

According to the research firm TNS Media Intelligence/CMR, Pfizer spent over $71 million to advertise Celebrex during the first nine months of 2004, up 55 percent from the level of advertising purchased during the same period last year. Consumers have been bombarded with commercials urging them to "celebrate" with Celebrex, and doctors have been heavily courted encourage them to prescribe the drug.

As a result of this advertisement, Meier notes, "Within little more than a year, the drugs had grabbed about 40 percent of the market from traditional anti-inflammatory drugs like ibuprofen."

The two drugs—Vioxx and Celebrex—became critical for their respective producers. Pfizer estimates that since the FDA approved Celebrex in 1998, it has been prescribed to 27 million Americans. It has generated over $3 billion in sales for the company in 2004, and some estimates predicted sales to soar to as much as $9 billion in 2005, in part due to the withdrawal of Vioxx. This would be 9 percent of the company's entire revenue.

The drug industry as a whole has faced a growing crisis during the past five years, as many major drugs have reached their patent limit, the point after which the drugs can legally be made as generics and sold at much lower prices. Companies such as Pfizer and Merck have become increasingly dependent upon the revenues generated by a handful of drugs. They spend large portions of their revenues on promoting these drugs and increasing sales as much as possible.

While COX-2 inhibitors may have important uses for some patients, their mass promotion was entirely unnecessary. Not only did purchasing these drugs cost patients billions in medical expenses, tens of thousands may have needlessly died due to the drugs' harmful side effects.

The success of the drugs was only possible with the help of the FDA and the decline of regulation of the drug industry. The explosion in drug advertising, particularly in direct-to-consumer advertising, was only possible after regulatory changes implemented during the late 1990s.

The FDA's Office of New Drugs (OND), which is responsible for approving drugs for the market, has been greatly expanded at the expense of the sections of the FDA responsible for monitoring the safety of drugs already on the market. At the same time, the OND has been made more dependent on the industry it is supposed to regulate. Indeed, much of the office's funding comes directly from the drug industry, in the form of fees intended to speed up the drug approval process. Both Vioxx and Celebrex were approved after expedited reviews, even though little was known about their potential benefits and side effects.

Some FDA scientists have alleged that they were pressured to bury findings that suggested problems with drugs already on the market. One survey found that one-fifth of scientists at the FDA said they felt pressure to approve a new drug despite concerns about safety, effectiveness or quality.

David Graham, a scientist in the FDA's Office of Drug Safety, has denounced the FDA for its failure to regulate Vioxx and other drugs. He has charged that officials in the FDA sought to suppress his own research indicating problems with the drug. Since he came out with broad accusations, he says he has been sidelined and threatened with a job change by officials in the agency.


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