

## **Celebrex Drama May Finally Prompt Changes at the FDA**

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Staff Reporters of THE WALL STREET JOURNAL  
December 20, 2004; Page B1

**The still-unfolding drama involving Pfizer Inc.'s blockbuster painkiller Celebrex highlights two trends: the power of marketing to lure millions of Americans to embrace new drugs quickly, and the Food and Drug Administration's challenge in detecting and responding to problems in drugs that emerge after the agency has deemed them safe.**

**A powerful gatekeeper, the FDA has always been hamstrung in crucial ways once a drug is on the market. These days it may have less time than ever to find and act on safety problems that weren't clear before a drug's approval. As new medicines are promoted like movies, with marketing campaigns revving up huge demand quickly, drugs can be used by millions before evidence of an unwelcome side effect comes to the agency's attention. That is different from years past, when the FDA had a safety net because drugs frequently were sold overseas before they were approved here.**

**When drugs are launched rapidly and widely that can be "a setup for potentially finding the serious adverse events here after a large number of patients have already been exposed to the drug," says John Jenkins, director of the FDA's office of new drugs, though he notes that in some cases, such widespread use can help bring safety problems to light earlier.**

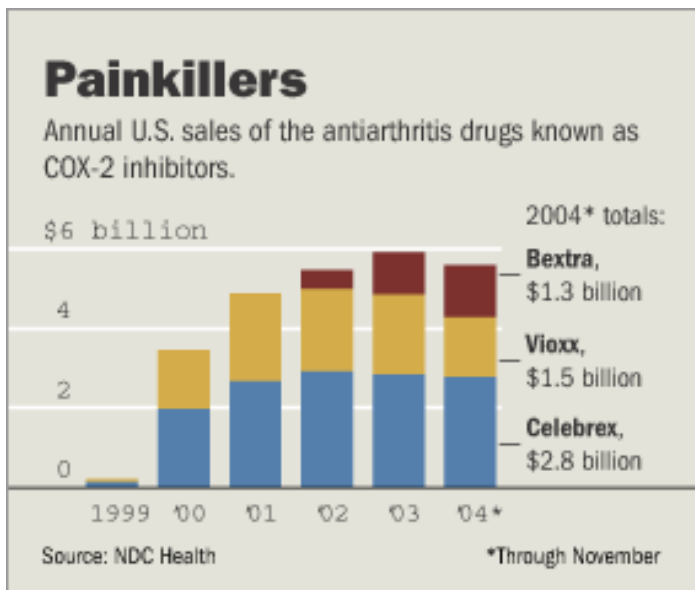
**Now, the furor over Celebrex, which in recent days was linked in a clinical trial to an increased risk of cardiovascular problems, and Vioxx, the similar Merck & Co. drug withdrawn for a similar reason, is likely to re-energize FDA and legislative efforts to find a better way to discover such hazards and respond to them.**

**The debate is in full swing. Yesterday, Sen. Edward M. Kennedy, a Massachusetts Democrat, called the FDA's drug-safety record "a catastrophic failure," while White House Chief of Staff Andrew Card said the agency was doing a "spectacular job" during an appearance on ABC News's "This Week With George Stephanopoulos." On Friday, the House Energy and Commerce Committee wrote to Pfizer demanding information about Celebrex, while Senate Finance Committee Chairman Charles Grassley, an Iowa Republican, called for a review of the FDA by an independent commission.**

**The FDA, in fact, has already ordered a review from the Institute of Medicine, a federal scientific advisory organization, and is expected to put forth a new plan for improvement. The agency may seek to ramp up earlier ideas that never came to**

Another longstanding idea that has gained new attention is restructuring the FDA, perhaps by separating the job of monitoring the safety of approved drugs from the division that clears drugs in the first place, though this might be difficult because of how the agency is set up. Others say the agency needs the firepower to crack down on manufacturers that fail to conduct requested safety studies.

One cause of the FDA's conundrum is clear: The clinical trials conducted by drug companies before their products receive approval have never been able to detect every possible side effect. "There are conspicuous, and perhaps irredeemable,



deficits in what we can know about a drug before it is approved," says Donald Kennedy, a former FDA commissioner. Compounding that, he says, is "you have to be very careful about the introduction of a drug because your ability to deal with it after it is on the market is sharply limited."

The pharmaceutical industry's sales efforts, aided by patients' Internet-fueled awareness of potential new cures, may make it tougher in some ways for

regulators to deal with side effects once they are known. When the companies, at the FDA's behest, do add warnings to their labels and package inserts, the cautions are rarely emphasized in the blast of promotional materials. Drugs that might once have been used primarily by specialists are routinely promoted to, and prescribed by, doctors who are less familiar with the medicines' full research record. The drugs can end up in the hands of patients who aren't necessarily the best candidates.

The agency is trying to exert more control over the use of certain drugs that may pose safety problems, by pressing drug makers to restrict distribution or, in some cases, promotion. For example, it asked Purdue Pharma LP, maker of the powerful painkiller Palladone, to initially limit the drug's marketing. "We wanted to try to limit the use of those products to physicians and patients who really fit the profile of what the products were approved for," says FDA's Dr. Jenkins.

**The FDA does have the ultimate power -- to force dangerous drugs off the market. But that step is so drastic that it is mulled only for the starkest cases, while most situations, including Celebrex's, are murky. In those cases, the FDA has only a limited ability to force companies to do research, or to take other measures, such as limiting distribution. The law governing the agency's authority is "a red light/green light statute," says Daniel Troy, former chief counsel of FDA. A drug is "either approved as safe and effective under the conditions on the label or it isn't."**

**Many of the laws that govern the FDA's powers were written decades ago, for a different industry. Today, big, consolidated pharmaceutical conglomerates wield their bulked-up sales muscle to sell medicine chests of products, many of which treat chronic conditions like high cholesterol or "lifestyle" problems like erectile dysfunction. Drug companies spent \$8 billion on "detailing" to office-based physicians -- sales people dropping off marketing materials and speaking to them about drugs -- in the 12 months through October, according to Verispan, a health-information company. That's up from \$3.6 billion in 1996. At the same time, drug makers are reaching out directly to patients. They spent \$4 billion on direct-to-consumer advertising this year through September, up from up from less than \$1 billion in all of 1997.**

**The sales pitch has clearly worked. The number of blockbusters, defined as drugs with more than \$1 billion in annual retail prescription sales, grew to 34 in 2003, according to Verispan. That was up from 33 in 2002 and only 15 in 1999.**

**Among the biggest sales victories, and a prototype for later promotions, were Celebrex, Vioxx and the later entrant Bextra, all painkillers known as Cox-2 inhibitors. They were developed in response to concerns that older pain drugs such as aspirin and ibuprofen damaged the stomach and intestines. Both Pfizer and Merck spent heavily marketing their painkillers -- \$406.3 million and \$459.8 million, respectively, on direct-to-consumer advertising of Celebrex and Vioxx from 1999 to 2003, said Verispan.**

**Even as Cox-2 drugs became ubiquitous, there were still questions about their safety benefits, such as whether they were safer on the stomach than older drugs. Lurking in the background was another issue: the drugs' possible connection to heart attacks and other cardiovascular problems. Researchers had theorized that the Cox-2 drugs might not carry the anticlotting benefits of aspirin, which protects against heart attacks. Though there were signals of possible cardiovascular problems in various studies of Vioxx over the years, Celebrex raised few flags. The later Pfizer Cox-2 drug Bextra, however, did raise concerns even before its approval in 2001.**

**The FDA wasn't able to answer questions about the heart risks of the Cox-2 drugs using its main tool for detecting problems in approved drugs, the adverse-event reporting system, which many experts say is seriously limited. Drug companies must report side effects and injuries caused by their products. But they depend largely on doctors, who have no obligation to report side effects either to the manufacturers or**

**the FDA. The FDA receives about 280,000 reports a year, or an estimated 10% or less of actual events. The system isn't well-suited to detecting a drug's potential link to problems that are common among the general population -- like heart attacks among the older patients who took Vioxx and Celebrex.**

**The FDA seeks to supplement the voluntary reports by funding studies of particular safety problems -- as it eventually did with Vioxx and Celebrex, with results that emerged last August, just a month before Merck took Vioxx off the market. But its resources are limited.**

**The problem was highlighted by Bayer AG's cholesterol-lowering drug Baycol, which was pulled off the market in 2001 after it was tied to at least 31 deaths from a muscle condition. In the spring of 2000, the FDA and outside research partners had to hold off studying possible muscle problems. "It was decided that this ... issue, as a public health priority, was not sufficient to divert limited resources from other higher priorities," such as a different safety study, an agency safety official said in an e-mail in March, 2001.**

**Instead, the FDA did its own internal review of its side-effects database in June 2000, and the scope of the problem when the drug was used alone wasn't then obvious. The agency proceeded to approve a higher dose of Baycol. The following April, the FDA took another in-depth look at the muscle problem -- and found a number of deaths potentially tied to Baycol when taken alone. Bayer pulled the drug from the market that August. Phil Beck, lead outside counsel for Bayer on Baycol litigation, said the company "fully complied with our disclosure obligations and responsibilities."**

**In recent years, the FDA has increasingly turned to restrictions on the distribution, marketing or other aspects of drugs that can pose big hazards -- such as in the case of Accutane, the Roche Holdings AG acne drug that can cause birth defects when used by pregnant women. But it doesn't have the power to impose such plans, and it doesn't regulate the activities of doctors or pharmacists. Following the recommendation of an advisory committee, the FDA pushed the company for a tough plan to prevent use by pregnant women in a letter in October 2000. But its plan, rolled out in early 2002, fully met only one of the agency's five goals, according to the FDA.**

**In February 2004, the FDA reported that the number of Accutane pregnancies hadn't dropped. A new, tougher plan by Roche and its generic competitors is expected next summer. A Roche spokeswoman said officials felt that the 2002 plan met "at least in spirit, the goals" of the advisory committee.**

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