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Dartmouth epidemiologist John Baron chaired the committee that called a halt to the controversial Vioxx trial.

DMS's John Baron was at eye of Vioxx storm

Timing can be everything, especially in clinical drug trials. That's one lesson of the recent worldwide withdrawal of Vioxx, a multibillion-dollar anti-inflammatory medication for arthritis and acute pain. Vioxx's manufacturer, Merck, voluntarily pulled the drug after results of an ongoing study showed that its prolonged use could double the risk of heart attack and stroke. The news was startling, especially for a drug that had been on the market since 1999. Why was such a significant risk not known before?

Data: "If you did a study that lasted 18 months, you would have seen exactly nothing [based on] our data," explains John Baron, M.D. He is a professor of medicine at DMS and chaired the steering committee for the study, known as the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial. Baron is not an employee of Merck but was paid to offer advice on protocols and to serve as the top liaison between the data-safety monitoring committee, which was responsible for the safety of participants and which made the initial recommendation to halt the study, and the steering committee, which made the final decision to discontinue the trial.

APPROVe began in 2000 and was de-

signed to judge Vioxx's potential to prevent a recurrence of colon cancer, Baron's area of research specialty. The doubling of cardiovascular risk emerged only after 18 months, he explains. And since participants entered the trial at different times, the trend did not appear conclusively until September 2004, nearly five years after the study began. The Food and Drug Administration (FDA) had approved the drug based on studies with shorter time frames.

Vioxx belongs to a class of drugs that target COX-2, an enzyme responsible for inflammation, while avoiding another closely related enzyme, COX-1, which has a protective effect on the stomach. Though comparable to aspirin in relieving pain, COX-2 inhibitors are not as damaging to the stomach and digestive tract. "After the discovery of COX-1 versus COX-2 and the different enzymes, these drugs were developed very quickly," says Baron.

Trial: Since COX-2 is over-expressed in many cancers, researchers wondered if such drugs could be used to treat cancer. The prospect was "very exciting, almost delicious," says Baron. In the APPROVe trial, participants were divided into two groups of 1,293

each. One group received a placebo, while the other received 25mg a day of Vioxx. In the placebo group, there were 25 confirmed cardiovascular events—heart attacks or strokes. In the Vioxx group, there were 45 events. Those numbers represent 1.9% and 3.5% of participants, respectively, and translate into a near doubling of risk.

And because "people who get into clinical trials tend to be healthy," says Baron, researchers worried what would happen in "a more real-world situation, where the rate of cardiovascular disease depends on age and sex and smoking and all those other factors."

In fact, Vioxx had been in a "real-world situation" for five years. It was being taken by 20 million people in the U.S. and millions more worldwide. According to one FDA estimate, Vioxx may have been responsible for as many as 27,785 heart attacks, fatal and non-fatal, in this country between 1999 and 2003. Though the risk of Vioxx causing a heart attack in an individual patient is small, the elevated risk is significant because of the drug's widespread use. Its withdrawal spurred hundreds of lawsuits against Merck.

Coverage: Meanwhile, the coverage of the withdrawal in the lay press and even in scientific journals has been "loud and deceptive and sometimes ill-informed," believes Baron. Merck's response was "quite impressive and very fast," he contends. "There was absolutely no push-back."

While the controversy surrounding Vioxx is unlikely to be resolved soon, he sees lessons to be learned from the situation. The discovery of COX-2 inhibitors was "really a marvel of modern science," says Baron, but "the promise of molecular medicine has some limitations." It would be safer to evaluate all drugs for longer periods before approval, he says, "but you can easily imagine that people would be complaining" that the FDA is bureaucratic and slow. Balancing rapid approval of potentially useful drugs against possible long-term or delayed side effects "is a difficult issue for a society to handle," he says. "It's not going to be easy." JENNIFER DURGIN