



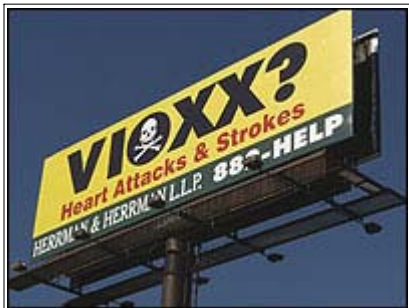
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Health & Science

Conflicted Safety Panel Let Vioxx Study Continue

by Snigdha Prakash

- [The Vioxx Study: Part I of the Story](#)
- [The Vioxx Study: Part II of the Story](#)



Bob Daemmerich/Corbis

Since Vioxx's withdrawal from the market in 2004, 13,000 product-liability lawsuits have been filed against Merck. Here, a law firm in Texas advertises for clients who may have a case against the drug maker.

Timeline: The Fall of Vioxx

The FDA approved Vioxx in May 1999. Seven years later, more than 23,000 people are suing Merck, alleging the drug caused heart attacks and strokes. A look at how Vioxx's demise unfolded.

- June 8, 2006
[Read the timeline.](#)

Q&A: Monitoring Patient Safety

To learn more about data safety monitoring boards and their role in protecting patients who participate in drug studies, NPR turned to statistician David DeMets.

He says the current watchdog system is a good one, but that there are practical limits on the extent to which drug safety can be monitored.

- June 8, 2006

NPR.org, June 8, 2006 · *NPR is providing a full transcript of this story.*

ROBERT SIEGEL, host: In 2004, Merck pulled its painkiller Vioxx from the market. The drug was causing heart problems, strokes and deaths among patients in a large study that was under way at the time. Merck stopped the study early when those results became clear. Thousands of former Vioxx patients and their families are suing the company.

Now, documents obtained by NPR show that five years earlier, in 1999, during another large Vioxx study, patients had similar heart problems. But that study was not stopped.

During those five years, millions of Americans took Vioxx. And a Food and Drug Administration scientist has estimated that some 38,000 people who took the drug died.

NPR's Snigdha Prakash reports on why the earlier study wasn't stopped and the public warned that Vioxx was unsafe.

SNIGDHA PRAKASH, reporter: The decision to stop a large study of a new medicine involves complex scientific and ethical issues.

To find out if Merck responded appropriately to the heart problems it saw back in 1999, NPR consulted with three scientists who are authorities on heart disease and clinical studies.

We showed each of them charts and graphs from the large Vioxx study called VIGOR. The charts and graphs showing the study's early results have never been made public before.

The first of the three experts NPR consulted is cardiologist Eric Topol of Case Western Reserve University. He's been a leading critic of Merck's Vioxx research, and was subpoenaed to testify in the Vioxx product-liability lawsuits.

ERIC TOPOL: This is the most compelling and worrisome data that's come out about the VIGOR trial, and it's amazing it's taken this long, from November 1999 to 2006 to come out.

PRAKASH: The data Topol's talking about show that as of December 1999, 3-1/2 months before the VIGOR study ended, Vioxx patients had

[Read the Q&A.](#)

Q&A: Vioxx Health Risks

Independent analysis of data sent to the FDA show that the cardiovascular risks from Vioxx begin shortly after a patient starts taking the drug. The data also indicate that the risks from Vioxx remain long after patients stop taking the drug.

- May 18, 2006
[NPR Health Editor discusses what's known about Vioxx's health risks.](#)

suffered twice as many strokes, heart attacks and deaths as patients on naproxen -- the older painkiller to which Vioxx was being compared.

As in most large drug studies, patients in the study were being tracked by a panel of experts to make sure they weren't harmed by the drug they were testing. The study's official safety panel was told about these heart attacks. But the minutes of the panel's December 1999 meeting show the panel didn't stop the study.

Cardiologist Eric Topol says the safety panel made the wrong decision.

TOPOL: You have a very dangerous situation. It was incumbent on the watchdog committee to stop the trial, to alert the responsible parties and the public.

PRAKASH: Topol singles out a graph the safety panel saw. It has two lines. One line shows deaths in the Vioxx group; the other, deaths in the

naproxen group.

For the first few weeks of the study, the two lines rise gently because the number of deaths is small. And the lines move in tandem because the number of deaths is about the same in the Vioxx group as in the naproxen group.

TOPOL: Everything looks about the same until four to six weeks, and then around six weeks, one curve is going way apart from the other.

PRAKASH: That curve is the Vioxx line. It separates from the naproxen line and starts climbing, and it keeps climbing every month for the next nine months.

The naproxen line stays flat; hardly any of the naproxen patients are dying.

TOPOL: And so what you see is a highly divergent trend that implicates Vioxx of having a higher risk of death.

PRAKASH: We showed the same graph to the second expert we consulted, cardiologist Paul Armstrong of the University of Alberta. He's served on the safety panels of many large scientific studies.

Armstrong points to that steadily climbing line on the graph -- the one that shows the monthly total of Vioxx deaths in the study-- and says it tells you something else about patients on Vioxx:

ARMSTRONG: The longer the exposure, the greater the risk.

PRAKASH: Armstrong says had he served on the safety panel, he would have been in a hurry to stop the study after seeing that graph.

The third expert NPR consulted is Curt Furberg. He's a former head of clinical trials at the National Heart, Lung and Blood Institute. He's now a professor at Wake Forest University, and has served on the safety panels of some 50 studies.

Furberg agrees with cardiologists Eric Topol and Paul Armstrong.

FURBERG: A doubling in risk is quite remarkable. The committee, in my view, should have told the sponsor to stop the study and told the world this drug is harmful. Unfortunately that was not done, and I

think that contributed to the tragedy with Vioxx.

PRAKASH: To find out why the safety panel continued the study, we requested interviews with the panel members. The safety panel, known officially as a data and safety monitoring board, or DSMB, declined NPR's interview request, but sent written answers to our questions.

First, the safety panel said it didn't stop the study because there were several possible explanations for the differences in cardiovascular problems between the Vioxx and naproxen groups. An actor reads from the panel's statement.

ACTOR, reading DSMB statement: The DSMB was unable to determine whether the difference were due to some adverse effect on Vioxx, the lack of the protective anti-platelet effects of naproxen, or some combination of those factors.

PRAKASH: In other words, the safety panel said, it couldn't tell if Vioxx was causing the heart problems or if naproxen, acting like low-dose aspirin, protected people from them, making Vioxx just look risky by comparison.

ARMSTRONG: Whichever is true, it's immaterial to the patients who are dead and receiving Vioxx. To continue the trial when you already see excess hazard seems to me to be unwise.

Moreover, our expert, Curt Furberg, says the safety panel's reasoning is based on an assumption that's never been proven in any scientific study: that naproxen prevents heart attacks.

FURBERG: It comes across as a way of protecting the drug and protecting the company.

PRAKASH: The second point the safety panel makes is that the heart problems in the study were small in number and the diagnoses came from the patient's own doctors and could turn out to be wrong.

Curt Furberg concedes the number of heart problems and deaths was small. But he says it's clear the results weren't due to chance. He says the patterns were the same in every population group in the study.

FURBERG: In old people, young people, those who have hypertension, those who don't, etc. And the findings were very, very consistent. So in my mind, this confirms that the findings are real.

PRAKASH: Another reason the safety panel says it didn't stop the study in December 1999 was because the study was nearing its end anyway.

Curt Furberg says it does take time to stop a large, multinational study, and only a few additional heart attacks or deaths could have been predicted to occur in the remaining time.

But he says:

FURBERG: I think we have obligations -- ethical, moral obligations. You don't want to expose patients to a harmful drug in a drug study. They should not be treated like guinea pigs. They are human beings. And we need to respect their rights.

PRAKASH: The safety panel also emphasized that this was an important study for patients. Vioxx could save lives, if the study showed that Vioxx caused less gastrointestinal bleeding.

But cardiologist Paul Armstrong counters such bleeding isn't common.

ARMSTRONG: The frequency with which that occurs is minor, and I would say unlikely to be

counterbalanced by this excess in death and cardiovascular events.

PRAKASH: The experts NPR consulted say that by not stopping the VIGOR study after Vioxx's heart problems became clear, the safety panel failed not just the 4,000 Vioxx patients in the study, but the millions who would go on to take Vioxx, until it was taken off the market almost five years later.

MICHELE NORRIS, host: In a moment, experts say the safety panel was too close to Merck.

NORRIS: We're going to continue now with our story about Vioxx, and what Merck and Co. knew about its safety problems long before it was pulled from the market.

As we've heard, a safety panel allowed a large Vioxx study to continue in 1999, even though patients were having heart trouble.

Experts say conflicts of interest and the involvement of a Merck employee influenced the panel's decision.

NPR's Snigdha Prakash continues our report.

PRAKASH: The Food and Drug Administration recommends the use of safety panels to keep patients from being harmed in large drug studies. But it doesn't require them, and drug companies are free to run the panels as they like.

In 1999, Merck appointed rheumatologist Michael Weinblatt of Brigham & Women's Hospital in Boston to head the safety panel for the Vioxx study called VIGOR.

When he became chair of the safety panel, Weinblatt and his wife owned \$73,000 of Merck stock.

Drummond Rennie is deputy editor of the *Journal of the American Medical Association*, and a noted expert on conflicts of interest in medicine. He says, in his view, Weinblatt couldn't have evaluated the study's safety problems objectively.

RENNIE: That is more than enough money to influence somebody unconsciously, and perhaps even consciously. And that sum of money makes that person no longer independent. And if you're not independent, you shouldn't be on the DSMB.

PRAKASH: We asked Weinblatt about his Merck stock. He declined to speak with us, but gave us a written statement, read here by an actor.

ACTOR, reading Weinblatt statement: At all times, I exercised my independent medical judgment on the issues presented to the board, uninfluenced by any other considerations or interests. I also believe I complied to the best of my ability with all applicable regulations and standards regarding financial disclosures and conflicts.

PRAKASH: David Bjorkman, now dean of the University of Utah School of Medicine, also served on the five-member safety panel.

In a written statement to NPR, Bjorkman backed up Weinblatt's assertion. Bjorkman also told NPR he didn't own any Merck stock. He added that he didn't advise or speak for Merck while he was on the safety panel, or in the following year.

But Merck documents obtained by NPR show that Bjorkman did consult for Merck in that period. When asked for clarification, Bjorkman sent this statement. It's read by an actor.

ACTOR, reading Bjorkman statement: Your recent inquiry caused me to go back and review my records, something I had not previously done. In reviewing my records for 1999, I discovered that I participated in the Merck speakers bureau and gave presentations in the summer of 1999 that I did not recall at the time of my prior email.

PRAKASH: Experts NPR consulted say the safety panel's capacity to protect patients in the study was compromised, not just by these financial conflicts of interest, but by the presence of a Merck employee. The employee attended all the panel's meetings -- including its private deliberations. She even wrote the meetings' minutes.

The safety panel told NPR that the employee's role was limited to analyzing the study's results. But clinical-trial expert Curt Furberg of Wake Forest University

says having a company employee in the room, in any capacity, would make it harder for the safety panel to act on problems it might see.

FURBERG: If you have a Merck employee on a DSMB, some members may feel inhibited expressing their inner views, concerns and so on, because that information could be communicated to the company.

PRAKASH: And then the company may be unwilling to give research grants in the future to members who express their reservations openly.

Lawyer Jim Fitzpatrick represents Merck in lawsuits brought by former Vioxx users. He says the presence of the Merck employee didn't stifle the safety panel's discussions.

FITZPATRICK: These are some respected doctors and scientists that are on this board, and I'm confident that they're capable of exercising their medical judgment in an independent manner, whether or not there is a statistician from Merck who is providing them with the data.

PRAKASH: At its last meeting, in December 1999, when the safety panel decided the heart problems weren't serious enough to stop the study, it also said that the problems merited analysis. The panel asked Merck to do that as soon as possible. Merck sent back word that it wanted to wait.

When the safety panel's chairman Michael Weinblatt insisted, Merck proposed a plan. The company would analyze heart problems it was told about by a "cutoff" date -- one month before the study ended. Weinblatt agreed.

As a result of that cut-off date, three of the 20 heart attacks among Vioxx patients weren't included when Merck wrote up the study in the *New England Journal of Medicine*. And, Vioxx looked safer than it really was.

Soon after agreeing to Merck's plan, Weinblatt signed a new consulting contract to sit on a Merck advisory board. Merck agreed to pay him \$5,000 a day for 12 days over a two-year period. Weinblatt received an initial check for \$15,000 a few weeks later.

In a written statement to NPR, Michael Weinblatt defended the consulting contract and his work on the DSMB. His words are read by an actor:

ACTOR, reading Weinblatt statement: I deeply resent the suggestion that there was any conflict of interest between my brief service on the advisory board and my work as chair of the VIGOR DSMB. The DSMB had completed its task.

PRAKASH: The safety panel's formal meetings were done, but the study wasn't. Some patients were still

taking their drugs when Weinblatt signed the new contract.

Curt Furberg of Wake Forest says the consulting deal calls into further question Weinblatt's independence from Merck.

FURBERG: I mean you can see it as a payback for being a loyal, supportive investigator. It just looks bad.

Drummond Rennie of the *Journal of the American Medical Association* agrees.

RENNIE: And it looks as though the DSMB could not have been reliable, and certainly as a patient myself, I would not have trusted it, and I would have objected profoundly to these arrangements.

And, says Curt Furberg, it wasn't just patients in this study that suffered.

FURBERG: If the trial had been stopped on the recommendation by an independent DSMB, the world would have been alerted to a problem much much sooner, and we may have taken action at an earlier stage.

PRAKASH: The experts NPR consulted say if the safety panel had stopped the VIGOR study early, Vioxx wouldn't have become as popular, as profitable, or as dangerous as it became.

Research published in the medical journal *Lancet* estimates that between 1999 and 2004, when Vioxx was withdrawn from the market, 88,000 Americans had heart attacks from taking the drug, and 38,000 of them died.

Snigdha Prakash, NPR News, Washington