

Merck Canceled an Early Study of Vioxx

New York Times - BARRY MEIER

02/08/05 - Merck & Company executives have long insisted that they never pursued a clinical trial to directly study the heart risks of the pain drug Vioxx because other tests they were conducting would supply those answers just as quickly.

But previously undisclosed company documents show that the drug maker was poised to begin a major cardiovascular study of the drug in 2002, and abruptly dropped the project just before it was set to start. The trial was scheduled to produce data by March 2004 but may have provided answers about Vioxx's risks even earlier if patients had shown ill effects.

It was not until September 2004 that Merck halted a separate study when patients in that trial experienced heart attacks and strokes at twice the rate of those receiving a placebo. At the same time, Merck withdrew Vioxx from the market.

In a statement, Merck said it had decided not to do the study because, among other things, it would have involved "high-risk" patients. The test in question would have involved patients with acute coronary syndrome, a condition characterized by chest pain from cardiovascular disease.

Merck officials briefly cited their plan to run a study in patients with chest pain as part of a 176-page document recently submitted by the company to the Food and Drug Administration. It submitted the document ahead of agency hearings next week on problems with a class of widely used pain relievers known as COX-2 inhibitors, which include Vioxx, Celebrex from Pfizer and other drugs.

However, Merck has never disclosed how extensively it planned that study, which was known inside the company as the Valor trial, or how close it came to starting it. By early 2002, the drug maker had already contacted outside researchers to oversee the test, had approached a competing drug maker to obtain anti-ulcer drugs to ease the possibility of side effects, and had prepared a 70-page protocol that spelled out how the test was to be conducted, according to documents reviewed by The New York Times.

One planning document, for example, shows that the first patients were supposed to enter the study in June 2002 and the last patient was to leave it in January 2004. But in mid-March 2002, just days before company researchers had planned to submit the study's protocol to the F.D.A., top executives of the drug maker ordered work on the project halted. It was never revived.

"I have the unpleasant task of having to inform you that the VIOXX CV Outcomes Study has been placed on hold," a memo dated March 13, 2002, and sent to dozens of Merck employees worldwide, stated. "At this time we do not have any of the details that led to this decision, however, we have been informed that upper management is in the process of reviewing the various study options."

In a statement issued yesterday, Merck said that even after the company had developed the trial's protocol "we continued to ask ourselves and our consultants whether this was the right study to definitively answer" the question of whether Vioxx posed cardiovascular risks. "We ultimately decided not to conduct that particular study." In clinical trials, drug companies usually retain outside specialists

as consultants who help design the trial.

Merck officials have previously said that, rather than running a specific cardiovascular study of Vioxx, they decided to collect such data from studies in which Vioxx was being tested for other possible uses. One of those studies, which began in 2000, examined the drug's potential for preventing colon polyps. Two other studies, one of which started in 2002 and the other in 2003, looked at the drug as a possible treatment for colorectal and prostate cancer.

It was the result from the colon polyp trial that led Merck to withdraw Vioxx.

Work on the Valor trial was halted at the same time that officials from Merck and the F.D.A. were concluding lengthy and heated negotiations over how Vioxx's label would reflect data from an earlier trial, known as the Vigor study, which indicated that the widely used painkiller posed potential cardiovascular risks.

Merck officials said yesterday that the company's decision to not go forward with the planned trial was not related to those talks, which culminated in April 2002.

In its statement, Merck said both it and some of its consultants were also concerned that, because patients with acute coronary syndrome in the Vioxx study would also be taking low doses of aspirin to prevent heart attack and stroke, their experiences might not translate to patients who were not taking aspirin.

Joan Wainwright, a Merck spokeswoman, said it was not unusual for trial planning to go forward while company officials and consultants debated a study's merits. "There was a wide range of opinions about whether this was or was not the study we were going to do and in the end we decided it was not," she said.

Asked to provide a copy of a document from March 2002 which summarized the decisions given at the time for not going forward with the study, Ms. Wainwright said that no such document existed.

In recent months, federal investigators, state officials, Congressional committees and plaintiffs' lawyers have obtained thousands of internal Merck documents while pursuing investigations and lawsuits related to Vioxx. The Times obtained documents citing the Valor trial through public officials.

A proposal to directly examine Vioxx's cardiovascular risks by testing it in patients with acute coronary syndrome was first made in mid-2001 to Merck officials by cardiologists from the Cleveland Clinic. The proposal followed the group's publication in a medical journal of a study that found both Vioxx and Celebrex appeared to increase the risk of heart attack and stroke but that the dangers from Vioxx appeared particularly high.

One researcher involved, Dr. Deepak L. Bhatt, acknowledged that the proposal was potentially controversial because patients involved had a form of cardiovascular disease. It is unethical to test a drug in patients solely to examine its potential risks. But Dr. Bhatt said his proposal did not face that problem because it was then believed that inflamed blood vessels were a cause of the acute coronary syndrome, and so giving patients an anti-inflammatory drug like Vioxx held a potential benefit.

In separate interviews yesterday, both Dr. Bhatt and another Cleveland Clinic

researcher, Dr. Eric Topol, said they were stunned to learn about the company's advanced plans to run such a trial.

They said that Merck officials had rejected their proposal. Both physicians said they believed that if Merck had run the study they had proposed the issue of Vioxx's risks might have been settled earlier.

Merck executives had first considered and rejected the possibility of directly studying Vioxx's cardiovascular risks in 2000, but they apparently soon altered course after the publication of the medical journal article by Dr. Topol and others.

Initially, Merck considered three possibilities to address the issue. One was reviewing cardiovascular data from continuing trials of Vioxx for new uses like colon polyp treatment. The second was repeating a study similar to the Vigor trial the study that had raised questions about possible cardiovascular risk. And the third option was doing the type of study in high-risk patients posed by the Cleveland Clinic group.

In December 2001, a top Merck official publicly made reference to the company's plans to run cardiovascular safety studies involving Vioxx but made no mention of the Valor trial.

By early 2002, internal Merck records show, the drug maker had decided to move forward with a major worldwide trial in 20,000 patients with acute coronary syndrome, a test similar in many ways to the proposal from Dr. Bhatt. Several researchers had been selected to take part in the trial, and study sites had been selected in the United States, Sweden and South Africa, among other places, documents indicate. Merck memos also show that another pharmaceutical company, AstraZeneca, would be asked to supply discounted or free supplies of its anti-ulcer drug, omeprazole, which the company sells as Nexium or Prilosec. Patients in the test were scheduled to take the drug to reduce the risk of gastrointestinal problems caused by Vioxx or aspirin.

By March 2002, Merck was fine-tuning the test's protocol so that it could be submitted to the F.D.A.

"We are asking that you please provide comments to me by noon, Wednesday March 6," a Merck medical director, Dr. Ned S. Braunstein, wrote in an internal e-mail message. "Assuming there is consensus, we target sending this to the agency by end of next week/beginning of following week."

On March 13, the memo was sent out shutting the Valor project down.

Ms. Wainwright, the Merck spokeswoman, said the company had informal discussions in February 2002 about the Valor study with F.D.A. officials but did not elaborate. The company never submitted its protocol to the agency because of its decision not to go forward with the trial, Ms. Wainwright said.

In a statement, a spokeswoman for the F.D.A., Kathleen Quinn, said that the agency was barred, as a matter of policy, from confirming or denying that it had held discussions with Merck about the project.

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