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DANGEROUS DATA

Despite Warnings, Drug Giant Took Long Path to Vioxx Recall

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In May 2000, executives at **Merck**, the pharmaceutical giant under siege for its handling of the multibillion-dollar drug Vioxx, made a fateful decision.

The company's top research and marketing executives met that month to consider whether to develop a study to directly test a disturbing possibility: that Vioxx, a painkiller, might pose a heart risk. Two months earlier, results from a clinical trial conducted for other reasons had suggested such concerns.

But the executives rejected pursuing a study focused on Vioxx's cardiovascular risks. According to company documents, the scientists wondered if such a study, which might require as many as 50,000 patients, was even possible. Merck's marketers, meanwhile, apparently feared it could send the wrong signal about the company's confidence in Vioxx, which already faced fierce competition from a rival drug, Celebrex.

"At present, there is no compelling marketing need for such a study," said a slide prepared for the meeting. "Data would not be available during the critical period. The implied message is not favorable."

Merck decided not to conduct a study solely to determine whether Vioxx might cause heart attacks and strokes - the type of study that outside scientists would repeatedly call for as clinical evidence continued to show cardiovascular risks from the drug. Instead, Merck officials decided to monitor clinical trials, already under way or planned, that were to test Vioxx for other uses, to see if any additional signs of cardiovascular problems emerged.

It was a recurring theme for the company over the next few years - that Vioxx was safe unless proved otherwise. As recently as Friday, in newspaper advertisements, Merck has argued that it took "prompt and decisive action" as soon as it knew that Vioxx was dangerous.

But a detailed reconstruction of Merck's handling of Vioxx, based on interviews and internal company documents, suggests that actions the company took - and did not take - soon after the drug's safety was questioned may have affected the health of potentially thousands of patients, as well as the company's financial health and reputation.

The review also raises broader questions about an entire class of relatively new painkillers, called COX-2 inhibitors; about how drugs are tested; and about how aggressively the federal Food and Drug Administration monitors the safety of medications once they are in the marketplace.

The decisions about how to test Vioxx were made in a hothouse environment in which researchers fiercely debated how the question should be pursued, and some even now question whether the drug needed to be withdrawn. It also took place amid a fierce battle between Vioxx and Celebrex in which federal regulators said marketing claims ran ahead of the science.

Today Merck faces not only Congressional and Justice Department investigations, but also potentially thousands of personal-injury lawsuits that could tie the company up in litigation for years and possibly cost it billions to resolve.

In late September, more than four years after that May 2000 meeting, Merck announced that it was pulling the drug off the market because a long-term clinical trial showed that some patients, after taking the drug for 18 months, developed serious cardiovascular problems. The data that ultimately persuaded the company to withdraw the drug indicated 15 cases of heart attack, stroke or blood clots per thousand people each year over three years, compared with 7.5 such events per thousand patients taking a placebo.

But the company never directly tested the theory that it used to explain the worrisome results of the clinical trial in 2000. Merck was criticized for what some charged was playing down the drug's possible heart risks; in one case, it received a warning letter from the Food and Drug Administration for minimizing "potentially serious cardiovascular findings." And when outside researchers found evidence indicating Vioxx might pose dangers, Merck dismissed their data.

In 2001, Dr. Deepak L. Bhatt, a cardiologist at the Cleveland Clinic, proposed to Merck a study of Vioxx in patients with severe chest pain. Merck declined, saying the patients proposed for the study did not reflect typical Vioxx users. In Dr. Bhatt's view, the company feared what it might find if it directly examined the dangers of Vioxx, one of Merck's biggest products, with sales last year of \$2.5 billion.

"They should have done a trial like this," Dr. Bhatt said. "If they internally thought this drug was safe in patients with heart disease, there was no reason not to do it."

Merck executives said last week that the company acted responsibly, voluntarily withdrawing Vioxx as soon as it had clear evidence the drug was harmful. And they said that even if they had conducted the type of study they discussed internally and rejected in 2000, the company might not have detected Vioxx's risks any sooner.

"Merck wasn't dragging its feet," said Kenneth C. Frazier, the company's general counsel. "It's pretty hard for me to imagine that you could have done this more quickly than we did." The F.D.A., which Merck consulted, also agreed that designing a trial to specifically assess Vioxx's cardiovascular risks would have been difficult and, unless constructed to provide benefits to patients, would have been unethical as well.

But the F.D.A. itself is now under scrutiny for its handling of Vioxx. Congressional investigators are looking at whether the agency, which is charged with protecting Americans from dangerous medicines, was too lax in its monitoring of the mounting evidence against Merck's drug. Internal memos show disagreement within the F.D.A. over a study by one of its own scientists, Dr. David Graham, that estimated Vioxx had been associated with more than 27,000 heart attacks or deaths linked to cardiac problems.

So far, no clinical evidence has linked the next best-selling version, Celebrex, to cardiovascular risks. But its maker, [Pfizer](#), has acknowledged that its other COX-2 drug, Bextra, has been shown to pose

risks to patients after heart surgery. Scientists outside the company say there is evidence that Bextra's problems may affect wider groups of patients.

But Merck is the company drawing fire. Senator Charles E. Grassley, the Republican chairman of the Senate Finance Committee, has summoned Merck's chief executive, Raymond V. Gilmartin, to testify this week as part of the committee's investigation of the matter. The Justice Department recently started a criminal investigation of the company, and the Securities and Exchange Commission has begun an informal inquiry.

Some people associated with lawsuits against Merck, and company officials, provided internal Merck documents to [The New York Times](#). The Wall Street Journal previously disclosed some of those records.

Controversy had shrouded Vioxx almost since its introduction in 1999. The drug was among the first of the COX-2 inhibitors, which were developed to reduce pain and inflammation without the risk of ulcers and other gastrointestinal side effects posed by aspirin and other over-the-counter medications. Thousands of Americans die every year from internal bleeding caused by the older drugs.

But when studies on Vioxx and Celebrex became available in 1998 and 1999, many doctors were disappointed. Neither drug alleviated pain any better than the older medicines. And the drugs cost close to \$3 a pill; over-the-counter pain relievers, in contrast, cost pennies a dose.

Analysts say, however, that the success of Vioxx was critical to Merck. The patents on several popular Merck drugs expired in 2000 and 2001, opening them to generic competition. Merck badly needed Vioxx to replace those lost sales, said Michael Krensavage, a drug industry analyst at the investment bank Raymond James & Associates. "Vioxx was Merck's savior, it's as simple as that."

The Critics: Outside Scientists Sounded an Alarm

The data that first alerted Merck to the heart risks with Vioxx arrived in March 2000, derived from a study of 8,100 rheumatoid arthritis patients begun in January 1999. In the study, called Vigor, patients were treated with either Vioxx or naproxen, an older pain reliever. While Vioxx reduced the risk of internal bleeding, it also appeared to raise the incidence of heart problems. Five times as many patients taking Vioxx had heart attacks as those taking naproxen.

Merck disclosed the Vigor data almost immediately and said it believed the difference resulted not from problems with Vioxx but from naproxen's strong protective effect on the heart. Many scientists outside the company found that theory implausible, and a rush to examine Vioxx, as well as Celebrex, began.

In 2001, the first major study critical of the drugs appeared in *The Journal of the American Medical Association*. The report, written by Dr. Eric J. Topol and cardiologists at Cleveland Clinic, reanalyzed data from several clinical trials of Vioxx and Celebrex. It reported that both drugs appeared to increase the risk of heart attack and stroke, but that the danger from Vioxx appeared higher.

Dr. Topol, the chairman of the clinic's department of cardiovascular medicine, immediately called for trials to specifically determine whether the drugs increased cardiovascular risk. Both Merck and Pfizer rebuffed that request, and said the Cleveland Clinic report was flawed because it failed, among other things, to include data from other studies.

Dr. Topol became a harsh critic of both drugs, but his ire focused on Vioxx and Merck. Even before his

2001 report appeared, he said in a recent interview, company scientists came to Cleveland to try to persuade him not to publish it; Merck officials deny doing so.

A year later, in October 2002, a study by Dr. Wayne Ray, an epidemiologist at Vanderbilt University, found that Medicaid patients in Tennessee who were taking high doses of Vioxx - greater than the recommended long-term dosage of 25 milligrams daily - had significantly more heart attacks and strokes than similar patients who were not taking high doses.

In an interview, Dr. Ray said that he had become concerned about Vioxx's safety as soon as the Vigor data became public. The Tennessee study confirmed his doubts, he said.

"A heart attack in exchange for an ulcer is a poor treatment," said Dr. Ray, who is now consulting with lawyers suing Merck.

But Merck said at the time, and still maintains, that the study from Dr. Ray and others like it did not shake its confidence in Vioxx's safety. Dr. Ray had examined patient records to look for a correlation between patients taking Vioxx and having heart problems, in what scientists call an epidemiological study. But such studies are considered less reliable than clinical trials, which medical researchers consider the gold standard of tests. In clinical trials, scientists enroll patients, carefully control their drug intake and monitor their reactions so that a drug's risks and benefits can be determined.

The quandary facing Merck and others in the Vioxx controversy was how to design a trial that could quickly identify any risks posed by the drug while also conferring some kind of benefit to the patients involved.

Dr. Rory Collins, an epidemiologist at Oxford University, said that examining patient records alone was useful only to find very large differences in risk, like those caused by cigarette smoking. While Dr. Ray's study showed a link between Vioxx and heart attacks, other studies did not, said Dr. Collins, who has conducted studies financed by Merck.

But other researchers were also finding worrisome signs. In 2002, Elucida Research, a small laboratory in Massachusetts, examined the way that Vioxx and other anti-inflammatory drugs interacted with lipids, or fatty compounds found in blood. That laboratory study found that Vioxx damaged the lipids in a way that made them more susceptible to clotting, said R. Preston Mason, the lead investigator on the study.

Meanwhile, more epidemiological studies backed Dr. Ray's findings. In an April 2004 study in the journal *Circulation*, researchers from Harvard Medical School found that Vioxx raised the risk of heart attacks relative to Celebrex; two months later, several of the same researchers reported in another journal that Vioxx increased the risk of hypertension.

Then, in August 2004, an epidemiological study by an F.D.A. researcher, based on data from 1.4 million patients in the Kaiser Permanente health care system, also showed a heightened cardiovascular risk for Vioxx.

The Company: An Indirect Road to Assessing Risk

For Merck, the Vioxx episode has been bitter.

Company executives and researchers say that from the moment they were told in March 2000 about the

preliminary results from the Vigor trials, they sought every possible explanation for the signs of increased cardiovascular risk. And, they say, they were open to the possibility that Vioxx was at fault.

"We were stunned," by the finding, said Dr. Alise S. Reicin, the Merck researcher who ran the Vigor study. "It's fair to say that we were all concerned."

She and other Merck officials said in interviews last week that nothing in any previous tests of Vioxx, including those submitted by the company in November 1998 to win its regulatory approval, suggested the drug posed a danger of increased heart attacks or stroke. Within days of learning the Vigor results, Dr. Reicin said that she, along with colleagues and academic consultants retained by Merck, were chasing the question of why the rate of heart problems was so high.

One possibility was that it was the result of chance. Another was that the problems were caused by Vioxx. And the third was that naproxen provided heart protection and had skewed the results. Merck researchers looked for data from other studies, aware that studies of two other little-used painkillers in the same class as naproxen had shown cardioprotective effects.

In the spring of 2000, Merck researchers also reviewed safety data from a continuing study in which Vioxx was being used in patients with Alzheimer's disease to test a theory that the painkiller might slow the disease's progress. Dr. Reicin said that there was no evidence in that study, which had started in 1998, that Vioxx posed a risk.

Merck researchers soon concluded that naproxen was cardioprotective. Some academic researchers, including some who consulted for Merck, also supported this theory.

One of them, Dr. Marvin A. Konstam, the chief of cardiology at the New England Medical Center in Boston, said his review of the data suggested Vioxx was safe.

"Based on these data, there was nothing that suggested to me that there was an increase in cardiovascular events with Vioxx," said Dr. Konstam in a recent interview.

But Merck never ran a clinical trial seeking to scientifically establish the heart-protecting properties of naproxen or to quantify how powerful an effect might be. In recent interviews, company officials said they did not believe there was a reason to conduct such tests because the critical issue was not proving naproxen's benefits but determining if Vioxx posed a risk.

Meanwhile, company scientists began to discuss the possibility of designing a trial to directly examine the drug's cardiovascular risks, Merck documents show.

At a meeting in May 2000, a top policy-making group met to discuss ways to defend Vioxx against competing drug makers' accusations that it posed risks. Among the issues they considered was whether to finance the development of a cardiovascular risk study, meeting documents show.

The documents show that Merck's researchers were not in agreement about how, or even whether, a trial could be performed. The documents also make clear that marketing executives were opposed to it.

Mr. Frazier, Merck's top lawyer, acknowledged that the decision to forgo the cardiovascular study was made at the meeting, but said that the decision was not driven by marketing concerns. He added that even if such a study had been undertaken, it would have taken years to produce results and would not necessarily have provided faster answers.

Merck executives opted to take a different road. In early 2000, the company had started a clinical trial to determine whether Vioxx could prevent the recurrence of colon polyps. Merck decided to intensely monitor the cardiovascular condition of patients in that test, known as the Approve trial, as well as subsequent studies. Dr. Reicin said last week that she and others at Merck felt devastated when they learned this past September about the findings from the colon polyp trial. But she said she believed that running the trials as the company did was the best way to learn whether the drug had a problem or not.

"We did our best to think of the most comprehensive study we could have done," she said. "I'm sorry that I didn't know four years ago what I know now, but the data didn't lead us there four years ago."

The Regulator: Balancing Ethics Against Suspicions

The F.D.A., already under fire for its recent handling of pediatric antidepressants, faces a new round of questions from Congress this week over why it allowed Vioxx to be sold for so long while evidence mounted against it.

For years, drug reviewers at the F.D.A. had raised the possibility that Vioxx might be a danger to the heart, but without being able to answer the question, or even agreeing on the best way to get an answer.

Even before Vioxx's approval, an F.D.A. drug reviewer had written that Vioxx could conceivably hurt the heart. Studies of the drug at that point, however, showed nothing more than a suggestion of a risk.

That suggestion became more powerful when Merck presented the preliminary results of the Vigor study to the F.D.A. in March 2000. In that study, those taking Vioxx were clearly at greater risk than those taking naproxen; Merck officials argued that the difference was a result of naproxen's cardioprotective properties.

"We just didn't buy that," said Dr. Sandra Kweder, deputy director of the F.D.A.'s office of new drugs. Still, data in mid-2000 from other clinical trials did not show a heart risk. Flummoxed, the agency hired a cardiologist to take a careful look at the studies, and it summoned a panel of independent experts to discuss the data publicly.

The panel met in February 2001, and while several members expressed concerns about the heart risks, none suggested that the drug be withdrawn. Doctors on the panel who treated ulcers argued that Vioxx's protective effects far outweighed its possible harm to the heart; cardiologists argued that the drug's possible harm to the heart was a real problem. All agreed that more studies should be done.

The agency consulted with Merck and discussed the idea of a study designed solely to answer questions about the heart risks. As Merck officials had done in May 2000, the agency concluded that such a trial was difficult to envision. Giving placebos and Vioxx to groups of at-risk patients solely for the purpose of comparing side effects would be unethical, Dr. Kweder said.

Besides, Merck already had begun placebo-controlled trials assessing Vioxx's benefits against colon polyps, she said.

But the F.D.A. did require Merck to add to Vioxx's label a warning that patients with a history of heart disease should use the drug with caution.

And the agency underwrote a study at Kaiser Permanente, the giant health maintenance organization, to see if patients given Vioxx had a higher incidence of heart-related problems.

Meanwhile, the marketing battle between Vioxx and Celebrex grew heated. The F.D.A. scolded both drugs' makers for exaggerated claims about their drugs. In September 2001, the agency sent Merck a warning letter stating that Merck's promotional campaign for Vioxx "minimizes the potentially serious cardiovascular findings" in Vigor. The agency required Merck to send letters to physicians across the country "to correct false or misleading impressions and information."

This past August, the results of the Kaiser Permanente study came in and, according to Dr. Graham, who works in the F.D.A.'s office of drug safety, they were damning. Dr. Graham eventually concluded that high doses of Vioxx increased the risk of heart disease 3.7 times.

Dr. Graham contends that his bosses delayed his efforts to have the study published and, in a series of testy e-mail messages, demeaned his conclusions. A message from one superior called his findings "nothing more than a scientific rumor."

Dr. Kweder pointed out that Dr. Graham was unable to tell which patients had taken aspirin and whether patients given Vioxx were already at a higher risk of heart disease before the study started. In the end, she said, Dr. Graham's study did little more than to suggest that Vioxx might harm the heart.

"That's nothing new," Dr. Kweder said. "We knew that from Vigor."

A month later, when Merck informed the agency that the company would withdraw Vioxx, based on the polyp study, Dr. Kweder said agency officials were stunned.

Some experts still contend that Vioxx could be helpful for those at great risk of ulcer who do not have weak hearts. Asked if the agency would have required the drug's withdrawal if Merck had come to a different decision, Dr. Kweder said the agency would have had to examine the polyp study closely "and determine where the benefit might outweigh the risk."

"We haven't done that," she said. "We wish we had had the opportunity to do that."

Some critics say the episode highlights a more systemic problem - that the F.D.A., having approved a drug for the market, does not adequately monitor it afterward for safety problems.

But Dr. Kweder said she had no regrets about the handling of Vioxx. "The case of Vioxx," she said, "is one where the agency left no stone unturned."

The Plaintiffs: Coming Soon, a Flood of Litigation

Jamie Gregg, a 32-year-old construction worker from Katy, Tex., and father of three boys, had just reported for a job at Houston's Hobby Airport last May 28 when he collapsed, apparently from a heart attack.

He was rushed to the hospital, where a medical team saved his life. But his brain had been deprived of oxygen for so long that Mr. Gregg is now in a nursing home in Lufkin, Tex., fed through a tube, unable to move more than his head or to utter more than a few syllables.

"We really don't know what he's thinking in his head," said his wife, Lisa Gregg, who said she was not sure if her husband even recognized his family.

Mr. Gregg, who had undergone a series of back surgeries, had been taking a high dosage of Vioxx, 50

milligrams a day, for four years to treat back pain. So the day after Mrs. Gregg heard that Vioxx was being withdrawn from the market, she walked into the offices of Goforth Lewis Sanford, a law firm in Houston. That firm, along with W. Mark Lanier, a prominent Houston plaintiffs' lawyer, are now preparing a lawsuit against Merck.

"This has got to be the reason" for her husband's problem, she said. "And if it is the reason, they've got to pay. There's people's lives that have been ruined by this, and I'm one of them."

Stories like the Greggs' underscore the very human nature of Merck's business problems. So far, 375 personal-injury lawsuits, representing 1,000 plaintiff groups, have been filed against Merck, according to the company's third-quarter filing with securities regulators. Some of the suits predate Vioxx's withdrawal. But with people like the Greggs just awakening to the issue, attorneys expect the number to grow markedly.

"From the scope of how many people are affected, it's as big as anything that ever occurred with a pharmaceutical," said Justin G. Witkin, a personal injury lawyer in Gulf Breeze, Fla.

Another plaintiffs' lawyer amassing Vioxx clients is Andy D. Birchfield Jr., of Montgomery, Ala., who noted that fen-phen, the diet drug combination linked to heart valve problems, was used by six million people. "You've got 20 million Americans who took Vioxx," he said. **Wyeth**, which manufactured two drugs, either of which was combined with a third to make the fen-phen combination, has set aside \$16.6 billion to cover its liability.

Some of the first Vioxx cases are expected to go to trial next year. Lawyers and courts are still trying to sort out whether to consolidate the lawsuits and in which courts to try them.

Last Tuesday, about 300 personal-injury lawyers gathered in a ballroom at the Ritz-Carlton Huntington Hotel & Spa in Pasadena, Calif., for a combination strategy session and pep rally on Vioxx claims.

But the plaintiffs' lawyers face a big obstacle in convincing juries that a person's heart attack or stroke was caused by Vioxx, because many people suffer such attacks for many reasons.

Merck has not discussed its defense strategy in detail. But besides arguing that it took the drug off the market as soon as it had solid evidence of Vioxx's dangers, it is also likely to argue in many cases that a person's problems could have other causes. Mr. Gregg, for instance, smoked half a pack of cigarettes a day, his wife said. And since April 2002, the Vioxx label recommended that the 50-milligram dose Mr. Gregg used not be taken for extended periods.

Thomas B. Moore, a Los Angeles lawyer who represents pharmaceutical companies in such matters, although not Merck in this case, predicted that even the estimate by Dr. Graham of the F.D.A. that the drug caused more than 27,000 deaths and heart attacks would not help plaintiffs win cases. "The problem is that David Graham can't name one of them," Mr. Moore said. "He can't name one of those 27,000."

He said Merck did not appear to have hidden any data, but instead disagreed about the interpretation, and had withdrawn the drug voluntarily. "Voluntary withdrawals do much better with jurors than a withdrawal by the F.D.A.," he said.

The Future: Merck's Costs Still Lie Ahead

As if trial lawyers, federal prosecutors and congressional committees were not challenges enough, Merck has had little success introducing new drugs since Vioxx. The company's laboratories, once among the most productive in the pharmaceutical industry, have suffered a long string of failures and the company's new drug pipeline is nearly bare.

Merck's stock has fallen 40 percent since it announced the Vioxx recall in September, lowering its market value by about \$50 billion. Merck shares closed Friday at \$26.45, up 30 cents.

Merck will not disclose its strategy for resolving the Vioxx-related suits. But analysts who have studied the issue say that Merck may follow the route taken by [Bayer](#), which faced thousands of suits claiming injury from its cholesterol drug Baycol, which was linked to a serious muscle disorder.

Bayer tried to settle most of the stronger suits, while pushing for trials in cases where it felt plaintiffs had overreached and the company had a tactical advantage. Bayer won a crucial case in Texas last year, and its stock has nearly tripled since March 2003, when concerns about its legal liability peaked.

Still, Merck's legal liability could top \$10 billion, according to two studies by Wall Street analysts. Merrill Lynch estimated that the company's legal liability would be \$4 billion to \$18 billion, depending on the number of people who suffered heart attacks while taking Vioxx and how much the company pays to resolve each claim. But that estimate did not include potential punitive damages, Merrill noted.

In an estimate last month, since withdrawn, Sanford C. Bernstein & Company estimated that the company could spend \$12 billion. But Richard Evans, the Bernstein analyst, said he withdrew the estimate because the company faced so many uncertainties that an accurate calculation was impossible. He said, though, that he did not think the company faced a serious risk of bankruptcy.

Merck is expected to have \$20 billion in sales and \$6 billion in profits next year, not counting its Vioxx costs, giving it the financial flexibility to settle thousands of suits. And its legal liabilities and relatively weak prospects for new drugs could actually provide a protective effect, by making Merck an unpromising takeover candidate for other big drug companies.

For now, Merck appears likely to limp along independently, analysts say.