

# GLOBEANDMAIL.COM

## The painful battle over the 'wonder

**CAROLYN ABRAHAM reports on the Canadian doctor who found herself smack in the middle of the controversy over Vioxx**

**BY CAROLYN ABRAHAM**

SATURDAY, FEBRUARY 19, 2005  
UPDATED AT 5:50 PM EST

The night before Merck & Co. officials pulled Vioxx off the market last September, after their popular painkiller was found to double the risk of heart attack and stroke, they called a small, trusted group of scientists for advice.

Claire Bombardier was one of them. Director of rheumatology at the University of Toronto and holder of a prestigious Canada research chair in the field, Dr. Bombardier has been a consultant to Merck on Vioxx since 1997.

That night, Merck officials described fresh evidence that Vioxx increased heart risks. Dr. Bombardier agreed the data confirmed the problem. Still, she told them, it would be a shame to lose it given that it was a matter of weighing benefits and risk. "It was a good drug," she told them. Patients, she said, would miss it: "I was on the fence."

It was a careful answer, as befits a physician who is both research scientist and drug-company consultant -- and someone who is a key figure in one of medicine's biggest drug controversies.

Dr. Bombardier headed the 1999 Merck-sponsored drug trial that first provided evidence of the alarming heart risks of Vioxx, and she was the lead author of the resulting study published in the New England Journal of Medicine.

That study is now under attack for the heart-risk data it did not include. Critics say the full information from the study should have prompted the drug company and drug regulators to take swift action against Vioxx five years ago.

This week, a special panel of the U.S. Food and Drug Administration held hearings into the safety of Vioxx, and the new generation of painkillers to which it belongs. The hearings are just one of several investigations and legal actions surrounding the drug, and Dr. Bombardier says she must be careful about what she says, since she might find herself on a witness stand. As she puts it: "If you are in the car when there is a car accident, you have to testify."

The FDA panel voted to allow the possible return of Vioxx, provided it carries a black-box warning of heart-attack risks and faces other severe restrictions that make people aware of its dangers. FDA whistleblower David Graham, who earlier warned of the Vioxx risks, said those measures are "five years too late."

A Globe and Mail investigation involving internal Merck documents, congressional testimony, files made available through the FDA and interviews, paints a disturbing picture about the way public safety seemed to have taken a back seat on the road to turning a vaunted new drug into a

blockbuster marketing hit.

While Vioxx became one of the fastest-selling drugs in history -- with sales of more than \$2.5 billion (U.S.) -- behind the scenes, serious concerns about whether it might be harming, even killing people were raised steadily.

Documents show Merck fighting a war on a number of fronts: against its chief competitor, Pfizer, and its drug Celebrex; against outside scientists who questioned the drug's safety; and against drug regulators who seemed to have been unable or unwilling to compel the company to do all the investigations it wanted.

Marlene Gauthier, a spokesperson for Merck Frosst Canada, said due to the ongoing legal proceedings against the company it could not respond to questions about its actions at this time.

In the United States, the Vioxx saga has triggered not only government hearings, but a criminal investigation and an inquiry by the Securities and Exchange Commission. At least 700 lawsuits have been filed against the company.

In Canada, where the drug was invented and where pharmacies dispensed roughly three million prescriptions a year, 30 class-action lawsuits have been filed, though not all have been certified.

There has been no public airing here of the events surrounding the withdrawal of Vioxx, nor how Health Canada, which has also been named in lawsuits, dealt with the drug. Health Minister Ujjal Dosanjh called this week for public hearings into its class of medication and for greater transparency. Due to the legal proceedings against it, Health Canada officials would not answer key questions for this article.

Vioxx, one in a class of drugs known as cox-2 inhibitors, was once touted to be the best remedy to hit medicine cabinets since a German chemist turned willow bark into Aspirin. Now, the fallout from their explosion onto the market is drawing comparisons to the lessons learned in the wake of thalidomide.

"Potentially, out of all of this there may be a need to take a stronger stand and not let drug companies dictate things," said James Wright, director of the Therapeutics Initiative at the University of British Columbia. "In the future, we'll look back at thalidomide as having had a major impact [on the way new drugs are monitored] and these cox-2 drugs as well."

Dr. Bombardier agrees: "There are lessons to be learned."

Vioxx was part of a revolutionary class of anti-inflammatory pain relievers that promised to be easy on patients' stomachs.

The older generation of drugs -- such as Aspirin and ibuprofen -- worked by blocking two cyclooxygenase enzymes, known as cox-1 and cox-2 for short. Blocking cox-1, unfortunately, had the nasty effect of stripping the stomach lining, which could cause ulcers, gastrointestinal tears and stomach bleeds.

It was a painkiller market in desperate need of relief. When companies found drugs that blocked only the cox-2 enzyme, they seemed to have hit on the answer.

But Merck's own documents show that even before any drug approvals there were concerns about the heart risk cox-2 drugs, specifically Vioxx, might carry.

In 1998, as part of the drug trials leading up to approval, Merck submitted information to the FDA from pharmacology tests that suggested these drugs could contribute to blood clots.

Then, FDA reviewer Maria Lourdes Vilallba noted in 1999 in light of Merck's submission that: "Thromboelc events [such as heart attack and stroke] are more frequent in patients receiving Vioxx than placebo . . ."

Dr. Vilallba concluded that it was impossible to determine the cardiovascular risk of the drug with the data the company had submitted.

Despite this, regulators both in Canada and the United States kept Vioxx on a fast track for review.

In 1998, Pfizer's Celebrex was the first cox-2 inhibitor to be approved in the United States. It came out in Canada in April, 1999. The United States approved Vioxx in May, and the Canadian okay came in October of that year.

Testifying before a U.S. congressional hearing this month, Gurkirpal Singh, a cox-2 expert and adjunct clinical professor of medicine at Stanford University, noted that there were 30 similar painkillers on the market when Vioxx was approved. "There was certainly no emergent need to approve Vioxx without further studies if there were lingering safety concerns," he said.

But the war in the marketplace had begun. With more relaxed U.S. laws governing direct-to-consumer advertising, companies pushed the drugs as early designer compounds of the biotech era, just in time to ease the aches and pains of aging boomers.

And Merck had catching up to do. Searle, then the makers of Celebrex, had a six-month head start getting U.S. approval.

Merck still needed to prove the drug actually caused fewer stomach woes than earlier drugs. It had been planning a "megatrial" for just that reason as far back as 1996, but company researchers realized early they faced a major problem in designing it.

If they stacked Vioxx up against an older pain reliever such as Aspirin, which can harm the stomach but potentially prevent heart disease, the overall results could backfire. Merck documents show company researchers feared they were in a "no-win situation" because such a comparison might suggest Vioxx was good for the stomach but bad for the heart.

One possible way to prevent the possibility of a bad-heart outcome would be to test people at low risk of heart disease. This way, according to one Merck researcher, "a difference between the two groups would not be evident."

Eric Topol, chief of cardiovascular medicine at the Cleveland Clinic who assessed the drug's heart risks in 2001, criticized the company's decision. He said older people at risk of heart disease were among the prime candidates to take the arthritis drug and yet were deliberately left out of safety studies.

"There was a mismatch between who was taking these drugs in the real world and who it was being tested on," Dr. Topol said.

When it came to finding the right person to run the crucial trial, Merck researcher Alise Reicin e-mailed a colleague in 1997 saying: "We want the person to be academic and well-connected; ideally this person should play a major role in helping to recruit other investigators."

Claire Bombardier fit the bill. Not only did she come with an impressive list of academic credentials, she was a consultant to Health Canada and to provincial governments. And she had also been a consultant to Searle in their development of Celebrex.

"When you're an expert in the field, people come to you," Dr. Bombardier said, explaining that she consults to six or seven drug companies and signs confidentiality agreements with each of them. "I would be concerned by someone who only consults for one drug company."

Asked how she reconciles advising drug companies as well as drug regulators, Dr. Bombardier said, "You declare your conflict of interest, or your potential conflict of interest. You have to be professional."

When Merck contacted her to run the trial, which began in January, 1999, she was excited by the challenge of such a large study - 8,000 patients in 22 countries, including 300 in Canada.

"There had never been a trial of that size in rheumatology," she said.

It became known as the VIGOR trial, short for Vioxx Gastrointestinal Outcomes Research, and Dr. Bombardier pegs its costs at roughly \$100-million. She stresses that she was not paid for her work as a scientist to conduct the study, nor did she receive an honorarium. Her consulting arrangement with Merck, she said, was separate.

The VIGOR trial compared the safety results of some 4,000 rheumatoid arthritis patients taking Vioxx against an equal number taking the traditional painkiller naproxen, sometimes sold under the brand name Aleve.

The final results became available to Merck in March, 2000.

As hoped, Vioxx users suffered half the gastrointestinal problems as those taking naproxen. But, as feared, they were twice as likely to suffer serious cardiac problems such as blood clots, strokes and, most dramatically, a five-fold increase in heart attacks, meaning five in 1,000 patients as opposed to one in 1,000.

This striking difference, a trend visible after only one month of treatment, prompted Merck research chief Edward Scolnick to write in an e-mail to staff on March 9 that "the cardiovascular events are clearly there." He wrote that "it is a shame but it is a low incidence and it is mechanism-based, as we worried it was."

When the Wall Street Journal first published Dr. Scolnick's comments last November, Merck issued a statement saying that in the selective release of its documents "the business practices of Merck may well be misrepresented in any reporting."

A Merck lawyer told the Journal that the internal Merck documents filed in connection to ongoing proceedings "were taken out of context" and "do not accurately represent the conduct of Merck employees."

Merck Frosst Canada said it could not respond to written questions from The Globe about these documents.

Despite Dr. Scolnick's e-mail that seems to acknowledge the heart risks linked to Vioxx, company officials later offered theories that would otherwise explain the negative heart findings in meetings and articles.

They noted that Vioxx users in the trial had taken the drug at twice the recommended dosage for chronic use. And though they had tried to exclude high-risk heart patients, they said, in retrospect, some of those in the Vioxx group were at increased risk.

But Merck's most forceful defence -- the theory Dr. Bombardier and her Merck co-authors offered in the VIGOR report they submitted to the New England Journal of Medicine in May, 2000 -- was that naproxen may prevent blood clotting in the same way as Aspirin. In other words, Vioxx did not increase heart risk, naproxen decreased it, making Vioxx look bad by comparison.

Critics feel it would be implausible that naproxen could lower the heart-attack risk by the magnitude seen in the VIGOR trial.

The VIGOR paper has since been widely criticized for the data that it did not include. Critics complain that it left out detailed information about the number of people who suffered from blood clots, strokes, hypertension and heart failure. Neither, they say, did the paper note that Vioxx users suffered more serious adverse events overall compared to those taking naproxen, or discuss the fact that even those people with no history of heart trouble appeared to face a higher risk of cardiovascular problems.

In an interview with The Globe, Gregory Curfman, executive editor of the New England Journal of Medicine, said: "We reported what we had and I don't know what else Merck had, if they had anything else, I don't know."

But Dr. Curfman stressed that "the editors here in our office spent a lot of time with authors ensuring that those data [which had been submitted] were accurately reflected in the article we published."

Doctors who eventually saw the data that Merck had available, which were submitted to the FDA before the New England Journal article was published in November, 2000, were scathing.

Dr. Singh at Stanford University described it as "selective reporting."

"I think that publication was scientifically inaccurate," Dr. Singh said in an interview, insisting Merck "had data and they didn't show it."

Dr. Bombardier insists no information was deliberately left out: "It's always easy with the eyes of retrospect."

Asked if she would report the paper differently if she had to do it again, Dr. Bombardier said, "What we've learned from that is that we needed to look at the totality [of the outcomes and adverse events], not just what was statistically significant," adding that they had reported what was statistically significant.

"The myocardial infarctions were clearly stated in the paper, that's what brought up the whole debate [of the heart safety of cox-2 drugs] so you could say it was helpful."

In response to complaints doctors sent to the British Medical Journal about the VIGOR paper, Dr. Bombardier also suggested that some safety data were left out due to the "limited space of a peer-reviewed journal."

She wrote: ". . . a figure highlighting withdrawals due to adverse events that was submitted with the original manuscript was removed at the request of the publisher."

This week, Dr. Bombardier also described receiving the reams of raw data as an overwhelming experience and that the cardiovascular side effects seen in the trial were, to her, a surprise. She said she did not know of internal company correspondence suggesting Merck researchers had feared such an outcome.

"I thought, 'Oh my God,' this was so unexpected," she said.

Dr. Bombardier explained that there were no neat tables available to her comparing the various adverse cardiac events in each patient group. But it was the heart-attack rate that jumped out at her, and the heart-attack rate she reported, she said.

But the safety questions it raised, however, concerned her enough that she went home to discuss the results with her husband, who had been taking Vioxx for his arthritis, and asked him if he wanted to stop taking the drug.

"He said, 'Claire, you told me the risks and I still want to take it.' "

Other doctors, meanwhile, complained that they were unable to have similar discussions with their patients because Merck had not made the information available to them.

James Fries, a professor of medicine at Stanford University wrote to Merck CEO Raymond Gilmartin on Jan. 9, 2001, that doctors worry Vioxx has "some serious and underemphasized drug-toxicity problems."

Dr. Fries said doctors turned out in big numbers to recent rheumatology meetings to hear about VIGOR, but the talks "did not contain data on the side effects."

Dr. Bombardier, who made several presentations of the trial shortly after its completion, said she always included the data in her talks.

Arthur Schafer, director of the Centre for Professional and Applied Ethics at the University of Manitoba, said, in relation to Dr. Bombardier: "Any scientist associated with VIGOR ought to have vigorously spoken out against this trial and demanded further research to test [the cardiovascular risks] of this drug."

On this point, however, Dr. Bombardier said she is a rheumatologist with expert knowledge in her field and its associated gastrointestinal side effects, not cardiac matters. Dr. Bombardier said she could not offer advice on how to design a cardiovascular clinical trial.

Dr. Bombardier said she was not involved in the internal Merck debates about whether to conduct a heart-safety trial after VIGOR.

"I wasn't involved in all of that and ,to tell you the truth, I didn't want to get involved in all of that," she said. "If you follow [the events], you see I don't become visible after" the months following the VIGOR trial. She explained that there was a point after the trial when she stopped giving presentations on its results.

"It had gone beyond a scientific issue; it became a very big marketing battle between the two cox-2 drug companies," said Dr. Bombardier, who did continue to consult for Merck on scientific questions.

At the time, Merck officials were apparently debating conducting a pure heart-safety trial, but decided against it. A New York Times article reported that top Merck executives were told in a May, 2000, slide presentation: "At present, there is no compelling marketing need for such a study. Data would not be available during the critical period. The implied message is not favourable."Despite the disturbing cardiovascular results from VIGOR, Merck was determined to use the positive stomach data to improve the safety information on its label and soon found itself in a protracted debate with regulators.

They had turned their raw study data over to the FDA and Health Canada in the summer of 2000, and that included the grim heart-risk numbers.

Yet it was two years before the FDA added the information to the Vioxx package and two years before Health Canada issued a "public advisory" about the cardiovascular problems linked to the drug.

Vioxx flew off pharmacy shelves during that time, for menstrual cramps, migraines, stiff backs and tendinitis. In 2001, Canadian pharmacies dispensed nearly four million Vioxx prescriptions.

Health Canada spokesperson Jirina Vlk said the department would not reveal the substance of the discussions it had with Merck during that two-year period due to pending lawsuits.

Health Canada has said in the past that "there was no consensus" on the actual dangers associated with Vioxx, or any of the cox-2 class.

FDA documents suggest, however, that the company forcefully negotiated with regulators during that time against unfavourable changes to its label.

An e-mail from Merck's Dr. Scolnick reveals the battle-ready mentality the company was prepared to take to the FDA talks.

He e-mailed staff on Jan. 21, 2001, that they should push for a safer GI label given data from Vioxx at a lower dosage: "The agency can moan and groan as usual but we can win the argument [on GI safety] . . . we can now formulate a correct strategy to the meeting and the upcoming round-two

battle with this group and win the public-affairs war."

In the February, 2001, meeting with the FDA, which Dr. Bombardier attended, Merck officials pointed out other company studies testing Vioxx at a lower dosage than the one used in the VIGOR trial showed no increased heart risk was evident.

A timeline document the FDA released in the run-up to this week's hearing reveals the vigorous back-and-forth debate that followed between Merck and the agency.

On Nov. 6, 2001, the FDA file notes that Merck "rejected FDA proposed labelling." Two weeks later, the FDA "requested that the sponsors [Merck] reconsider their proposal in light of our comments . . ."

Negotiations continued into 2002 with the FDA noting repeatedly that there was a "substantial distance" between the two sides.

Not until April, 2002, did they reach an agreement in which the positive gastrointestinal data from VIGOR was added to the Vioxx label and the cardiovascular risks were included on the box under "precautions."

Critics felt the FDA, which argued at this week's hearing that they "were not asleep at the switch," had bent to drug-company pressure and that the heart risks should have been prominently featured on the label in a black-boxed warning.

Health Canada issued a public advisory in April, 2002, that discussed the cardiovascular risks uncovered in the VIGOR trial.

But the information led to no changes of the Vioxx label in Canada. Instead, Health Canada opted to have the company include both the positive GI data and the heart-risk information in the product monograph in June, 2002. (The product monograph is the detailed small-print document often folded inside medication packages. Patients do not often read it, Dr. Bombardier agreed this week, adding: "A lot of doctors don't read it.")

Dr. Bombardier agreed that information from the VIGOR trial should have been featured on the drug label in Canada.

Arthur Schafer, as the FDA's Dr. Graham has said, feels drug regulators negotiating with drug companies are in a conflict of interest. "Both the FDA in the States and Health Canada regard the drug industry as their clients. It's not the safety of the public they're most concerned with."

FDA documents show the agency tried more than once to have Merck conduct a study to explicitly investigate the heart risks of Vioxx.

Merck, meanwhile, had all along been testing Vioxx for other indications and said in December, 2002, that it would pool data from these trials to further investigate the drug's cardiovascular risks. These studies, testing the power of Vioxx to prevent Alzheimer's disease, prostate and colon cancers against a placebo, would offer strong data, the company said.

Still, FDA officials felt the approach "might not be sufficient to address the ongoing cardiovascular

safety concerns surrounding Vioxx." But the agency did not compel the company to take another approach.

As Merck wrangled with drug regulators, it also found itself in tussles with outside scientists raising questions about the safety of Vioxx.

In 2001, Dr. Topol and colleagues from the Cleveland Clinic analyzed all the cardiovascular data available on cox-2 drugs and older pain relievers and found that Vioxx carried an increased heart risk.

"I had sent a draft of the paper to Merck to check for accuracy," Dr. Topol said in an interview. "When we did that . . . they had people come to the Cleveland Clinic from Merck to tell us not to publish it. They said we would be embarrassed, and that the study would be shown to be invalid.

"Never in 20 years had anyone asked me not to publish a paper."

In testimony to the U.S. Senate committee in November, Dr. Singh said that when he called looking for more detailed information on the heart risks from the VIGOR trial, the company refused to provide it.

Dr. Singh, who had been a Merck consultant at the time, continued to raise questions about the unavailable safety data on Vioxx in his lectures and told Merck he would stop speaking about its drug. Then, he said in an interview, he had others, namely drug-purchasing groups, ask for the information as well.

"That," Dr. Singh said, "is when they came after me."

Dr. Singh testified that a Merck official contacted him and said "there would be serious consequences for me."

In the January, 2001, letter that Stanford's Dr. Fries sent to Merck's Mr. Gilmartin, the professor of medicine wrote that he had received a call at home from a Merck official complaining that Dr. Singh "had an anti-Merck bias and was giving lectures that were irresponsibly anti-Merck and specifically anti-Vioxx. . . . [The official] suggested if this continued Dr. Singh would 'flame out' and there would be consequences for myself and for Stanford."

Dr. Fries complained of "a consistent pattern of intimidation of investigators by Merck staff," listing the names of eight researchers who felt they had been "intimidated" by the company.

Mr. Gilmartin wrote back on Jan. 23, 2001, saying Merck had a "deep and abiding commitment to the highest ethical standards in all our dealings with physicians and other health care providers." Mr. Gilmartin said he would hold an information meeting with interested doctors and look into Dr. Fries' allegations.

Dr. Singh testified that the threats against him stopped immediately and that the company subsequently made the data available.

Meanwhile, Merck continued with its massive marketing effort.

The company spent an unprecedented \$100-million (U.S.) a year on promotions, particularly high-priced television commercials featuring hit songs, celebrities and people running marathons. Many were seen by Canadians watching U.S. networks.

At the same time, drug representatives fanned out to pitch doctors. Many were receptive.

Arthur Bookman, medical adviser to the Arthritis Society, said: "We had drugs here that for the first time in my career patients could tolerate. Usually three days after taking [the older drugs] I'd get a call saying, 'My stomach's burning.' "

But Dr. Bookman said he and many colleagues wonder if they were aggressive enough in assessing the cardiovascular risks of Vioxx.

Drug representatives could be "defensive," he said, when dealing with the difficult questions: "You know that when you're dealing with drug reps, they are trying to sell drugs."

Internal Merck documents suggest company sales representatives were well schooled to handle doctors' tough questions, with one training document entitled "Dodge Ball Vioxx" featuring safety queries physicians might ask.

Another document instructs sales reps that it's time to target orthopedic surgeons who write the fewest Vioxx prescriptions: "Why is this so crucial? Orthopedic surgeons . . . write twice the number of scripts versus rheumatologists!"

On Sept. 17, 2001, the FDA's Division of Drug Marketing, Advertising and Communications wrote Merck a stern warning letter that certain Vioxx promotions were "false, lacking in fair balance and otherwise misleading . . ."

The letter said the campaign "minimizes the potentially serious cardiovascular findings that were observed in the (VIGOR) study."

The letter goes on to state: "Your minimizing these potential risks and misrepresenting the safety profile of Vioxx raise significant public health and safety concerns."

The letter also pointed specifically to a May, 2002, company press release that read, "Merck confirms favourable cardiovascular safety profile of Vioxx." The FDA concluded that such a claim was "simply incomprehensible."

It is unclear what, if anything, Health Canada did in response to Merck's promotional activities.

In its defence, Health Canada's Mark Bethiaume, director of the marketed pharmaceuticals division, emphasized that the federal department didn't do anything different on these drugs, or Vioxx, than any other regulatory agency, namely the FDA. Yet, the FDA has come under criticism for its approach, even from one of its own scientists.

Dr. Graham of the FDA said in an interview with The Globe, "Throughout the world, many different countries look to the FDA to set the standard [on drug safety]. Maybe they should reassess that wisdom."

By 2004, evidence was mounting that Vioxx could be linked to astounding numbers of cardiovascular problems and deaths.

In May of last year, researchers from Toronto's Institute for Clinical Evaluative Sciences found seniors who took Vioxx in Ontario had an 80-per-cent increased risk of being hospitalized for heart failure. The study prompted Ontario government officials to schedule a meeting to review the status of Vioxx that fall, said study author and senior scientist Muhammad Mamdani, but the meeting was pre-empted when Merck withdrew the drug itself.

Health Canada never issued a response to the report.

"I don't even know that they saw it," Dr. Mamdani said. "It's very disappointing."

In an e-mail request for information, Health Canada said Vioxx-related adverse-events reports, which are provided with limited information by doctors on a voluntary basis, had prompted the department to consider safety changes to the Vioxx label last summer.

At that time, the FDA's Dr. Graham had found evidence, which he alleges his agency tried to suppress, to suggest that Vioxx might be responsible for more than 80,000 excess heart- and stroke-related events in the United States.

But by last fall, one of Merck's own trials led to the drug's undoing after people taking Vioxx in a trial to prevent the recurrence of colon polyps had twice the risk of heart attack and stroke compared to those taking a placebo.

With yesterday's FDA panel decision, it is possible Vioxx will return. But severe restrictions against its use will likely keep it from ever reaching blockbuster status again, Dr. Graham predicts.