MNGT 3711: Business Ethics and Society

Merck, the FDA, and the Vioxx Recal

By
Anee T. Lawrence, & James Weber

Lawrence, A. T., & Weber, J. (2014). Case Study: Merck, the FDA, and the Vioxx Recall. *Business and Society: Stakeholders, Ethics, Public Policy* (Fourteenth ed.). New York, NY : McGraw-Hill Education.

CASE FIVE

Merck, the FDA, and the Vioxx Recall

In 2006, the pharmaceutical giant Merck faced major challenges. Vioxx, the company's once best-selling prescription painkiller, had been pulled off the market in September 2004 after Merck learned it increased the risk of heart attacks and strokes. When news of the recall broke, the company's stock price had plunged 30 percent to $33 a share, its lowest point in eight years, where it had hovered since. Standard & Poor's had downgraded the company's outlook from "stable" to "negative." In late 2004, the Justice Department had opened a criminal investigation into whether the company had "caused federal health programs to pay for the prescription drug when its use was not warranted."[1] The Securities and Exchange Commission was inquiring into whether Merck had misled investors. By late 2005, more than 6,000 lawsuits had been filed, alleging that Vioxx had caused death or disability. From many quarters, the company faced troubling questions about the development and marketing of Vioxx, new calls for regulatory reform, and concerns about its political influence on Capitol Hill. In the words of Senator Charles Grassley, chairman of a congressional committee investigating the Vioxx case, "a blockbuster drug [had become] a blockbuster disaster."[2]

Merck, Inc.

Merck, the company in the eye of this storm, was one of the world's leading pharmaceutical firms. As shown in Exhibit A, in 2005 the company ranked fourth in sales, after Pfizer, Johnson & Johnson, and GlaxoSmithKline. In assets and market value, it ranked fifth. However, Merck ranked first in profits, earning $7.33 billion on $30.78 billion in sales (24 percent).[3]

Merck had long enjoyed a reputation as one of the most ethical and socially responsible of the major drug companies. For an unprecedented seven consecutive years (1987 to 1993), *Fortune* magazine had named Merck its "most admired" company. In 1987, Merck appeared on the cover of *Time* under the headline, "The Miracle Company." It had consistently appeared on lists of best companies to work for and in the portfolios of social investment funds. The company's philanthropy was legendary. In the 1940s, Merck had given its

 An earlier version of this case was presented at the Western Casewriters Association Annual Meeting, Long Beach, California, March 30, 2006. This case was prepared from publicly available materials.

[1] "Justice Dept. and SEC Investigating Merck Drug," *The New York Times,* November 9, 2004.

[2] "Opening Statement of U.S. Senator Chuck Grassley of Iowa," U.S. Senate Committee on Finance, Hearing, "FDA, Merck, and Vioxx: Putting Patient Safety First?" November 18, 2004, *http://finance.senate.gov.*

[3] A history of Merck may be found in Fran Hawthorne, *The Merck Druggernaut: The Inside Story of a Pharmaceutical Giant* (Hoboken, NJ: John Wiley & Sons, 2003).

Exhibit A

The World's Top Pharmaceutical Companies, 2005

Company	Sales ($bil)	Profits ($bil)	Assets ($bil)	Market Value ($bil)
Pfizer	40.36	6.20	120.06	285.27
Johnson & Johnson	40.01	6.74	46.66	160.96
Merck	**30.78**	**7.33**	**42.59**	**108.76**
Novartis	26.77	5.40	46.92	116.43
Roche Group	25.18	2.48	45.77	95.38
GlaxoSmithKline	34.16	6.34	29.19	124.79
Aventis	21.66	2.29	31.06	62.98
Bristol-Myers Squibb	19.89	2.90	26.53	56.05
AstraZeneca	20.46	3.29	23.57	83.03
Abbott Labs	18.99	2.44	26.15	69.27

Source: Forbes 2000, *www.forbes.com*. Listed in order of overall ranking in the Forbes 2000.

patent for streptomycin, a powerful antibiotic, to a university foundation. Merck was especially admired for its donation of Mectizan. Merck's scientists had originally developed this drug for veterinary use, but later discovered that it was an effective cure for river blindness, a debilitating parasitic disease afflicting some of the world's poorest people. When the company realized that the victims of river blindness could not afford the drug, it decided to give it away for free, in perpetuity.[4]

In 1950, George W. Merck, the company's longtime CEO, stated in a speech, "We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they never fail to appear. The better we have remembered that, the larger they have been."[5] This statement was often repeated in subsequent years as a touchstone of the company's core values.

Merck was renowned for its research labs, which had a decades-long record of achievement, turning out one innovation after another, including drugs for tuberculosis, cholesterol, hypertension, and AIDS. In the early 2000s, Merck spent around $3 billion annually on research. Some felt that the company's culture had been shaped by its research agenda. Commented the author of a history of Merck, the company was "intense, driven, loyal, scientifically brilliant, collegial, and arrogant."[6] In 2006, although Merck had several medicines in the pipeline—including vaccines for rotavirus and cervical cancer, and drugs for insomnia, lymphoma, and the effects of stroke—some analysts worried that the pace of research had slowed significantly.

Estimating the company's financial liability from the Vioxx lawsuits was difficult. Some 84 million people had taken the drug worldwide over a five-year period from 1999 to 2004. In testimony before Congress, Dr. David Graham, a staff scientist at the Food and Drug Administration, estimated that as many as 139,000 people in the United States had had

[4] Merck received the 1991 Business Enterprise Trust Award for this action. See Stephanie Weiss and Kirk O. Hanson, "Merck and Co., Inc.: Addressing Third World Needs" (Business Enterprise Trust, 1991).

[5] Hawthorne, *The Merck Druggernaut*, pp. 17–18.

[6] Ibid., p. 38.

heart attacks or strokes as a result of taking Vioxx, and about 55,000 of these had died.[7] Merrill Lynch estimated the company's liability for compensatory damages alone in the range of $4 to $18 billion.[8] However, heart attacks and strokes were common, and they had multiple causes, including genetic predisposition, smoking, obesity, and a sedentary lifestyle. Determining the specific contribution of Vioxx to a particular cardiovascular event would be very difficult. The company vigorously maintained that it had done nothing wrong and vowed to defend every single case in court. By early 2006, only three cases had gone to trial, and the results had been a virtual draw—one decision for the plaintiff, one for Merck, and one hung jury.

Government Regulation of Prescription Drugs

In the United States, prescription medicines—like Vioxx—were regulated by the Food and Drug Administration (FDA).[9] Before a new drug could be sold to the public, its manufacturer had to carry out clinical trials to demonstrate both safety and effectiveness. Advisory panels of outside medical experts reviewed the results of these trials and recommended to the FDA's Office of Drug Safety whether or not to approve a new drug.[10] After a drug was on the market, the agency's Office of New Drugs continued to monitor it for safety, in a process known as "postmarket surveillance." These two offices both reported to the same boss, the FDA's director of the Center for Drug Evaluation and Research.

Once the FDA had approved a drug, physicians could prescribe it for any purpose, but the manufacturer could market it only for uses for which it had been approved. Therefore, companies had an incentive to continue to study approved drugs to provide data that they were safe and effective for the treatment of other conditions.

In the 1980s, the drug industry and some patient advocates had criticized the FDA for being too slow to approve new medicines. Patients were concerned that they were not getting new medicines fast enough, and drug companies were concerned that they were losing sales revenue. Each month an average drug spent under review represented $41.7 million in lost revenue, according to one study.[11]

In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA). This law, which was supported by the industry, required pharmaceutical companies to pay "user fees" to the FDA to review proposed new medicines. Between 1993 and 2001, the FDA received around $825 million in such fees from drug makers seeking approval. (During this period, it also received $1.3 billion appropriated by Congress.) This infusion of new revenue enabled the agency to hire 1,000 new employees and to shorten the approval time for new drugs from 27 months in 1993 to 14 months in 2001.[12]

Despite the benefits of PDUFA, some felt that industry-paid fees were a bad idea. In an editorial published in December 2004, the *Journal of the American Medical Association (JAMA)* concluded, "It is unreasonable to expect that the same agency that was responsible for approval of drug licensing and labeling would also be committed to actively seek

[7] "FDA Failing in Drug Safety, Official Asserts," *The New York Times,* November 19, 2004. The full transcript of the hearing of the U.S. Senate Committee on Finance, "FDA, Merck, and Vioxx: Putting Patient Safety First?" is available at *http://finance.senate.gov.*

[8] "Despite Warnings, Drug Giant Took Long Path to Vioxx Recall," *The New York Times,* November 14, 2004.

[9] A history of the FDA and of its relationship to business may be found in Philip J. Hilts, *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (New York: Alfred A. Knopf, 2003).

[10] Marcia Angell, *The Trust about the Drug Companies* (New York: Random House, 2004), ch. 2.

[11] Merrill Lynch data reported in "A World of Hurt," *Fortune,* January 10, 2005, p. 18.

[12] U.S. General Accounting Office, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities,* September 2002.

evidence to prove itself wrong (i.e., that the decision to approve the product was subsequently shown to be incorrect)." *JAMA* went on to recommend establishment of a separate agency to monitor drug safety.[13] Dr. David Kessler, a former FDA Commissioner, rejected this idea, responding that "strengthening postmarketing surveillance is certainly in order, but you don't want competing agencies."[14]

Some evidence suggested that the morale of FDA staff charged with evaluating the safety of new medicines had been hurt by relentless pressure to bring drugs to market quickly. In 2002, a survey of agency scientists found that only 13 percent were "completely confident" that the FDA's "final decisions adequately assess the safety of a drug." Thirty-one percent were "somewhat confident" and 5 percent lacked "any confidence." Two-thirds of those surveyed lacked confidence that the agency "adequately monitors the safety of prescription jobs once they are on the market." And nearly one in five said they had "been pressured to approve or recommend approval" for a drug "despite reservations about [its] safety, efficacy or quality."[15]

After the FDA shortened the approval time, the percentage of drugs recalled following approval increased from 1.56 percent for 1993–1996 to 5.35 percent for 1997–2001.[16] Vioxx was the ninth drug taken off the market in seven years.

Influence at the Top

The pharmaceutical industry's success in accelerating the approval of new drugs reflected its strong presence in Washington. The major drug companies, their trade association PhRMA (Pharmaceutical Research and Manufacturers of America), and their executives consistently donated large sums of money to both political parties and, through their political action committees, to various candidates. The industry's political contributions are shown in Exhibit B.

Following the congressional ban on soft money contributions in 2003, the industry shifted much of its contributions to so-called stealth PACs, nonprofit organizations that were permitted by law to take unlimited donations without revealing their source. These organizations could, in turn, make "substantial" political expenditures, providing political activity was not their primary purpose.[17]

In addition, the industry maintained a large corps of lobbyists active in the nation's capital. In 2003, for example, drug companies and their trade association spent $108 million on lobbying and hired 824 individual lobbyists, according to a report by Public Citizen.[18] Merck spent $40.7 million on lobbying between 1998 and 2004.[19] One of the industry's most effective techniques was to hire former elected officials or members of their staffs. For example, Billy Tauzin, formerly a Republican member of Congress from Louisiana and head of the

[13] "Postmarketing Surveillance—Lack of Vigilance, Lack of Trust," *Journal of the American Medical Association* 92, no. 21 (December 1, 2004), p. 2649.

[14] "FDA Lax in Drug Safety, Journal Warns," November 23, 2004, *www.sfgate.com*.

[15] 2002 Survey of 846 FDA scientists conducted by the Office of the Inspector General of the Department of Health and Human Services, *www.peer.org/FDAscientistsurvey*.

[16] "Postmarketing Surveillance."

[17] "Big PhRMA's Stealth PACs: How the Drug Industry Uses 501(c) Nonprofit Groups to Influence Elections," *Congress Watch*, September 2004.

[18] "Drug Industry and HMOs Deployed an Army of Nearly 1,000 Lobbyists to Push Medicare Bill, Report Finds," June 23, 2004, *www.citizen.org*.

[19] Data available at *www.publicintegrity.org*.

Exhibit B

Pharmaceutical/Health Products Industry: Political Contributions 1990–2006

Election Cycle	Total Contributions	Contributions from Individuals	Contributions from PACs	Soft Money Contributions	Percentage to Republicans
2006	$5,187,393	$1,753,159	$3,434,234	N/A	70%
2004	$18,181,045	$8,445,485	$9,735,560	N/A	66%
2002	$29,441,951	$3,332,040	$6,957,382	$19,152,529	74%
2000	$26,688,292	$5,660,457	$5,649,913	$15,377,922	69%
1998	$13,169,694	$2,673,845	$4,107,068	$6,388,781	64%
1996	$13,754,796	$3,413,516	$3,584,217	$6,757,063	66%
1994	$7,706,303	$1,935,150	$3,477,146	$2,294,007	56%
1992	$7,924,262	$2,389,370	$3,205,014	$2,329,878	56%
1990	$3,237,592	$771,621	$2,465,971	N/A	54%
Total	$125,291,328	$30,374,643	$42,616,505	$52,300,180	67%

Source: Center for Responsive Politics, *www.opensecrets.org.*

powerful Committee on Energy and Commerce, which oversaw the drug industry, became president of PhRMA at a reported annual salary of $2 million in 2004.[20]

Over the years, the industry's representatives in Washington had established a highly successful record of promoting its political agenda on a range of issues. In addition to faster drug approvals, these had more recently included a Medicare prescription drug benefit, patent protections, and restrictions on drug imports from Canada.

The Blockbuster Model

In the 1990s, 80 percent of growth for the big pharmaceutical firms came from so-called "blockbuster" drugs.[21] Blockbusters have been defined by *Fortune* magazine as "medicines that serve vast swaths of the population and garner billions of dollars in annual revenue."[22] The ideal blockbuster, from the companies' view, was a medicine that could control chronic but usually nonfatal conditions that afflicted large numbers of people with health insurance. These might include, for example, daily maintenance drugs for high blood pressure or cholesterol, allergies, arthritis pain, or heartburn. Drugs that could actually cure a condition, and thus would not need to be taken for long periods, or were intended to treat diseases, like malaria or tuberculosis, that affected mainly the world's poor, were often less profitable.

Historically, drug companies focused most of their marketing efforts on prescribing physicians. The industry hired tens of thousands of sales representatives—often, attractive young men and women—to make the rounds of doctors' offices to talk about new products and give out free samples.[23] Drug companies also offered doctors gifts—from free meals to

[20] "Rep. Billy Tauzin Demonstrates That Washington's Revolving Door Is Spinning Out of Control," *Public Citizen,* December 15, 2004, press release.

[21] "The Waning of the Blockbuster," *BusinessWeek,* October 18, 2004.

[22] "A World of Hurt," p. 20.

[23] In 2005, 90,000 sales representatives were employed by the pharmaceutical industry, about one for every eight doctors. *The New York Times* revealed in an investigative article ("Give Me an Rx! Cheerleaders Pep Up Drug Sales," November 28, 2005) that many companies made a point of hiring former college cheerleaders for this role.

tickets to sporting events—to cultivate their goodwill. They also routinely sponsored continuing education events for physicians, often featuring reports on their own medicines, and supported doctors financially with opportunities to consult and to conduct clinical trials.[24] In 2003 Merck spent $422 million to market Vioxx to doctors and hospitals.[25]

During the early 2000s, when Vioxx and Pfizer's Celebrex were competing head-to-head, sales representatives for the two firms were hard at work promoting their brand to doctors. Commented one rheumatologist of the competition between Merck and Pfizer at the time, "We were all aware that there was a great deal of marketing. Like a Coke–Pepsi war."[26] An internal Merck training manual for sales representatives, reported in *The Wall Street Journal,* was titled "Dodge Ball Vioxx." It explained how to "dodge" doctors' questions, such as "I am concerned about the cardiovascular effects of Vioxx." Merck later said that this document had been taken out of context and that sales representatives "were not trained to avoid physicians' questions."[27]

Direct-to-Consumer Advertising

Although marketing to doctors and hospitals continued to be important, in the late 1990s the focus shifted somewhat. In 1997, the FDA for the first time allowed drug companies to advertise directly to consumers. The industry immediately seized this opportunity, placing numerous ads for drugs—from Viagra to Nexium—on television and in magazines and newspapers. In 2004, the industry spent over $4 billion on such direct-to-consumer, or DTC, advertising. For example, in one ad for Vioxx, Olympic figure skating champion Dorothy Hamill glided gracefully across an outdoor ice rink to the tune of "It's a Beautiful Morning" by the sixties pop group The Rascals, telling viewers that she would "not let arthritis stop me." In all, Merck spent more than $500 million advertising Vioxx.[28]

The industry's media blitz for Vioxx and other drugs was highly effective. According to research by the Harvard School of Public Heath, each dollar spent on DTC advertising yielded $4.25 in sales.

The drug companies defended DTC ads, saying they informed consumers of newly available therapies and encouraged people to seek medical treatment. In the age of the Internet, commented David Jones, an advertising executive whose firm included several major drug companies, "consumers are becoming much more empowered to make their own health care decisions."[29]

However, others criticized DTC advertising, saying that it put pressure on doctors to prescribe drugs that might not be best for the patient. "When a patient comes in and wants something, there is a desire to serve them," said David Wofsy, president of the American College of Rheumatology. "There is a desire on the part of physicians, as there is on anyone else who provides service, to keep the customer happy."[30] Even some industry executives expressed reservations. Said Hank McKinnell, CEO of Pfizer, "I'm beginning to think that direct-to-consumer ads are part of the problem. By having them

[24] The influence of the drug industry on the medical professional is documented in Katharine Greider, *The Big Fix: How the Pharmaceutical Industry Rips Off American Consumers* (New York: Public Affairs, 2003).

[25] "Drug Pullout," *Modern Healthcare,* October 18, 2004.

[26] "Marketing of Vioxx: How Merck Played Game of Catch-Up," *The New York Times,* February 11, 2005.

[27] "E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage," *The Wall Street Journal,* November 1, 2004.

[28] IMS Health estimate reported in "Will Merck Survive Vioxx?" *Fortune,* November 1, 2004.

[29] "With or Without Vioxx, Drug Ads Proliferate," *The New York Times,* December 6, 2004.

[30] "A 'Smart' Drug Fails the Safety Test," *Washington Post,* October 3, 2004.

Exhibit C

Vioxx Sales in the United States, 1999–2004

	U.S. Prescriptions Dispensed	U.S. Sales	U.S. Sales of Vioxx as % of Total Merck Sales
1999	4,845,000	$372,697,000	2.2%
2000	20,630,000	$1,526,382,000	7.6%
2001	25,406,000	$2,084,736,000	9.8%
2002	22,044,000	$1,837,680,000	8.6%
2003	19,959,000	$1,813,391,000	8.1%
2004*	13,994,000	$1,342,236,000	5.9%

*Withdrawn from the market in September 2004.

Sources: Columns 1 and 2: IMS Health (*www.imshealth.com*); column 3: Merck Annual Reports (*www.merck.com*).

on television without a very strong message that the doctor needs to determine safety, we've left this impression that all drugs are safe. In fact, no drug is safe."[31]

The Rise of Vioxx

Vioxx, the drug at the center of Merck's legal woes, was known as "a selective COX-2 inhibitor." Scientists had long understood that an enzyme called cyclo-oxygenase, or COX for short, was associated with pain and inflammation. In the early 1990s, researchers learned that there were really two kinds of COX enzyme. COX-1, it was found, performed several beneficial functions, including protecting the stomach lining. COX-2, on the other hand, contributed to pain and inflammation. Existing anti-inflammatory drugs suppressed both forms of the enzyme, which is why drugs like ibuprofen (Advil) relieved pain, but also caused stomach irritation in some users.

A number of drug companies, including Merck, were intrigued by the possibility of developing a medicine that would block just the COX-2, leaving the stomach-protective COX-1 intact. Such a drug would offer distinctive benefits to some patients, such as arthritis sufferers who were at risk for ulcers (bleeding sores in the intestinal tract).[32] As many as 16,500 people died each year in the United States from this condition.[33]

In May 1999, after several years of research and testing by Merck scientists, the FDA approved Vioxx for the treatment of osteoarthritis, acute pain in adults, and menstrual symptoms. The drug was later approved for rheumatoid arthritis. Although Merck, like other drug companies, never revealed what it spent to develop specific new medicines, estimates of the cost to develop a major new drug ran as high as $800 million.[34]

Vioxx quickly became exactly what Merck had hoped: a blockbuster. At its peak in 2001, Vioxx generated $2.1 billion in sales in the United States alone, contributing almost 10 percent of Merck's total sales revenue worldwide, as shown in Exhibit C. The retail

[31] "A World of Hurt," p. 18.

[32] "Medicine Fueled by Marketing Intensified Troubles for Pain Pills," *The New York Times,* December 19, 2004.

[33] "New Scrutiny of Drugs in Vioxx's Family," *The New York Times,* October 4, 2004.

[34] This estimate was hotly debated. See, for example, "How Much Does the Pharmaceutical Industry Really Spend on R&D?" ch. 3 in Angell, *The Trust about the Drug Companies;* and Merrill Goozner, *The $800 Million Pill: The Truth behind the Cost of New Drugs* (Berkeley: University of California Press, 2004).

price of Vioxx was around $3.00 per pill, compared with pennies per pill for older anti-inflammatory drugs like aspirin and Advil. Of course, Vioxx was often covered, at least partially, under a user's health insurance, while over-the-counter drugs were not.

Safety Warnings

Even before the drug was approved, some evidence cast doubt on the safety of Vioxx. These clues were later confirmed in other studies.

Merck Research: Internal company e-mails suggested that Merck scientists might have been worried about the cardiovascular risks of Vioxx as early as its development phase. In a 1997 e-mail, reported in *The Wall Street Journal,* Dr. Alise Reicin, a Merck scientist, stated that "the possibility of CV (cardiovascular) events is of great concern." She added, apparently sarcastically, "I just can't wait to be the one to present those results to senior management!" A lawyer representing Merck said this e-mail had been taken out of context.[35]

VIGOR: A study code-named VIGOR, completed in 2000 after the drug was already on the market, compared rheumatoid arthritis patients taking Vioxx with another group taking naproxen (Aleve). Merck financed the research, which was designed to study gastrointestinal side effects. The study found, as the company had expected, that Vioxx was easier on the stomach than naproxen. But it also found that the Vioxx group had nearly five times as many heart attacks (7.3 per thousand person-years) as the naproxen group (1.7 per thousand person-years).[36] Publicly, Merck hypothesized that these findings were due to the heart-protective effect of naproxen, rather than to any defect inherent in Vioxx. Privately, however, the company seemed worried. In an internal e-mail dated March 9, 2000, under the subject line "Vigor," the company's research director, Dr. Edward Scolnick, said that cardiovascular events were "clearly there" and called them "a shame." But, he added, "there is always a hazard."[37] At that time, the company considered reformulating Vioxx by adding an agent to prevent blood clots (and reduce CV risk), but then dropped the project.

The FDA was sufficiently concerned by the VIGOR results that it required Merck to add additional warning language to its label. These changes appeared in April 2002, after lengthy negotiations between the agency and the company over their wording.[38]

Kaiser/Permanente: In August 2004, Dr. David Graham, a scientist at the FDA, reported the results of a study of the records of 1.4 million patients enrolled in the Kaiser health maintenance organization in California. He found that patients on high doses of Vioxx had three times the rate of heart attacks as patients on Celebrex, a competing COX-2 inhibitor made by Pfizer. Merck discounted this finding, saying that studies of patient records were less reliable than double-blind clinical studies.[39] Dr. Graham later charged that his superiors at the FDA had "ostracized" him and subjected him to "veiled threats" if he did not qualify his criticism of Vioxx. The FDA called these charges "baloney."[40]

[35] "E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage."

[36] "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *New England Journal of Medicine,* 2000, p. 323.

[37] "E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage."

[38] At one of the early Vioxx trials, the plaintiff introduced a Merck internal memo that calculated that the company would make $229 million more in profits if it delayed changes to warning language on the label by four months (*The New York Times,* August 20, 2005). The FDA did not have the authority to dictate label language; any changes had to be negotiated with the manufacturer.

[39] "Study of Painkiller Suggests Heart Risk," *The New York Times,* August 26, 2004.

[40] "FDA Official Alleges Pressure to Suppress Vioxx Findings," *Washington Post,* October 8, 2004.

APPROVe: In order to examine the possibility that Vioxx posed a cardiovascular risk, Merck decided to monitor patients enrolled in a clinical trial called APPROVe to see if those taking Vioxx had more heart attacks and strokes than those who were taking a placebo (sugar pill). This study had been designed to determine if Vioxx reduced the risk of recurrent colon polyps (a precursor to colon cancer); Merck hoped it would lead to FDA approval of the drug for this condition. The APPROVe study was planned before the VIGOR results were known.

Merck Recalls the Drug

On the evening of Thursday, September 23, 2004, Dr. Peter S. Kim, president of Merck Research Labs, received a phone call from scientists monitoring the colon polyp study. Researchers had found, the scientists told him, that after 18 months of continuous use individuals taking Vioxx were more than twice as likely to have a heart attack or stroke than those taking a placebo. The scientists recommended that the study be halted because of "unacceptable" risk.[41]

Dr. Kim later described to a reporter for *The New York Times* the urgent decision-making process that unfolded over the next hours and days as the company responded to this news.

> On Friday, I looked at the data with my team. The first thing you do is review the data. We did that. Second is you double-check the data, go through them and make sure that everything is O.K. [At that point] I knew that barring some big mistake in the analysis, we had an issue here. Around noon, I called [CEO] Ray Gilmartin and told him what was up. He said, "Figure out what was the best thing for patient safety." We then spent Friday and the rest of the weekend going over the data and analyzing them in different ways and calling up medical experts to set up meetings where we would discuss the data and their interpretations and what to do.[42]

According to later interviews with some of the doctors consulted that weekend by Merck, the group was of mixed opinion. Some experts argued that Vioxx should stay on the market, with a strong warning label so that doctors and patients could judge the risk for themselves. But others thought the drug should be withdrawn because no one knew why the drug was apparently causing heart attacks. One expert commented that "Merck prides itself on its ethical approach. I couldn't see Merck saying we're going to market a drug with a safety problem."[43]

On Monday, Dr. Kim recommended to Gilmartin that Vioxx be withdrawn from the market. The CEO agreed. The following day, Gilmartin notified the board, and the company contacted the FDA. On Thursday, September 30, Merck issued a press release, which stated in part,

> Merck & Co., Inc. announced today a voluntary withdrawal of VIOXX®. This decision is based on new data from a three-year clinical study. In this study, there was an increased risk for cardiovascular (CV) events, such as heart attack and stroke, in

[41] "Painful Withdrawal for Makers of Vioxx," *Washington Post,* October 18, 2004. Detailed data reported the following day in *The New York Times* showed that 30 of the 1,287 patients taking Vioxx had suffered a heart attack, compared with 11 of 1,299 taking a placebo; 15 on Vioxx had had a stroke or transient ischemic attack (minor stroke), compared with 7 taking a placebo.

[42] "A Widely Used Arthritis Drug Is Withdrawn," *The New York Times,* October 1, 2004.

[43] "Painful Withdrawal for Makers of Vioxx."

patients taking VIOXX 25 mg compared to those taking placebo (sugar pill). While the incidence of CV events was low, there was an increased risk beginning after 18 months of treatment. The cause of the clinical study result is uncertain, but our commitment to our patients is clear. . . . Merck is notifying physicians and pharmacists and has informed the Food and Drug Administration of this decision. We are taking this action because we believe it best serves the interests of patients. That is why we undertook this clinical trial to better understand the safety profile of VIOXX. And it's why we instituted this voluntary withdrawal upon learning about these data. Be assured that Merck will continue to do everything we can to maintain the safety of our medicines.