

DIRECT-TO-CONSUMER ADVERTISING AND PHARMACEUTICAL ETHICS: THE CASE OF VIOXX

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In the pharmaceutical industry, one of the most valuable assets a company has is its reputation. The work we do is a public trust. When you are researching, developing, and manufacturing drugs that people rely on to prevent or treat disease in themselves or their families, you should be expected to maintain the highest standards of ethics and integrity. At Merck, that is the standard to which we hold ourselves.¹

– Raymond V. Gilmartin,
President and CEO, Merck & Co., Inc.

I. INTRODUCTION

At press conferences held in Washington and Paris on October 21, 1987, Merck & Co. announced it would supply Mectizan, a new drug for the treatment of river blindness, to everyone who needed it, for as long as necessary, at no charge.

Mectizan is a nearly miraculous drug. One pill taken once a year both cures and prevents river blindness. This disease—which afflicts millions of people in some of the poorest regions of Africa and South America—is caused by a fly-born parasite. Once in the body, the parasite causes intense itching, disfiguring dermatitis, eye lesions, and, over time, blindness. In regions where river blindness is prevalent, children believe that going blind is a normal part of growing up. Since the introduction of Mectizan, and Merck's global program of supplying and distributing the drug for free, river blindness has been eradicated in many of its traditional strongholds.²

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1. Raymond V. Gilmartin, President and CEO, Merck & Co., Inc., The Raytheon Lectureship in Business Ethics at Bentley College: Ethics and the Corporate Culture, Lecture at Bentley Center for Business Ethics 10 (Nov. 10, 2003), *available at* <http://www.bentley.edu/cbe/documents/Gilmartin.pdf>.

2. See DAVID BOLLIER, *AIMING HIGHER: 25 STORIES OF HOW COMPANIES PROSPER BY COMBINING SOUND MANAGEMENT AND SOCIAL VISION* 280-93 (1996) (discussing the development of Mectizan). For an adaptation of this case, see RONALD M. GREEN, *THE ETHICAL MANAGER: A*

Fast-forward twenty years. Merck, the same drug company that committed itself to the development and distribution at no profit and substantial cost of a desperately needed drug to some of the world's poorest people, is now the defendant in thousands of lawsuits accusing it of deceptively marketing a drug, Vioxx, that it knew to be dangerous in order to bolster its corporate bottom line.

How did we go from Mectizan to Vioxx? How does a company with the highest ethical reputation and a corporate philosophy that "[m]edicine is for the people . . . not for the profits"³ undergo such a sharp reversal of fortune? What are the factors that contributed to Merck's current legal and reputational difficulties?

I do not intend to fully answer this question here. Many factors that business historians and students of organizational behavior will study contributed to this episode. Among them is the highly competitive environment of the pharmaceutical industry during the 1990s, and Merck's insecurity in the face of expiring patents on some of the company's most profitable drugs.⁴ A change in leadership from the kind of research-oriented, medically trained individual represented by Dr. P. Roy Vagelos, who presided over Mectizan's development, to a business school-trained manager like Raymond V. Gilmartin, also may have played a role.

But what I want to focus on is the part played by direct-to-consumer ("DTC") pharmaceutical advertising and poor corporate decision-making during this period. DTC advertising, I will argue, provided much of the impetus that drove Merck's scientific and corporate leadership into a series of decisions to continue the aggressive marketing of Vioxx despite evidence that the drug was dangerous.

The role of DTC advertising in this episode can be traced to FDA rule changes in 1997 that reduced the required amount of information in broadcast ads about a drug's adverse effects.⁵ This led to a proliferation of such advertising, as even a few moments' viewing of primetime television will show.⁶ In Europe, by contrast, the DTC advertising of

NEW METHOD FOR BUSINESS ETHICS 390-97 (1994).

3. George W. Merck, son of the company's founder and its former chairman, first enunciated this philosophy over fifty years ago. *See generally* *What the Doctor Ordered*, TIME, Aug. 18, 1952, available at <http://www.time.com/time/magazine/article/0,9171,816710,00.html> (follow "Read the Cover Story" hyperlink).

4. *See* MARCIA ANGELL, THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT 76-82 (2004) (discussing the marketing techniques used by drug companies when a lucrative drug is about to go "off patent").

5. *See id.* at 123-24.

6. For discussions of these developments, and DTC in general, see Joseph M. Farrell, *The Ethical Implications of Direct-to-Consumer Pharmaceutical Advertising*, PHIL. & PUB. POL'Y Q.,

prescription pharmaceuticals has never been legally permitted.

The availability of DTC advertising, in turn, has had a pronounced effect on drug companies' priorities. As numerous critics have observed, DTC invites the development and promotion of drugs aimed at very large groups of users suffering from chronic and persistent—but not necessarily life-threatening—conditions. Prescription medications for pain and allergy relief, erectile dysfunction, asthma control, acid indigestion or insomnia are ideally suited to this medium. So are “me-too” drugs.⁷ When intensive advertising—promoting modest advantages over competitive drugs—can help a new medication capture a large share of a huge market, it is understandable that the drug development process should turn from genuine pharmaceutical innovation to incremental improvements in already existing mass-market, lifestyle drugs.⁸ Vioxx was one such drug.

II. THE VIOXX STORY

Vioxx belongs to a class of agents known as COX-2 inhibitors that work by impeding production of the enzyme cyclooxygenase-2. Vioxx suppresses this enzyme, responsible for producing pain and inflammation, while not inhibiting COX-1, the enzyme involved in the protection of the stomach lining. Inhibition of COX-1 can result in potentially serious consequences, such as stomach ulcers and perforation, which are recognized side effects of other non-steroidal anti-inflammatory drugs (“NSAIDs”).⁹

Vioxx was a latecomer to the COX-2 inhibitor market. It was preceded by Searle's Celebrex, approved by the FDA in late December 1998, while Vioxx only received approval in May 1999.¹⁰ But Vioxx

Summer 2003, at 20; Lewis H. Glinert, *TV Commercials for Prescription Drugs: A Discourse Analytic Perspective*, 1 RES. SOC. & ADMIN. PHARMACY 158 (2005); Meredith B. Rosenthal et al., *Promotion of Prescription Drugs to Consumers*, 346 NEW ENG. J. MED. 498 (2002); Tamar V. Terzian, Note, *Direct-to-Consumer Prescription Drug Advertising*, 25 AM. J.L. & MED. 149 (1999). See also Maryann Napoli, *Drug Advertising*, HEALTHFACTS (Ctr. for Med. Consumers), Dec. 2001, available at http://www.medicalconsumers.org/pages/newsletter_excerpts.html.

7. See ANGELL, *supra* note 4, at 74-93. Angell explains that “me too” drugs are “made by competing companies, who create their own versions of blockbuster drugs to cut into a market that has already proved both lucrative and expandable.” *Id.* at 80.

8. See *id.* at 83-84.

9. See JOHN S. MARTIN, JR., DEBEVOISE & PLIMPTON LLP, REPORT TO THE SPECIAL COMMITTEE OF THE BOARD OF DIRECTORS OF MERCK & CO., INC. CONCERNING THE CONDUCT OF SENIOR MANAGEMENT IN THE DEVELOPMENT AND MARKETING OF VIOXX 3 (2006), available at <http://161.58.184.45/martinreport/>.

10. NAT'L INST. FOR HEALTH CARE MGMT. FOUND., PRESCRIPTION DRUGS & MASS MEDIA ADVERTISING, 2000, at 2 (2001), available at <http://www.nihcm.org/DTCbrief2001.pdf#search=%22vioxx%20DTC%20expenditures%22>.

soon began to make up for its late start. In 2000, Merck spent \$160.8 million on DTC advertising, the largest amount spent on DTC for any drug that year—the antacid Prilosec was second with \$107.5 million in expenditures.¹¹

In the same year, Searle spent less than half that amount—\$78.3 million—on DTC advertising of Celebrex. Although Celebrex’s year 2000 sales exceeded those of Vioxx, Vioxx began closing the gap—with more than \$1.5 billion in sales versus over \$2 billion for Celebrex.¹²

On March 9, 2000, this marketing juggernaut encountered a small obstacle in the form of an incidental finding in a just-completed but unpublished study (the “VIGOR” study).¹³ Merck had actually sponsored the study in the hopes of demonstrating Vioxx’s minimal gastrointestinal effects and possibly doing away with the usual NSAID gastrointestinal warnings on the drug’s label.¹⁴ Here we see one impact of the DTC environment: the desire to minimize serious side effects warnings that might have to be included in broadcast ads.

Aimed specifically at determining the benefits of Vioxx for the treatment of rheumatoid arthritis, the study was a double-blind, randomized trial comparing the occurrence of gastrointestinal toxicity of Vioxx and naproxen (an NSAID sold under the brand name Aleve).¹⁵ It had enrolled over 8000 patients¹⁶ and involved a team consisting of Merck-supported and independent researchers known as the VIGOR Study Group (Vioxx Gastrointestinal Outcomes Research).¹⁷ On March 9, researchers working on the trial unblinded the results, allowing them to understand what the effects of the two drugs were on each arm of the large study population.¹⁸

Overall, the VIGOR Study seemed to be good news for Merck. It showed that while Vioxx and naproxen had similar treatment efficacy, Vioxx caused roughly half as many serious gastrointestinal events—perforation, obstruction and severe upper gastrointestinal bleeding—as the older drug.¹⁹

The cloud in this picture was the finding that the incidence of

11. *Id.* at 2, 7-8.

12. *Id.* at 7-9.

13. See MARTIN, *supra* note 9, at 5. The VIGOR study was eventually published later that year. See Claire Bombardier et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520, 1520-28 (2000).

14. See MARTIN, *supra* note 9, at 4-5.

15. See Bombardier et al., *supra* note 13, at 1520-21.

16. *Id.* at 1521.

17. See MARTIN, *supra* note 9, at 5.

18. See *id.*

19. *Id.*

myocardial infarction—irreversible heart damage usually resulting from blockage of a coronary artery (“MI”)—was approximately five times higher among patients in the Vioxx group than among those in the naproxen group.²⁰ But this effect was found only among the four percent of the study population with the highest risk of an MI, and for whom low-dose aspirin was an indicated therapy (aspirin had been withheld during the study to prevent its confounding of gastrointestinal effects).²¹ No increase in MI was found for healthier patients. Furthermore, the study showed that despite these instances of MI, the overall mortality rate and death rates from cardiovascular causes were similar in the two groups.²²

Documents released in the course of subsequent litigation show that in the weeks and months following their notification of the VIGOR data, Merck managers wrestled with the scientific and business complexities of the study’s findings.²³ Pre-approval reports had raised some concerns that Vioxx and other COX-2 inhibitors might encourage the formation of blood clots because they did not suppress the COX-1 enzyme that is associated with blood platelet coagulation.²⁴ But a number of scientists, both inside and outside Merck, believed that they had a better explanation of the VIGOR findings. The higher incidence of MI in the VIGOR study resulted, they argued, not from any risks of Vioxx, but from the possibly heart-protective effects of naproxen.²⁵ These cardioprotective effects, which were well established for aspirin but relatively unstudied for naproxen, could easily account for different MI rates in the populations.

Other uncertainties accompanied the VIGOR study. There was an established association between rheumatoid arthritis and cardiac problems. Could this be the cause of the higher incidence of infarctions? Furthermore, if, in fact, Vioxx itself was the cause of these findings because of its prothrombotic effects, how could one test for this? The most straightforward way to do so was to immediately undertake a large clinical trial pitting Vioxx against placebo. But ethical considerations, as upheld and enforced by the FDA, prohibited this experiment since subject participants would be exposed to added risk for no corresponding benefit.

Edward M. Scolnick, President of Merck Research Laboratories

20. See Bombardier et al., *supra* note 13, at 1520.

21. *Id.* at 1523.

22. *Id.*

23. See, e.g., MARTIN, *supra* note 9, at 7, 51-53.

24. See *id.* at 34-36 (discussing the “FitzGerald Prostacyclin Hypothesis”).

25. *Id.* at 49.

(“MRL”), gathered these concerns and brought them before Merck’s Board on April 25, 2000 at its first meeting following the unblinding of the VIGOR study.²⁶ The ten board members, of whom three were physicians and one a molecular biologist, served as a sounding board for the scientists.²⁷ Also present were Merck’s CEO Raymond V. Gilmartin, Merck’s General Counsel, the head of its U.S. Human Health Division, and its Chief Financial Officer. No mention is made in Merck documents of Jacqueline Brevard, the head of Merck’s Ethics Office, attending the meeting.

At the Board meeting Scolnick reiterated and strongly defended the hypothesis that naproxen’s cardioprotective effects could explain the VIGOR findings.²⁸ He was buoyed in this position by findings from another Vioxx study. This, too, was a randomized controlled clinical trial, with two arms. The aim was to test Vioxx’s efficacy in slowing the progression of Alzheimer’s disease.²⁹ With over 2000 participants, it pitted Vioxx against placebo. In response to the VIGOR study, scientists had partially unblinded the Alzheimer trial to see if there was any difference in the incidence of cardiac events in either arm of the trial. They found none.³⁰ Drawing heavily on this very recent information, Dr. Scolnick affirmed his and other MRL scientists’ view “that the between-arm difference in the incidence of cardiovascular events in the VIGOR Trial was best explained by naproxen’s cardioprotective effects.”³¹

Scolnick’s presentation was apparently persuasive. The recent report by attorney John S. Martin, Jr., commissioned by Merck to review the company’s performance in this episode, summarizes the meeting as follows:

After the April 25, 2000 Board meeting where Dr. Scolnick presented the various explanations of the VIGOR Trial data, members of the Board of Directors were satisfied that the naproxen cardioprotection hypothesis was a reasonable explanation for the cardiovascular results of the VIGOR Trial.³²

In the period following these meetings, Merck redoubled its efforts to market Vioxx and quell concerns about the drug’s safety. In a press release issued on March 27, 2000, Merck explained the VIGOR findings in the following manner:

26. *See id.* app. T at 5.

27. *See id.* app. T at 28.

28. *See id.* app. T at 8.

29. *Id.* app. T at 7.

30. *Id.*

31. *Id.* app. T at 6.

32. *Id.* app. T at 8.

[S]ignificantly fewer thromboembolic events were observed in patients taking naproxen in this GI outcomes study, which is consistent with naproxen's ability to block platelet aggregation. This effect on these events had not been observed previously in any clinical studies for naproxen. Vioxx, like all COX-2 selective medicines, does not block platelet aggregation and therefore would not be expected to have similar effects.³³

No mention was made in this press release of the possibility that Vioxx itself could have prothrombotic effects.

Buoyed in their confidence that Vioxx was safe, Merck's management engaged in a series of marketing efforts to quell concerns in the medical community raised by reports of the VIGOR study. For example, Merck's marketing managers prepared a series of targeted instructional materials for the over 3000 company sales representatives across the country who were assigned to engage in face-to-face discussions with physicians about Vioxx.³⁴

One of the items already available for use by sales reps was the "Cardiovascular Card," a convenient tri-fold brochure. It featured data from several pre-approval studies that supported the safety of Vioxx.³⁵ One panel depicting "Overall Mortality Rates" indicated that patients on Vioxx were "[eight] times less likely to die from heart attacks and strokes. . . . Another panel indicated that the rate of heart attack among patients on Vioxx was less than half of the rate of patients receiving placebo and virtually identical to that of patients receiving other anti-inflammatory drugs."³⁶ Merck executives knew that these short-term pre-approval studies, based on very limited populations and not always targeted at cardiovascular effects,³⁷ were of limited scientific value, but they supported their gut-level confidence in the new drug.³⁸ During this period, Merck also struggled with intensifying FDA demands that Merck increase Vioxx's cardiovascular warnings.³⁹ Such warnings could badly damage Vioxx's DTC campaign.

33. News Release, Merck, Merck Informs Investigators of Preliminary Results of Gastrointestinal Outcomes Study with VIOXX (Mar. 27, 2000), *reprinted in* MARTIN, *supra* note 9, app. E at 64, *available at* <http://161.58.184.45/martinreport/appendices.html>.

34. *See* Memorandum from Representative Henry A. Waxman to the Democratic Members of the Gov't Reform Comm. 3 (May 5, 2005), *available at* <http://oversight.house.gov/Documents/20050505114932-41272.pdf> (discussing Merck's post-VIGOR marketing efforts).

35. *See id.* at 17 (detailing relevant portions of the "Cardiovascular Card").

36. *Id.* (footnote omitted).

37. *Id.* at 18.

38. *See id.* at 25 (describing how a Merck executive instructed the company's field executives to "[s]tay focused with [their] confidence in cardiovascular safety and overall safety of VIOXX").

39. *See id.* at 26-27.

To better assess Vioxx's risks, Merck also sponsored a further large long-term clinical trial enrolling 2600 subjects in late 2002. The APPROVe (Adenomatous Polyp Prevention on Vioxx) trial "was designed to evaluate the efficacy of VIOXX . . . in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas."⁴⁰ The trial was abruptly stopped in September 2004 when a data safety monitoring board found a significantly "increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after [eighteen] months of treatment in the patients taking VIOXX compared to those taking placebo."⁴¹ At that time, more than four years after the VIGOR trial results were first known, Merck voluntarily withdrew Vioxx from the worldwide market and has never reintroduced it.

III. LESSONS LEARNED

It is said in medical practice that "the retrospectroscope is always 20-20."⁴² Those of us looking back from a time when Vioxx's risks are well established find it easy to fault Merck's decision-making in the difficult period following the unblinding of the VIGOR study. Nevertheless, with the benefit of hindsight, we can now see where Merck's senior management lost an opportunity to act quickly to forestall the huge legal and ethical embarrassment the company has suffered.

The core problem, I believe, has to do with the company's far too heavy reliance on the naproxen cardioprotective thesis. Faced with the elemental choice of believing that Vioxx was a relatively dangerous drug, or the more comforting, and financially attractive thesis that it was merely less beneficial than its NSAID competitor, Merck scientists and managers repeatedly chose the latter hypothesis.

In fact, the naproxen cardioprotection hypothesis had little science to support it. No clinical trials had been done to demonstrate this effect. Support for it relied largely on extrapolation from data based on aspirin or other NSAIDs like ibuprofen.⁴³ In addition, Merck managers and scientists were encouraged in the naproxen theory by only one further clinical trial beyond VIGOR, the much smaller and less statistically

40. News Release, Merck, Merck Announces Voluntary Worldwide Withdrawal of VIOXX (Sept. 30, 2004), available at http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf#search=%22merck%20approve%20trial%22.

41. *Id.*

42. See, e.g., Interview with Dr. Kerry Phelp, President, Austl. Med. Ass'n, in Canberra, Austl. (July 17, 2002), <http://www.ama.com.au/web.nsf/doc/WEEN-5GB3MC>.

43. See News Release, *supra* note 33, at 30-31.

significant Vioxx-placebo Alzheimer study, that appeared to exonerate Vioxx from cardiovascular dangers rather than support any claims of naproxen's benefits.⁴⁴

In his review of this chapter in the Vioxx story, John S. Martin, Jr., Merck's commissioned attorney-investigator, concludes that Merck managers cannot be faulted with acting in bad faith in this episode. "We believe," he says, "[that Merck] scientists and management genuinely believed that the naproxen cardioprotection hypothesis was the most likely explanation for the VIGOR Trial cardiovascular results."⁴⁵

This may be true. But "genuine belief" and "good faith" are not the standards by which the scientists and managers of a company manufacturing and marketing prescription pharmaceuticals should be judged. Rather, the standard should be whether they based their decision-making on what they knew to be reliable data, and whether they took every reasonable step to protect the consumers of their products. By this more demanding standard, Merck managers came up short.

This becomes even clearer when we see how seriously these same managers were warned about the flimsiness of their reasoning. In September 2001, Merck received a sharp rebuke from the FDA in the form of a warning letter taking the company to task for its marketing practices around Vioxx and for its heavy reliance in communications about the VIGOR study on the naproxen theory. In that letter Thomas Abrams, head of the FDA's Division of Drug Marketing, Advertising and Communications, paid special attention to Merck's heavy reliance on the naproxen thesis:

Although the exact reason for the increased rate of MIs observed in the Vioxx treatment group is unknown, your promotional campaign selectively presents the following hypothetical explanation for the observed increase in MIs. You assert that Vioxx does not increase the risk of MIs and that the VIGOR finding is consistent with naproxen's ability to block platelet aggregation like aspirin. That is a possible explanation, but you fail to disclose that your explanation is hypothetical, has not been demonstrated by substantial evidence, and that there is another reasonable explanation, that Vioxx may have pro-thrombotic properties.⁴⁶

John S. Martin, Jr. uses the word "hypothesis," to describe the naproxen explanation, but that term may be too strong. "Hunch" is more

44. See MARTIN, *supra* note 9, at app. T at 7.

45. *Id.* at 56-57.

46. Warning Letter from Thomas W. Abrams, Director, Div. of Drug Mktg., Adver., & Comm'ns, Food & Drug Admin., to Raymond V. Gilmartin, President and CEO, Merck (Sept. 17, 2001), http://www.fda.gov/foi/warning_letters/g1751d.pdf.

accurate because the company never undertook the effort to test its own theory. It is true that a clinical trial aimed directly at assessing Vioxx's risks was ethically and legally out of the question. This is why the company chose to support the longer-term APPROVe trial, where subjects receiving Vioxx stood a chance of benefiting from its effects on colon polyps.

But if Merck scientists, managers, and the members of the Board really believed that the VIGOR results were possibly explained by naproxen's benefits, why did no one actively champion an immediate, direct clinical trial to test the hypothesis? Although there might have been some logistical problems in putting this study together, it would not have needed to be prolonged or even be large in size. More importantly, such a trial would have passed any ethical or legal test with flying colors. In one arm of the trial would be people receiving a placebo and exposed to their own normal risks of cardiovascular events. People in the other arm would receive naproxen. Any significantly lower incidence of MI in the naproxen arm would provide scientific grounding for the hypothesis that underlay Merck's whole continued marketing effort on behalf of Vioxx. Of course, if the naproxen hypothesis were vindicated, Merck might then find itself in the odd position of having used company resources to demonstrate a medical benefit for a product in competition with Vioxx. Was the naproxen hypothesis more properly described as a convenient way of exonerating Vioxx rather than something the company was willing to prove if doing so might impede the successful marketing of their own drug?

IV. CONCLUSION

That the key naproxen hypothesis was never put to the test suggests to me that Merck managers at all decision-making levels, from Merck Research Labs to the Board, were looking for ways to ignore the disturbing information provided by the VIGOR study. Why were they so willing to get on with business in the wake of the March 2000 findings? The answer to this question, I believe, takes us back to the issue of DTC advertising. Recall that Vioxx was ideally suited to this new and challenging medium. Tens of millions of aging baby boomers were likely to be attracted to the drug, a fact driven home by the decision to feature skater Dorothy Hamill, one of the icons of this generation, in Vioxx ads.

Decades of experience with Tylenol had shown how effectively advertising could establish a brand's leadership in the pain relief market. With Vioxx almost ready to catch up and surpass Celebrex's sales,

Merck could see years of profits ahead if it led the market with Vioxx, Vioxx spin-offs and, maybe eventually, when the patent expired, Vioxx in over-the-counter branded form. Merck had already traveled this route with its successful stomach acid inhibitor Pepcid. Vioxx was an even bigger success story waiting to happen.

The VIGOR study cast a small dark shadow on this sunny future. It was a shadow that Merck's leadership chose to ignore.