

# VIOXX AND THE MERCK TEAM EFFORT

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On May 20, 1999, the FDA approved Merck's application to market Vioxx, a new arthritis pain-reliever. The effort to create a successful drug at Merck was no small task; not only did the company need to develop, test, and receive approval for a new product – it also needed to make sure the drug was successfully marketed to the right consumers. To heighten the appeal of Vioxx, Merck had began an additional clinical trial in January in hopes of establishing that their drug caused fewer gastrointestinal problems than a commonly used alternative, naproxen (generic Aleve®). An independently chaired Data Safety and Monitoring Board, which monitored the clinical trial, noted a heightened risk for cardiovascular events in the second month of the 3-month trial. Despite what now appear to be clear warning signs, Merck continued to aggressively market the drug. Amid mounting concerns Merck finally withdrew the drug five years after its release.

This retrospective case illustrates competing understandings of mission across organizational subdivisions and the difficulty of regulating drug safety in a market context.

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## Introduction

Merck was established in the U.S. in 1891, but its roots trace back to Friedrich Jacob Merck's purchase of a German drug store in 1668.<sup>1</sup> Today the company is a top tier global entity, a "research-driven" pharmaceutical company "dedicated to putting patients first."<sup>2</sup> Merck's mission is to "provide society with superior products...that improve the quality of life and satisfy customer needs; provide employees with meaningful work...and investors with a superior rate of return."<sup>3</sup> As a long time player in the U.S. pharmaceutical industry, Merck has had extensive experience in assigning and dividing complex tasks among its many specialized departments. Specialization allows Merck to operate efficiently and bring new drugs to American patients.

On May 20, 1999, the FDA approved Merck's application to market Vioxx, a new arthritis pain-reliever. The effort to create a successful drug at Merck was no small task; not only did the company need to develop, test, and receive approval for a new product—it also needed to make sure the drug was successfully marketed to the right consumers. By the end of 1999, over 5 million prescriptions had been written for Vioxx and it had been launched in 47 countries.<sup>4</sup>

The Vioxx launch went particularly well, and Merck splashed its success across the front page of its Annual Report with the lead, "*Vioxx*: Our biggest, fastest and best launch ever."<sup>5</sup> New Vioxx sales came at an important time for Merck. The exclusive patents to four major drugs were scheduled to expire in 2000 and 2001. The company faced plummeting revenues once generic equivalents entered the market. According to one industry analyst, "Vioxx was Merck's savior."<sup>6</sup> Although internal teams were raising questions about the safety risks associated with Vioxx in early 2000, the company's first quarter financial statements cited Vioxx for leading sales growth within the company and touted it as the "fastest growing prescription arthritis medicine in the United States."<sup>7</sup> In 2001, however, safety concerns about the drug were becoming public. Three years later, on September 30, 2004, Merck pulled Vioxx off the market. The Acting Commissioner of the FDA commended the action, stating "Merck did the right thing by promptly reporting these findings to [the] FDA and voluntarily withdrawing the product from the market."<sup>8</sup>

## The Clinical Trial

Before receiving approval from the FDA, every drug must pass through a series of clinical trials that test for intended effects and monitor side-effects. Even after being approved, some drugs, like Vioxx, continue in trials to test for new therapeutic uses or monitor the safety and effectiveness of approved uses. The stakes involved for clinical trials are very high. Everyone has a vested interest in the ultimate outcome—from patients taking the drug hoping their symptoms will be relieved to executives seeking a financial return on the cost of developing the drug.

1 Merck & Co. Inc., "The History of Merck," <http://www.merck.de/en/company/history/history.html>.

2 Merck & Co. Inc., "Mission Statement," <http://www.merck.com/about/mission.html>.

3 Ibid.

4 Merck & Co. Inc., "10-K," (December 31, 1999). (See p. 39.)

5 ———, "Merck Annual Report -- 1999," (December 31, 1999), <http://proquest.umi.com/pqdweb?did=1009549892&sid=1&Fmt=1&clientId=15020&RQT=309&VName=HNP>.

6 Alex Berenson, Gardiner Harris, and Andrew Pollack, "Despite Warnings, Drug Giant Took Long Path to Vioxx Recall," *The New York Times* (November 14, 2004), <http://www.nytimes.com/2004/11/14/business/14merck.html>.

7 Merck & Co. Inc., "10-Q," (March 31, 2000).

8 John S. Martin, Jr., "Appendix Q: Approve Trial Cardiovascular Data and Withdrawal of Vioxx," *Report of John S. Martin, Jr. 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* (2006), [http://www.merck.com/newsroom/vioxx/pdf/037\\_appendix\\_q\\_approve\\_trial\\_cardiovascular\\_data\\_and\\_withdrawal\\_of\\_vioxx.pdf](http://www.merck.com/newsroom/vioxx/pdf/037_appendix_q_approve_trial_cardiovascular_data_and_withdrawal_of_vioxx.pdf). (See pp. 65-66.)

Given the stakes at hand and the potential for various interpretations and possible biases in these interpretations, the trial participants, doctors, and companies sponsoring the clinical trial are “blind” to treatment; they are unaware of who receives the trial drug. Clinical trials throughout the U.S. are monitored by Data Safety and Monitoring Boards, or DSMBs. Among other responsibilities, DSMBs are charged with “protecting the safety of trial participants.”<sup>9</sup> Some of the independent scientists serving on DSMBs—those unaffiliated with the pharmaceutical company—monitor patients in an un-blinded fashion so that they know which patients are taking the trial drug.

DSMBs are intended to operate independently of the company that employs them and are composed of outside consultants who have no vote in company decisions. Independence of DSMBs protects the scientific integrity of trials, supports the goal of patient safety, and allows pharmaceutical company employees to follow the studies without knowing which patients are taking the trial drug.

While DSMBs are responsible for patient safety, they do not have the authority to change or halt clinical trials. At Merck, a Steering Committee composed of outside consultants and Merck employees has this authority. The Steering Committee holds “ultimate responsibility for deciding whether or not to implement [the] recommendations made by the DSMB.”<sup>10</sup> The Committee monitors trials blindly but in the event of safety concerns procedures exist to un-blind part, or all, of the Steering Committee in order to make a determination on the clinical trial.<sup>11</sup>

## The VIGOR Trial

In January 1999, protocols were established for a clinical trial testing Vioxx’s gastrointestinal outcomes. The trial was known as the VIGOR (Vioxx Gastrointestinal Outcomes Research) study, and involved 8,000 individuals. Half of the subjects used Vioxx (Group A), the other half (Group B) were given naproxen (generic Aleve®). Merck convened the first DSMB meeting that month and Dr. Alise Reicin, the Merck clinical monitor and a Steering Committee member, attended to set out the protocols and introduce members of the DSMB. Dr. Michael Weinblatt, a rheumatologist at Brigham & Women’s Hospital in Boston, chaired the DSMB, and Merck statistician Dr. Deborah Shapiro was assigned to support the Board, including taking the meeting minutes, throughout the trial. As prescribed by Merck’s policies, Shapiro’s responsibility was dedicated to full-time support of the DSMB, and she would serve as a liaison between the DSMB, Steering Committee member Reicin, and other Merck executives. The VIGOR study continued into the spring of 2000, and Reicin met frequently with the DSMB and Merck executives to discuss the VIGOR trial.

## DSMB Safety Concerns

By the end of 1999, doctors had written more than five million prescriptions for Vioxx—slightly more than 22,200 prescriptions *each day*. Merck had been successful at marketing the product to physicians. In October 1999, the DSMB reviewed initial results from the VIGOR trial and noted “several pulmonary deaths,” but nothing appeared abnormal or triggered concern.<sup>12</sup> On November 18, the Board met again and discussed “the excess deaths and

9 Merck & Co. Inc., “Medical Affairs Procedures and Policies,” *MRK-AFK0047773*, [www.VioxxDocuments.com](http://www.VioxxDocuments.com). (See p.41.)

10 Ibid. (See p. 39.)

11 Extensive efforts were made to determine the identities of the members of the VIGOR Steering Committee and their respective employers. Based on the available information, it appears that 12 of 14 members were outside consultants. In addition, two Merck employees served on the Steering Committee: Dr. Alise Reicin and Dr. Thomas Capizzi, a bio-statistician.

———, “Vigor Data Analysis Plan and Dsmb Interim Monitoring Guidelines,” (November 15, 2008), <http://www.vioxxdocuments.com/Documents/DSMBs/dsmb%20rules%20vigor.pdf>. (See p. 73.)

12 “Data Safety and Monitoring Board Meeting Minutes, Interim Analysis of Vigor - Unblinded Minutes,” *LEH 0114732 - 33* (October 4, 1999), [http://www.vioxxdocuments.com/Documents/DSMBs/vigor\\_dsmb\\_10\\_99%20meeting%20minutes.pdf](http://www.vioxxdocuments.com/Documents/DSMBs/vigor_dsmb_10_99%20meeting%20minutes.pdf).

cardiovascular adverse experiences in Group A.”<sup>13</sup> The analysis showed 52 serious cardiovascular (or “CV”) events in Group A compared to 29 in Group B. “The differences between the treatment groups were noted as being significant beyond the level of chance.”<sup>14</sup> Numerous charts plotted an elevated incidence line for Group A. Shapiro attended the November meeting and knew that the trends were “disconcerting” to the DSMB.<sup>15</sup> Some in the DSMB group noted that the data could be interpreted in two ways: that Group A had a higher incidence of CV events due to the trial drug, or that Group B had fewer CV events due to the trial drug. In other words, it was unclear whether Group A had received a harmful effect or Group B had received a cardiovascular protective effect.

The DSMB requested an additional safety analysis report and met in December to review the results. With safety concerns mounting, DSMB members agreed that publication of any of the study results should “include a discussion of the cardiovascular results.”<sup>16</sup> After the December meeting, Weinblatt and Shapiro also drafted a letter to Reicin requesting the development of a data analysis plan for the cardiovascular events that were occurring. They recognized the importance of having the plan in place to analyze the VIGOR results before Merck employees learned which group of patients had experienced increased cardiovascular problems. According to protocols, the analysis plan should have already been in place, but it had not yet been developed.

## Executives’ Reaction to the VIGOR Trial

The Vioxx DSMB operated with a relatively clear purpose—to protect the health of the trial participants. Reicin and other top executives involved in the clinical studies, however, had to weigh the obligation to respond to emerging safety risks from the VIGOR trial against other strategic concerns about Merck’s top-selling product.

Weinblatt, chair of the DSMB, did not agree with the statistical analysis plan proposed by Merck. On January 24, 2000, in a reply to Reicin, he stated that it was “not acceptable to only perform [a] pooled analysis,” a statistical method that would likely not be rigorous enough to investigate the possible problems with Vioxx.<sup>17</sup> Executives discussed amongst themselves what type of analysis plan might satisfy Weinblatt’s demands.<sup>18</sup> It was during the time period of these discussions that Merck offered Weinblatt a consulting position on the company’s Multidisciplinary Strategic Advisory Board for COX-2 inhibitors. As a consultant Weinblatt could contribute valuable knowledge of COX-2 inhibitors—Vioxx itself was a COX-2 class drug.<sup>19</sup> Weinblatt’s consulting agreement with Merck, which he signed in mid-February, narrowly avoided a conflict of interest with his chairmanship of the DSMB—it was scheduled to begin a few days after the VIGOR trial had concluded. For his new role on the Advisory Board, Weinblatt was compensated \$5,000 for each day of consulting work.

When the VIGOR trial concluded in early 2000, Ed Scolnick, president of Merck Research Laboratories, the research division at Merck, and member of the Merck Board of Directors, emailed Shapiro and Reicin with clear

13 “Data Safety and Monitoring Board Meeting Minutes, Interim Non-Endpoint Safety Analysis of Vigor - Unblinded Minutes,” *MRK-004200115464* (November 18, 1999), [http://www.vioxxdocuments.com/Documents/DSMBs/vigor\\_dsmb\\_11\\_99%20meeting%20minutes.pdf](http://www.vioxxdocuments.com/Documents/DSMBs/vigor_dsmb_11_99%20meeting%20minutes.pdf).

14 *Ibid.*

15 *Ibid.*

16 “Data Safety and Monitoring Board Meeting Minutes, Cardiovascular Safety Analysis of Vigor - Unblinded Minutes,” *MRK-00420015472 - 477* (December 22, 1999), <http://www.vioxxdocuments.com/Documents/DSMBs/december%20dsmb%20meeting%2012-22-1999.pdf>.

Note that companies are not required to publish the results of clinical trials.

17 Michael Weinblatt, “Letter to Alise Reicin, M.D.,” *MRK-ABC0016765* (January 24, 2000), <http://www.vioxxdocuments.com/Documents/DSMBs/Weinblatt%20letter%20to%20Reicin.pdf>.

18 Douglas J Watson, “Email to Alise Reicin, Deborah Shapiro, Thomas Capizzi, Linda S. Hostalley, Nancy Santanello, and Harry Nelsen. Change in Vigor Adjudicated Cv Events Timelines and Procedures?,” *MRK - NJ0120690* (February 7, 2000), <http://www.vioxxdocuments.com/Documents/DSMBs/reicin%20to%20watson%202-7-2000.pdf>.

19 COX-2 inhibitor drugs work by blocking the COX-2 enzymes causing pain. Vioxx, Celebrex, Aleve and other similar products are collectively referred to as a drug “class.”

excitement for the “great drug” Merck had developed.<sup>20</sup> Scolnick’s email also admitted that safety risks were evident, but he hoped that Merck could present the risks as a class effect, or, in other words, present the risks so that they appeared common to all drugs that function as COX-2 inhibitors.

The CV (cardiovascular) events are clearly there... It is important to find out about the cases that [O]ates told us about. When we present in May we should present those also...so it is clear to the world that this is a class effect.<sup>21</sup>

Scolnick closed the email with the following: “We have a great drug...there is always a hazard. The class will do well and so will we.”<sup>22</sup> Vioxx did clearly cause fewer GI side-effects than naproxen. In Scolnick’s judgment, Merck had a “great drug,” and the CV risks that the study revealed seemed less clearly correlated with Vioxx use. For Scolnick, they were probably common to the whole class of drugs.

## Making the Best of the VIGOR Results

If any one single committee at Merck was responsible to the array of stakeholders—customers, employees, and investors—outlined in the corporate mission, it would have been the Human Health Product Approval Committee (HHPAC). HHPAC was the “most senior cross-disciplinary committee” at Merck during the development of Vioxx.<sup>23</sup> The committee served “as a bridge between the research and commercial arms of Merck,” and was chaired by Ed Scolnick.<sup>24</sup> Reicin and Scolnick—not HHPAC as a whole—had the task of weighing the meaning of the VIGOR results and interpreting these for stakeholders. Meanwhile, the DSMB had concluded its responsibility to oversee patient safety with the closing of the clinical trial. At this point, the future of Vioxx lay in the work of two Merck divisions: the research division Merck Research Laboratories and the Marketing and Sales Division.

After the study results were unblinded on March 9, 2000, Scolnick and Reicin pored over the data and discussed how to frame the results for presentation to the FDA, academic journals, and scientific conferences. In her tenure as clinical monitor, Reicin had become aware of DBSM’s concern for CV events occurring in the study, but as the months rolled on Reicin and Scolnick focused on making the best of the raw data from the clinical trial to cast Vioxx in a favorable light.

The VIGOR results showed increased cardiovascular (CV) problems in patients taking Vioxx. One explanation proposed was the idea that naproxen provided protection for the heart, although this had yet to be demonstrated through any clinical trials. The protective benefits from naproxen would explain why those patients experienced significantly fewer heart problems. Early on, Reicin and Merck Research Laboratories scientists saw this “naproxen hypothesis” as an attractive explanation behind the cardiovascular events. Yet in order for naproxen to provide the magnitude of “benefits” observed in the VIGOR study, it would have to be proven to be more effective than aspirin. Such a finding alone would make news in the medical community. Not even the makers of naproxen had identified such a beneficial effect.

On June 15, 2000, Dr. Carlo Patrono, an antiplatelet specialist and consultant to Merck, withdrew his support for the naproxen hypothesis. He notified Merck that he would present a slide at an upcoming conference addressing

<sup>20</sup> Edward M. Scolnick, “Email to Deborah Shapiro,” *MRK-ABH0016219* (March 9, 2000), [www.VioxxDocuments.com](http://www.VioxxDocuments.com).

<sup>21</sup> Ibid.

<sup>22</sup> Ibid.

<sup>23</sup> John S. Martin, Jr., “Exhibit 1: Merck Leadership and Organizational Structure,” *Report of John S. Martin, Jr. 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* (2006), [http://www.merck.com/newsroom/vioxx/pdf/002\\_exhibit\\_1\\_merck\\_leadership\\_and\\_organizational\\_structure.pdf](http://www.merck.com/newsroom/vioxx/pdf/002_exhibit_1_merck_leadership_and_organizational_structure.pdf). (See p. 28.)

<sup>24</sup> Ibid.

the “Commonly Held Misperception” that naproxen and “NSAIDs...are likely to afford [similar] cardiovascular protection [to aspirin].”<sup>25</sup> The presentation would not be favorable for Vioxx. Reicin spoke at length with Patrono, and Patrono agreed not to focus on the cardiovascular problems in the VIGOR study. But Patrono argued that the “presentation of the VIGOR data must not mislead the audience into thinking that the difference in CV events could be explained by...naproxen”.<sup>26</sup>

## Marketing Vioxx

On November 23, 2000, the VIGOR results were published in the *New England Journal of Medicine (NEJM)*. The study showed that Vioxx patients were five times more likely to experience adverse CV events than patients taking naproxen. While the publication drew attention in the medical community and media, the Marketing and Sales team remained focused on its mission to promote products and bring new drugs to key consumer groups. Marketing and Sales had a clear understanding of how to meet its responsibilities. In what seems now like a preemptive strike, Merck had months earlier released a statement (see Exhibit 3) commenting on the preliminary results of VIGOR. Informational releases prior to a study’s conclusion are atypical for pharmaceutical companies. Industry analysts and others in the media began asking questions soon after, and the publication of the results in the *NEJM* added to mounting concerns about the safety of Vioxx.

On April 28, 2000, Marketing and Sales released a bulletin to sales representatives titled “NEW RESOURCE Cardiovascular Card.”<sup>27</sup> (See Exhibits 4 and 5.) The bulletin announced a “Roadmap to the CV Card,” which included complete step-by-step messages, page references, and talking points to inform salespeople what to say when questioned by physicians about the published CV results. Marketing wanted to move quickly to prepare these materials, fearing a delay would leave representatives unprepared to respond to questions in the field. However, in the push to improve the product’s image, Marketing and Sales excluded the VIGOR trial results on its informational card and even relied on a safety analysis that the FDA considered inappropriate. In fact, the CV card indicated that Vioxx could be 8 to 11 times safer than other anti-inflammatory drugs, information that was not in agreement with the published data.

The CV card was a useful pocket tool, but it was hardly the complete survival kit for sales representatives facing tough questions from physicians. The formal publication of the study on November 23 in the *NEJM* generated even more questions from doctors in the field and increased the pressure on Marketing to pursue more aggressive defense strategies. As the “lifeline” to a marketplace asking questions, Marketing needed to make sure its sales force was top-notch, prepared to handle any question in the field. The department launched an all-out effort to train its sales representatives, prepare them on emerging issues, and reframe the issues surrounding Vioxx.

First the department reframed challenges to the safety of Vioxx as “obstacles.” Next the department launched a series of videos presenting the “V-Squad,” a superhero-styled space duo who battled the real-world challenges of selling Vioxx. In training episodes, the V-Squad faced situations similar to the real-life challenges of the pharmaceutical sales force.<sup>28</sup> The futuristic “Cyber Obstaclizer” launched the V-Squad into a “virtual reality

25 ———, “Appendix E: Merck’s Interpretation of and Response to Vigor Trial Cardiovascular Data: March 9 - 27, 2000,” *Report of John S. Martin, Jr. 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* (2006), [http://www.merck.com/newsroom/vioxx/pdf/014-appendix%20\\_e\\_mercks\\_interpretation\\_of\\_and\\_response\\_to\\_vigor\\_trial\\_cardiovascular\\_data\\_march\\_9\\_27\\_2000.pdf](http://www.merck.com/newsroom/vioxx/pdf/014-appendix%20_e_mercks_interpretation_of_and_response_to_vigor_trial_cardiovascular_data_march_9_27_2000.pdf). (See pp. 26-27.)

26 *Ibid.* (See p. 28.)

27 U.S. House Committee on Government Reform, “The Marketing of Vioxx to Physicians,” (May 5, 2005), <http://oversight.house.gov/documents/20050505114932-41272.pdf>. (Herein after as *The Marketing of Vioxx*.)

28 Merck & Co. Inc., “Part 1 - Be the Power,” <http://www.vioxxdocuments.com/browse.php?display=list&dir=Be%20The%20Power/>.

training environment in which reps directly confront the obstacles that stand in the way of them and greater success for Vioxx.”<sup>29</sup>

The department also created a complete reference manual for field representatives called the “Obstacle Response Guide.” (This guide appears as Exhibit 6.) The manual included a comprehensive list of likely physician questions and complete talking points for the representatives to use in response. Marketing sent periodic updates with instructions to add the new “obstacle responses” to the field manual. To keep the sales team sharp, the department required representatives to “review and practice [the] obstacle response and use it in appropriate discussions on Vioxx.”<sup>30</sup> But obstacle responses were “not to be shown to or left with physicians.”<sup>31</sup>

The “obstacle response strategy” was Marketing’s primary tool to carry out its mission of promoting the drug to physicians who could prescribe it. All representatives were trained to “provide appropriate balancing information as part of all product discussions.”<sup>32</sup> The core message included two gastrointestinal messages and one efficacy message, and representatives tailored the core message to each physician’s belief about Vioxx. The Marketing and Sales focused on the strengths of Vioxx and sought to reframe and minimize any safety concerns.

In addition, the marketing division maintained consistent messages about Vioxx in press releases. In the research division of Merck, Reicin jockeyed at length with Patrono over the legitimacy of naproxen benefits, while the marketing division forged ahead with its public message. Immediately after Patrono’s presentation at the conference, Marketing issued a statement affirming that “the reduction in heart attacks [in the VIGOR study] is consistent with naproxen’s ability to block platelet aggregation.”<sup>33</sup>

## Mounting Concerns about the Safety of Vioxx

The aggressive marketing of Vioxx was creating a head-on collision with outsiders’ claims of safety problems. In February 2001, an FDA Arthritis Advisory Committee reviewed the VIGOR study and stated that “there is clear evidence to show...[an] increased risk of developing serious cardiovascular adverse events compared to naproxen.”<sup>34</sup>

Soon after the FDA met, *The New York Times* ran an article on May 22, 2001, that questioned the safety of Vioxx. The article referenced a Wall Street analyst who had urged his clients to follow the Vioxx issue closely because it might impact the stock price. The article also cited one doctor pleading, “There must be a warning...I’m sure there are many people out there who are taking these drugs that should not be.”<sup>35</sup> Merck responded to the article immediately. The company issued a press release the same day titled “Merck Confirms Favorable Cardiovascular Safety of Vioxx.” The next day Marketing and Sales sent a bulletin to all field representatives. The instructions were explicit: “DO NOT INITIATE DISCUSSIONS ON THE RESULTS OF THE... VIGOR STUDY, OR ANY RECENT ARTICLE IN THE PRESS ON VIOXX.”<sup>36</sup> (See Exhibit 5.)

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29 Ibid.

30 ———, “Bulletin for Vioxx: New Obstacle Response,” *MRK-H.3STM001295* (May 1, 2000), <http://dida.library.ucsf.edu/pdf/pjb00a10>.

31 Ibid.

32 Ibid.

33 John S. Martin, Jr., “Appendix F: Further Analysis and Public Presentation of Vigor Trial Cardiovascular Data: April 2000 - January 2001,” *Report of John S. Martin, Jr. 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* (2006), [http://www.merck.com/newsroom/vioxx/pdf/016-appendix\\_f\\_further\\_analysis\\_and\\_public\\_presentation\\_of\\_vigor\\_trial\\_cardiovascular\\_data\\_april\\_2000\\_january\\_2001.pdf](http://www.merck.com/newsroom/vioxx/pdf/016-appendix_f_further_analysis_and_public_presentation_of_vigor_trial_cardiovascular_data_april_2000_january_2001.pdf). (See p. 28)

34 Maria Lourdes and Qian Li Villalba, “Statistical Reviewer Briefing Document for the Advisory Committee. Nda # 21-042 S-007,” (February 7, 2001), [http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2\\_04\\_stats.pdf](http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_04_stats.pdf). (See p. 14)

35 Melody Petersen, “Doubts Are Raised on the Safety of 2 Popular Arthritis Drugs,” *The New York Times* (May 22, 2001), <http://www.nytimes.com/2001/05/22/business/doubts-are-raised-on-the-safety-of-2-popular-arthritis-drugs.html>.

36 U.S. House Committee on Government Reform, “The Marketing of Vioxx to Physicians.” (See p. 24.)

Thus far, 2001 had presented some major challenges to Marketing and Sales. Yet in the wake of the *The New York Times* article, the department remained undeterred. The strategy was simple—“emphasize that Vioxx demonstrated a potential advantage over narcotics for pain management.”<sup>37</sup> A Merck executive left voicemails for all the sales representatives encouraging them to “Stay focused. Stay focused with your efficacy and GI risk awareness messages and stay focused with your confidence in cardiovascular safety and overall safety of Vioxx.”<sup>38</sup>

Meanwhile at both Merck and FDA laboratories, further data analysis and new studies on Vioxx continued. By the end of the summer of 2001, Briggs Morrison, an associate director at Merck Research Laboratories, received an internally-generated paper on Vioxx for his review. In a series of comments about the paper, Morrison stated:

I guess what I am saying is that the data appears to have been interpreted to support a preconceived hypothesis rather than critically reviewing the data to generate hypotheses. The second line of the Discussion says ‘There was no evidence...that rofecoxib [Vioxx] was associated with excess CV events compared with either placebo or non-naproxen NSAIDs’ – that seems wishful thinking, not a critical interpretation of the data.

I guess my point is that one usually discusses the limitations of the paper – one of the limitations here is the paucity of data and therefore ‘conclusions’ may be too strong a word; ‘there is no evidence’ also seems (to me) to be a bit of a stretch...doesn’t one have an obligation to re-examine the rationale behind that decision as data accrues.<sup>39</sup>

But these concerns didn’t seem to reach Marketing. In October, Marketing would renew its efforts and use a new strategy coined “Project Offense” to emphasize the message of the drug’s efficacy to physicians.

## Epilogue

Throughout all of the difficulties with Vioxx, Marketing and Sales worked with a consistent goal in mind and developed clear strategies for representatives in the field. Merck continued to study the drug in clinical trials for Alzheimer’s disease and colon polyps. These additional trials consistently showed safety risks associated with Vioxx. On September 28, 2004, Merck requested an emergency meeting with the FDA. In the meeting, Merck shared data from the colon polyps study with the FDA. Two days later, on September 30, 2004, Merck made a public announcement that it planned to withdraw Vioxx from the market—nearly five years after initial safety concerns had surfaced.

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37 Ibid. (See p. 26.)

38 Ibid. (See p. 25.)

39 Morrison W. Briggs, “Email to Deborah Shaprio, James Bolognese, Rhoda Sterling, Alise Reicin, Leonard Oppenheimer, Eliav Barr, Barry Gertz, Alan Nies “*MRK-ACF0005697* (August 17, 2001), [www.VioxxDocuments.com](http://www.VioxxDocuments.com).



## Exhibits

1. The Market Size for Arthritis Pain-Relievers
2. Organization of Clinical Trials Involving a DSMB
3. March 27, 2000, Press Release Announces VIGOR Results
4. April 28, 2000, Bulletin with Instructions for the CV Card
5. May 22, 2001, Press Release Confirms Vioxx Safety  
May 23, 2001, Instructions to Sales Representatives
6. CV Obstacle Response Tip Sheet
7. Timeline of Events
8. Acronyms and Key Participants

## Exhibit 1: The Market Size for Arthritis Pain-Relievers

Prior to the launch of Vioxx, estimates of the market size for arthritis pain relieving drugs ranged between “60 to 80 million patients.” Such a large number of patients ensured that sales revenue would be among the highest in recent history. The market potential was important to every pharmaceutical company competing for a share and working to launch Cox-2 inhibitors. At Merck, analysts expected that revenue from Vioxx in the first 7 months would be roughly \$120M.<sup>1</sup>

Generally, the first manufacturer to file a New Drug Application with the FDA is the first to reach market. After assessing the arthritis market, Merck estimated that “the value of [Vioxx] being first to market versus second to market is \$611M.”<sup>2</sup> But on June 28, 1998 Pfizer made a virtual lock on being the first to enter the market. Pfizer submitted a New Drug Application to the FDA for Celebrex and won approval on November 23, 1998. Celebrex launched in February 1999 – three months before the FDA approved Vioxx. With Vioxx to be the second market entrant, the Marketing and Sales division aimed to cultivate an “in it to win it attitude.”<sup>3</sup>

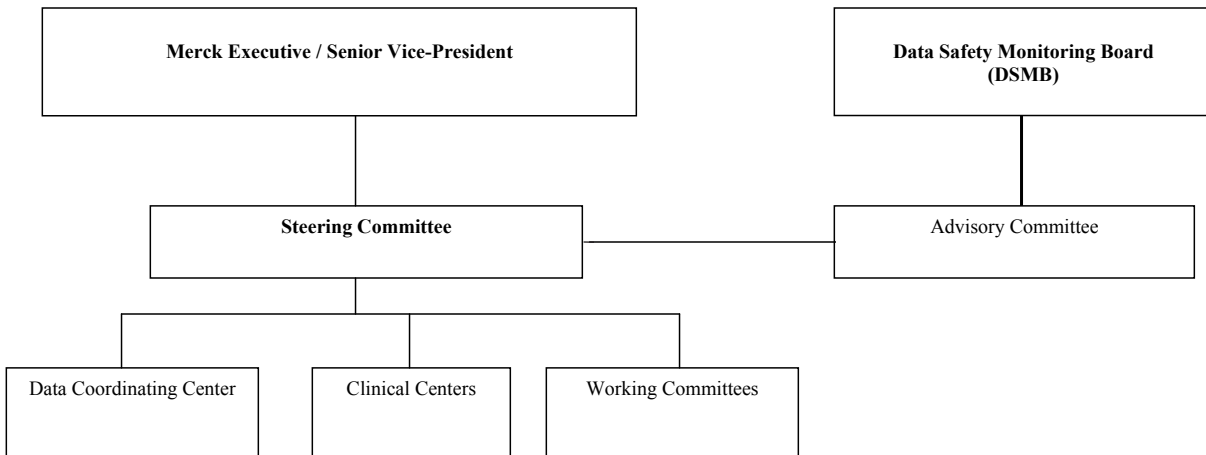
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<sup>1</sup> John S. Martin, Jr., “Appendix B: Pre-Approval Commercial Context,” *Report of John S. Martin, Jr. to the Special Committee of the Board of Directors of Merck & Co., Inc. Concerning the Conduct of Senior Management in the Development and Marketing of Vioxx* (2006), [http://www.merck.com/newsroom/vioxx/pdf/009\\_appendix\\_b\\_pre\\_approval\\_commercial\\_context.pdf](http://www.merck.com/newsroom/vioxx/pdf/009_appendix_b_pre_approval_commercial_context.pdf). (See p. 5.)

<sup>2</sup> *Ibid.* (See p. 7.)

<sup>3</sup> *Ibid.* (See p. 13.)

## Exhibit 2: Organization of Clinical Trials Involving a DSMB



## Exhibit 3: March 27, 2000, Press Release Announces VIGOR Results



News Release

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FOR IMMEDIATE RELEASE

Media Contacts:  
Jan Weiner  
215/652-6462

Mary Elizabeth Basamian  
215/652-5244

Investor Contact:  
Laura Jordan  
908/423-5185

**Merck Informs Investigators of Preliminary Results  
of Gastrointestinal Outcomes Study with VIOXX®**

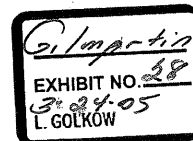
WEST POINT, Pa., March 27, 2000 -- Merck & Co., Inc. today informed its investigators of a preliminary analysis from a large gastrointestinal (GI) outcomes study that compared Vioxx® (rofecoxib) with naproxen in patients with rheumatoid arthritis. Among patients treated with Vioxx, there was a significantly reduced incidence of serious gastrointestinal events compared to patients treated with naproxen. Merck plans to submit the information to the U.S. Food and Drug Administration (FDA) and other regulatory agencies worldwide in the next few months.

In addition, significantly 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. As a result, Merck is notifying investigators, who are conducting other Merck studies with Vioxx or another investigational medicine in the same class, of protocol amendments to allow the addition of low-dose aspirin where appropriate. Patients using low-dose aspirin, which also blocks platelet aggregation, were excluded from the GI outcomes study. Vioxx does not interfere with the ability of low-dose aspirin to block platelet aggregation.

The completed study, called VIGOR (Vioxx Gastrointestinal Outcomes Research), compared the GI safety of Vioxx (50 mg once daily) to prescription-strength naproxen (500 mg twice a day) in approximately 8,000 patients with rheumatoid arthritis. The study specifically assessed the incidence of certain types of clinically significant upper GI events, including perforations, ulcers, obstructions and bleeds. Naproxen is a commonly used non-steroidal anti-inflammatory drug (NSAID) indicated for the treatment of a number of arthritic diseases, including rheumatoid arthritis. Vioxx is not approved for the treatment of rheumatoid arthritis, nor is an application for this use under review. Vioxx is approved in the U.S. for the relief of the

- more -

Vioxx® is the Merck registered trademark for rofecoxib.



MRK-PRL0000114

signs and symptoms of osteoarthritis, management of acute pain in adults and treatment of menstrual pain.

Researchers believe that NSAIDs work by inhibiting two related enzymes: COX-1, the enzyme that helps maintain the stomach lining and promotes platelet aggregation, and COX-2, the enzyme that triggers pain and inflammation. At therapeutic doses, Vioxx works by selectively inhibiting COX-2 without inhibiting COX-1; non-selective NSAIDs like naproxen inhibit both COX-1 and COX-2. Medicines like aspirin and naproxen that significantly inhibit COX-1 block platelet aggregation and therefore have the potential to provide cardioprotection.

An extensive review of safety data from all other completed and ongoing clinical trials, as well as the post-marketing experience with Vioxx, showed no indication of a difference in the incidence of thromboembolic events between Vioxx, placebo and comparator NSAIDs.

Further analyses are ongoing, and final results of the GI outcomes study with Vioxx will be presented at peer-reviewed medical meetings this year.

#### Important information about Vioxx

The recommended dose of Vioxx for the treatment of osteoarthritis is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily.

Serious stomach problems, such as bleeding, can occur without warning symptoms. Administration of low-dose aspirin with Vioxx may result in an increased rate of GI ulcers or other complications compared to use of Vioxx alone. Physicians and patients should remain alert for signs and symptoms of gastrointestinal bleeding.

Common side effects reported in osteoarthritis clinical trials with Vioxx were upper-respiratory infection, diarrhea, nausea and high blood pressure. People who have had an allergic reaction to Vioxx, aspirin or other NSAIDs should not take Vioxx. Safety and effectiveness in children below the age of 18 have not been studied.

Merck & Co., Inc. is a global, research-driven pharmaceutical company that discovers, develops, manufactures and markets a broad range of human and animal health products, directly and through its joint ventures, and provides pharmaceutical benefit services through Merck-Medco Managed Care.

###

Full prescribing information for Vioxx® is attached, and is also available by calling 1-800-753-0352, ext. 726.

MRK-PRL0000115

## Exhibit 4: April 28, 2000, Bulletin with Instructions for the CV Card

*C. J. P.*

No. COX 00-028  
Apr 28, 2000

**Bulletin for VIOXX®:  
NEW RESOURCE: Cardiovascular Card**

**TO:**

All Field Personnel with Responsibility for VIOXX®

**ACTION REQUIRED**

**Background**

The presentation of information regarding the VIGOR and CLASS trials has led to some misunderstanding in the field, as well as with physicians, regarding the cardiovascular effects of VIOXX.

To ensure that you are well prepared to respond to questions about the cardiovascular effects of VIOXX, Team VIOXX has developed a new resource, the Cardiovascular Card. The Cardiovascular Card will allow you to set the record straight with your physicians regarding the cardiovascular profile of VIOXX and how this profile compared to other NSAIDs in OA clinical trials with VIOXX. The Cardiovascular Card is an obstacle handling piece and should only be used with physicians in response to their questions regarding the cardiovascular effects of VIOXX. This bulletin contains a draft version of the Cardiovascular Card and a roadmap to explain the content of the Cardiovascular Card and how to use it to address obstacles from your physicians. This is for your background only. You may not use the Cardiovascular Card or the roadmap with your physicians. You will receive the final printed version of this resource to use with your physicians by Federal Express on Monday.

**Draft of Cardiovascular Card** (Note: The Cardiovascular Card is a tri-fold similar to the Renal Profile Card)



001390(5)\_sprade.pdf

The Cardiovascular Card is a resource which will allow you to address your HI COXIB or HI NSAID physician's concerns regarding the cardiovascular effects of VIOXX. The Cardiovascular Card contains the following information:

- Page 2 shows that patients who were at risk for cardiovascular disease were not excluded from the OA studies with VIOXX. In fact, many patients who were included in the study had risk factors for cardiovascular disease.
- Page 3 shows that the number of cardiovascular thromboembolic events that occurred in OA clinical trials with VIOXX was low and similar to ibuprofen, diclofenac, and nabumetone. Page 3 breaks the information down even further, specifically for MI, stroke, and angina, and shows that VIOXX was similar to comparator NSAIDs and placebo for all these CV events.
- Page 4 shows that the overall and CV mortality rates from the OA clinical trials with VIOXX were low.
- Page 6 shows that in OA clinical trial with VIOXX, the discontinuation rates for patients with hypertension was low, <0.1%. It also shows that the incidence of hypertension in these patients was 3.5% for VIOXX, which was similar to the comparator NSAIDs, diclofenac and ibuprofen.

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Order

MRK-AAR0038843

Please read the attached roadmap for this card. It will help you understand how to use this card to address physician's questions regarding the CV effects of VIOXX.



"CV Roadmap.doc"

If you have any questions regarding this bulletin, please contact the Merck National Service Center at 1-800-NSC MERCK.

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MRK-AAR0038844

**Exhibit 5:**

**May 22, 2001, Press Release Confirms Vioxx Safety  
May 23, 2001, Instructions to Sales Representatives**

No. COX 01-030  
May 23, 2001

**Bulletin for VIOXX®:  
Action Required: Response to New York Times Article**

**TO:**

All Field Representations with Responsibility for VIOXX	Action Required
All Hospital Representatives	Action Required
A & A Specialty Representatives	Action Required
A & A HSAs	Action Required
Urology Representatives	Action Required
Neurology Representatives	Action Required
Managed Care NAEs and Customer Managers (all segments)	Background Information

**DO NOT INITIATE DISCUSSIONS ON THE RESULTS OF THE VIOXX® GI OUTCOMES RESEARCH (VIGOR) STUDY, OR ANY OF THE RECENT ARTICLES IN THE PRESS ON VIOXX. YOU MAY RESPOND TO CUSTOMER INQUIRIES ONLY AS OUTLINED BELOW.**

**PURPOSE:**

To provide you with important background information, obstacle responses and faxable PIR instructions in the event that you are questioned by customers about the CV effects of VIOXX.

**ACTIONS REQUIRED:**

**Obstacle Response #38: (originally issued in Bulletin COX 00-029)**



"Doctor, there are no head-to-head studies comparing the cardiovascular profile of the two drugs. As a result, you cannot compare the drugs and conclude that one drug had fewer events than the other. What you may be referring to is press reports of the incidence rates in two separate studies. In the VIOXX GI Outcomes Trial (VIGOR), the incidence of MI was 0.5% with VIOXX and 0.1% with naproxen. In a separate GI outcomes trial of Celebrex, the CLASS study, Searle has reported that the incidence of MI was 0.5% with Celebrex, 0.3% with diclofenac, and 0.5% with ibuprofen. Again, doctor, I want to emphasize that the results of two different studies can't be compared, and that's particularly true here when you have studies of differing duration and in different patient populations."

**If the doctor asks you further for the incidence of MI from the OA studies presented in the package insert for VIOXX tell them:**



"In the clinical OA trials for VIOXX reported in our package insert, the incidence of MI was less than 0.1% with VIOXX."

Use your CV Card to show the data on studies involving VIOXX and various NSAIDs (ibuprofen, diclofenac, and nabumetone) on overall mortality and CV mortality rates

"Doctor, As you can see, Cardiovascular Mortality as reported in over 6,000 patients was VIOXX .1 vs. NSAIDs .8 vs. Placebo 0."

**Physician Inquiries:**

*In response to unsolicited requests for information regarding the recent press releases, Medical Services will make a personalized, faxable PIR available for your customers within 24 hours. In addition, for those customers who request more detailed information, a separate, more comprehensive PIR packet can be Federal Expressed within 2 days.*

Medical Services has made arrangements to extend the hours for the PIR hotline. Representatives should submit unsolicited PIR requests by either telephone or fax options by calling the PIR hotline 800MERCK66 (800-637-2566) during extended hours of 8:30 am to 6:30pm ET. During these hours, a staff member will verbally request the following information from you to process the PIR request from the HCP [After this time, the usual method options of INSIGHT, PIR hotline (800MERCK 66 – hours: 8:30 – 4:30pm ET) and fax can be followed].

**Faxable PIR Instructions:**

- Your name, field title and RDT
- The requesting HCP's full name and professional degree
- HCP's full mailing address
- HCP's phone number
- HCP's FAX number
- Provide the question(s) asked by the HCP.

*PIR Requests may also be sent to Medical Services from 4:30 pm – 8:30am ET by leaving a voice message at 800MERCK66. The information as listed above should be provided in your voice message to Medical Services staff. Additionally, PIR requests may be submitted to Medical Services in writing by sending a fax to 800MERCK68. The information listed above should be included on your fax to Medical Services.*

- If requested, a PIR will be faxed within 24 hours of receiving the request.
- If the physician requests more comprehensive information on the cardiovascular safety profile of VIOXX, you may request the comprehensive PIR. This will be sent via Fed EX within 2 days.
- Transition your discussion to the current strategy and messages for VIOXX®.

Do not proactively discuss any of the recent press stories. Respond to questions by requesting a PIR and in accordance with the obstacle-handling guide.

**This information is provided for your background information *only* and is not to be used in discussions with physicians. The following press release was issued in response to an article in Tuesday's New York Times on the cardiovascular effects of VIOXX.**

**Background Information:**

Tuesday May 22, 1:21 pm Eastern Time

Press Release

SOURCE: Merck & Co., Inc.

**Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx(R)**

UPPER GWYNEDD, Pa., May 22 /PRNewswire/ – In response to news and analyst reports of data the Company first released a year ago, Merck & Co., Inc. today reconfirmed the favorable cardiovascular safety profile of Vioxx® (rofecoxib), its medicine that selectively inhibits COX-2. Vioxx was approved by the Food and Drug Administration in May 1999 for the management of osteoarthritis and the relief of acute pain in adults based on efficacy and safety studies involving nearly 4,000 patients. More than 33 million prescriptions have been written for Vioxx in the United States since its introduction.

The results of the Vioxx Gastrointestinal Research study were first released in March 2000. Since that time, the data have been widely reported, published in *The New England Journal of Medicine* and discussed extensively by an FDA Advisory Committee.

In VIGOR, Vioxx 50 mg, a dose two-times the highest chronic dose approved for osteoarthritis, significantly reduced the risk of serious GI side effects by half compared to a commonly used dose of naproxen (1,000 mg) in rheumatoid arthritis patients. The Advisory Committee recommended that these results be included in the labeling for Vioxx. Vioxx is not indicated for rheumatoid arthritis.

Although the VIGOR study was a GI outcomes study and was not designed to show differences in cardiovascular effects, significantly fewer heart attacks were observed in patients taking naproxen (0.1 percent) compared to the group taking Vioxx 50 mg (0.5 percent) in this study. There was no difference in cardiovascular mortality between the groups treated with Vioxx or naproxen. Patients taking aspirin did not participate in VIGOR.

In extensive discussions, the Advisory Committee explored this finding, other studies of Vioxx and possible explanations for this result in VIGOR. In the completed osteoarthritis trials and on-going clinical trials with Vioxx 12.5 mg, 25 mg and 50 mg in 30,000 patients, there was no difference in the incidence of cardiovascular events, such as heart attacks, among patients taking Vioxx, other NSAIDs and placebo.

At the Advisory Committee meeting, Merck scientists said the VIGOR finding is consistent with naproxen's ability to block platelet aggregation by inhibiting COX-1 like aspirin, which is used to prevent second cardiac events in patients with a history of heart attack, stroke or other cardiac events. This is the first time this effect of naproxen on cardiovascular events has been observed in a clinical study. Other potential explanations were advanced by the FDA reviewer and were discussed with the Advisory Committee. The Committee recommended that the data on cardiovascular events in VIGOR be included in the labeling for Vioxx.

In addition, the Committee agreed that the prescribing information for both Vioxx and Celebrex® (celecoxib) should reflect the fact that neither of these selective NSAIDs confer cardioprotective benefits and are not a substitute for low-dose aspirin. The Committee also recommended that other studies be conducted to further explore the safety of concomitant use of selective NSAIDs and low-dose aspirin.

In a separate GI outcomes study in osteoarthritis and rheumatoid arthritis patients, celecoxib, another agent that selectively inhibits COX-2, was compared to the NSAIDs diclofenac and ibuprofen. Pharmacia, maker of celecoxib, has indicated that there were no differences among celecoxib, ibuprofen and diclofenac on these cardiovascular events. In Pharmacia's background package submitted to the FDA for the Advisory Committee meeting, the incidence of patients taking celecoxib who experienced a heart attack was cited as 0.5 percent, 0.3 percent among diclofenac patients, and 0.5 percent among patients taking ibuprofen.

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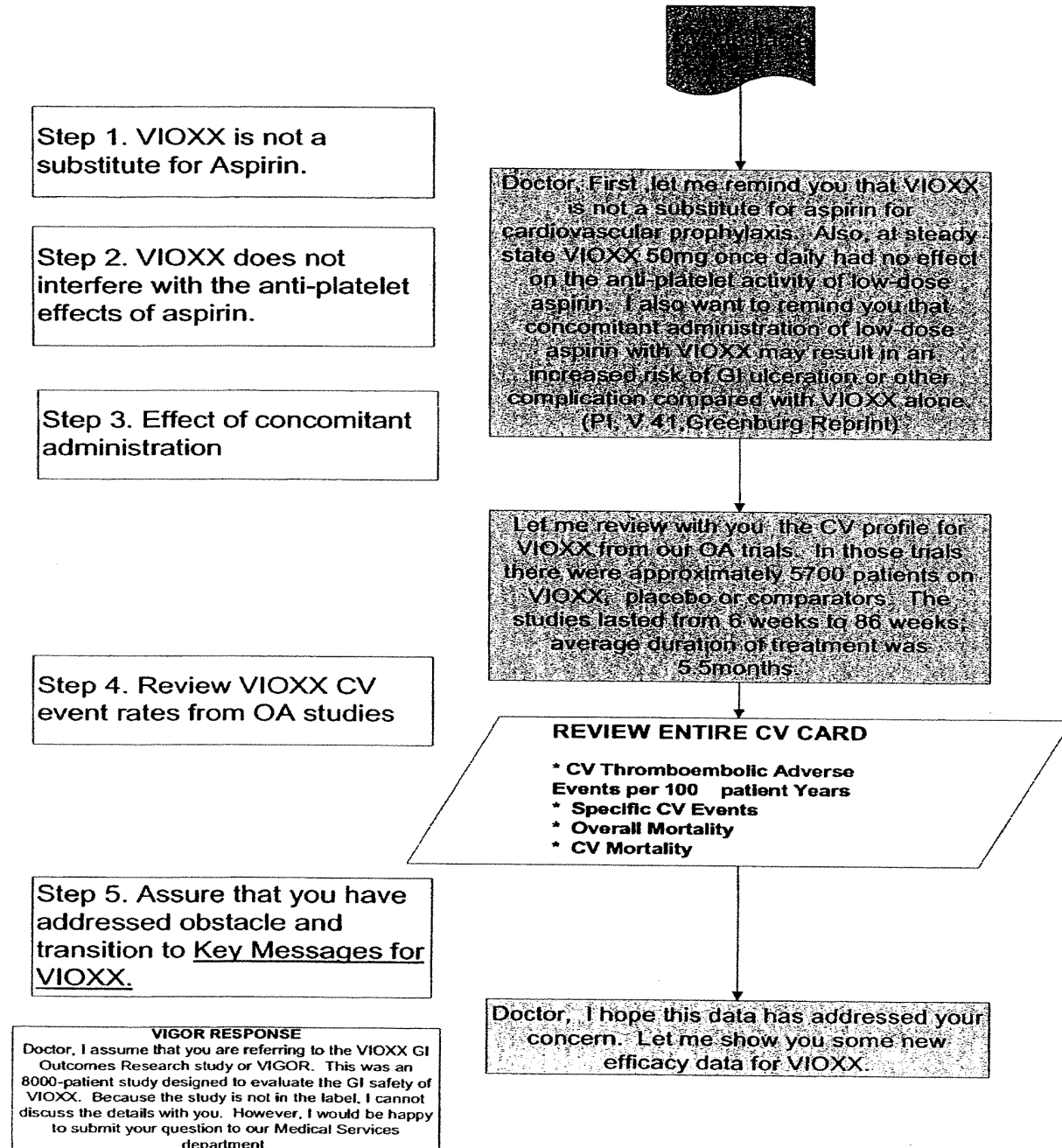
**Focus:**

**Remain focused on your efficacy messages for VIOXX. Remember that the primary attribute for physicians and patients is pain relief.**

**For product and service information, call the Merck National Service Center at 1-800-NSC MERCK (1-800-672-6372).**

Exhibit 6: CV Obstacle Response Tip Sheet

## CV OBSTACLE RESPONSE



For background use only. This document not to be shown to or used in discussions with customers

## Exhibit 7: Timeline of Events<sup>1</sup>

November 1998	Merck asks the Food and Drug Administration (FDA) for approval of the painkiller Vioxx, having tested the drug on 5,400 subjects in eight studies.
January 1999	Merck launches the Vioxx Gastrointestinal Outcomes Study (VIGOR). The study has 8,000 participants, with half taking Vioxx and the other half naproxen. The trial is designed to see whether Vioxx is safer for the digestive system than naproxen.
May 1999	The FDA approves Vioxx, making the drug available by prescription.
October 1999	The VIGOR DSMB board holds its first meeting. Study results as of 10/1/99 indicate that Vioxx patients have fewer ulcers and less gastrointestinal bleeding than patients taking naproxen.
November 1999	At the second meeting of the VIGOR safety panel, the discussion focuses on cardiovascular risks. As of 11/1/99, 79 patients out of 4,000 taking Vioxx have had serious heart problems or died, compared with 41 taking naproxen.
December 1999	The safety panel holds its last meeting. It notes that as of 12/1/99, the risk of serious heart problems and death among Vioxx patients is twice as high as in the naproxen group.  The DSMB votes to continue the study, but decides Merck needs to develop a plan to study cardiovascular risks.  Later, when defending its decision to continue the study, the DSMB said it could not tell if Vioxx was causing the heart problems or if naproxen, acting like low-dose aspirin, protected people from them.
January 2000	Merck balks at developing the DSMB-suggested analysis plan. DSMB chair Weinblatt, pushes for immediate analysis.
February 2000	Merck and Weinblatt agree to analyze heart problems by 2/10/2000, a month before the last patient leaves the study.
February 15, 2000	Weinblatt agrees to a new consulting contract with Merck.
March 2000	Merck gets the results of the VIGOR trial.
May 2000	Merck submits the VIGOR results paper to the New England Journal of Medicine for publication.
January 2002 - August 2004	Numerous epidemiological studies point to Vioxx's increased risk of cardiovascular problems.
September 2004	Merck withdraws Vioxx from the market.

<sup>1</sup> Timeline is adopted from the following: Prakash, Snigdha and Vikki Valentine. "Timeline: The Rise and Fall of Vioxx." N.D. National Public Radio. <http://www.npr.org/templates/story/story.php?storyID=5470430>

## Exhibit 8

### Acronyms

CV	Cardiovascular event
DSMB	Data Safety and Monitoring Board
FDA	Federal Drug Administration
HHPAC	Human Health Product Approval Committee at Merck
NSAID	Non-steroidal anti-inflammatory drugs
VIGOR	Vioxx Gastrointestinal Outcomes Research

### Key Participants

Briggs Morrison	Associate Director at Merck Research Laboratories
Carlo Patrono	Antiplatelet specialist and consultant to Merck
Alice Reicin	Merck clinical monitor for the DSMB; Steering Committee member
Ed Scolnick	President of Merck Research Laboratories; member of the Merck Board of Directors; chair of the HHPAC
Deborah Shapiro	Merck statistician, assigned to full-time support of the DSMB and served as liaison between the DSMB, Reicin, and Merck executives
Michael Weinblatt	Rheumatologist at Brigham & Women's Hospital, Boston; Chair of the VIGOR DSMB