Report of The Honorable 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

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DEBEVOISE & PLIMPTON LLP

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INTRODUCTION

This Report arises from Merck's announcement on September 30, 2004 that it was voluntarily withdrawing Vioxx from the market in light of new data from a Merck-sponsored clinical trial suggesting that Vioxx increased patients' relative risk of cardiovascular adverse events (such as heart attacks and strokes) after 18 months of continuous use. Merck's voluntary withdrawal of Vioxx – a widely used prescription pain medication – triggered immediate, extensive and often negative comments in the media and in personal injury cases against the Company suggesting that members of the Company's senior management were aware that Vioxx posed serious cardiovascular risks to patients and deliberately hid this fact from the public.

As described below, a Special Committee of the Board of Directors of Merck commissioned The Honorable John S. Martin, Jr., Of Counsel to Debevoise & Plimpton LLP, to conduct an independent investigation of senior management's conduct with respect to the cardiovascular safety profile of Vioxx during the period that Vioxx was developed and marketed.[1] Judge Martin and a team of lawyers and paralegals from Debevoise (collectively "Debevoise") spent over 53,000 hours conducting the investigation over a period of approximately twenty months.

In attempting to present the results of the investigation in a manner that is both concise and comprehensive, we have determined that it is best to limit the body of this

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[1] Prior to joining the litigation department of Debevoise in 2003, Judge Martin, among various other positions, served for thirteen years as a United States District Judge for the Southern District of New York and for three years as the United States Attorney for the Southern District of New York.

Report to a summary of the principal allegations of wrongdoing that have been made against Merck and our findings and conclusions with respect thereto and to attach to the Report a series of Appendices that discuss in great detail all of the key actions of Merck employees with respect to Vioxx both internally and in their communication with the United States Food and Drug Administration (the "FDA"), the scientific community and the public at large. This Introduction (i) provides a brief overview of the scientific issues involved, (ii) discusses the formation and mandate of the Special Committee, and (iii) details the scope and conduct of our investigation, including the materials reviewed. The Report then describes the central criticisms asserted against the Company and senior management and presents our findings and conclusions with respect to each such criticism.

I.

OVERVIEW OF SCIENTIFIC ISSUES.

Vioxx, an anti-inflammatory agent indicated for the treatment of arthritis, acute pain, and primary dysmenorrhea, was one of a new class of drugs known as "selective Cox-2 inhibitors" that first were introduced to the market in the late 1990s. The science behind selective Cox-2 inhibitors was new and developing when Vioxx and its leading competitor, Searle/Pfizer's Celebrex,[2] were launched, and the scientific community's understanding of how selective Cox-2 inhibitors operate has continued to evolve.

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[2] Searle and Pfizer co-developed Celebrex in the mid-1990s. At the time, Searle was the pharmaceutical business unit of Monsanto Company. In April 2000, Pharmacia & Upjohn merged with Monsanto and Searle creating Pharmacia Corporation. Pharmacia agreed to continue Searle's agreement with Pfizer to co-promote Celebrex. In April 2003, Pharmacia and Pfizer merged and

Before selective Cox-2 inhibitors were developed, the leading drugs on the market for the treatment of arthritis were non-selective non-steroidal anti-inflammatory drugs ("NSAIDs") – such as aspirin, ibuprofen and naproxen – that operated by inhibiting an enzyme in the human body called cyclooxygenase ("Cox"). While traditional non-selective NSAIDs were effective at relieving pain and inflammation, they often led to gastrointestinal side-effects such as ulcers, perforations and bleeds that were associated with thousands of deaths each year and severely compromised many patients' quality of life. As a result, the FDA required all NSAIDs to include a warning in the label or package insert concerning gastrointestinal side-effects (the "NSAID-class gastrointestinal warning").

In the early 1990s, however, scientists discovered that the human body creates two isoforms of cyclooxygenase: (i) Cox-1, which protects the lining of the gastrointestinal tract from ulcers and related injury; and (ii) Cox-2, which is expressed at sites of pain and inflammation. Scientists theorized that a drug targeted at suppressing Cox-2 alone would provide the relief from pain and inflammation of traditional non-selective NSAIDs (those that inhibited both Cox-1 and Cox-2) without inhibiting Cox-1's protective effect on the stomach lining. This breakthrough led to the development of selective Cox-2 inhibitors.

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began operating as Pfizer. http://www.pfizer.com/pfizer/history/2003.jsp. We refer to either or both companies as Searle/Pfizer in connection with Celebrex in this Report.

In late 1997, before Vioxx was approved for sale in the United States, Dr. Garret FitzGerald*, a highly regarded expert on prostaglandins at the University of Pennsylvania and a long-time consultant to Merck Research Laboratories ("MRL"), raised a theoretical question about the cardiovascular safety of Vioxx and other selective Cox-2 inhibitors. The question arose from a clinical trial that Dr. FitzGerald* had conducted with Vioxx (and a similar trial that he had conducted with Celebrex) in which he found that inhibition of Cox-2 suppressed urinary excretion of a metabolite of prostacyclin, a hormone-like substance that dilates blood vessels and inhibits blood clotting. Some scientists, including Dr. FitzGerald*, theorized that this meant that suppression of Cox-2 inhibited the creation of prostacyclin in the vasculature. Scientists previously had known that Cox-1 mediates the production of thromboxane, a counterpart to prostacyclin that has the opposite effect: it constricts blood vessels and promotes clotting. Dr. FitzGerald* thus hypothesized that by inhibiting Cox-2 and not Cox-1, selective Cox-2 inhibitors might cause an imbalance between prostacyclin and thromboxane that could place patients in a prothrombotic state and thus put them at increased risk for heart attacks and strokes (the "FitzGerald prostacyclin hypothesis"). Merck's clinical outcomes data on Vioxx did not at that time provide any support for Dr. FitzGerald's* hypothesis, nor did Merck have any other evidence to suggest that Vioxx was prothrombotic in humans.

The FDA approved Vioxx in May 1999, five months after it had approved Celebrex. One of Merck's principal regulatory and marketing objectives for Vioxx was

* Throughout this Report, we identify scientists and others external to Merck with an "*" following their name.

to prove to the FDA's satisfaction that Vioxx caused fewer gastrointestinal side effects than traditional non-selective NSAIDs and thus that the FDA should not require Vioxx to carry the standard NSAID-class gastrointestinal warning included on all NSAID labels. Although Merck had hoped that the FDA would agree based on then-available clinical data that Vioxx did not require the standard warning, the FDA believed that additional data would be required in order to eliminate the warning.

In 1999, Merck commenced a clinical trial in rheumatoid arthritis patients, called the Vioxx Gastrointestinal Outcomes Research trial (the "VIGOR Trial"), to determine if Vioxx provided greater gastrointestinal safety than naproxen, a traditional non-selective NSAID. Data from the trial were blinded (meaning that MRL did not know which patients were receiving Vioxx and which were receiving naproxen) until March 9, 2000.

The VIGOR Trial proved the Cox-2 hypothesis – that Vioxx caused fewer gastrointestinal complications than the non-selective NSAID comparator – but a statistically significantly greater number of patients in the Vioxx group of the trial experienced a serious cardiovascular adverse event than in the naproxen group. Although the absolute numbers were small – based on unadjudicated data available in March 2000, 92 of the 4,047 patients in the Vioxx arm of the study were reported to have experienced a serious cardiovascular event compared to 46 of the 4,029 patients in the naproxen arm – the VIGOR Trial data raised a serious, and no longer merely theoretical, question about the cardiovascular safety of Vioxx.

After reviewing the VIGOR Trial data in detail and analyzing data from a number of other Merck clinical trials, including two ongoing trials that tested Vioxx against

placebo, scientists at MRL came to the view that the between-treatment difference in the cardiovascular event rates most likely was caused not by any prothrombotic effect of Vioxx but instead by a cardioprotective effect of the comparator drug, naproxen. Traditional NSAIDs were long understood to temporarily block platelet aggregation due to their inhibition of Cox-1, although none except aspirin had been proven in large clinical trials to provide cardioprotection. Because naproxen was one of the longest-acting traditional non-selective NSAIDs and provided a relatively high degree of platelet inhibition, MRL scientists believed that its antiplatelet effects had provided cardioprotection to patients in the naproxen arm of the trial. In other words, they came to believe that Vioxx had not increased the incidence of cardiovascular events, but that naproxen had reduced it.

Merck submitted to the FDA complete data from the VIGOR Trial, including cardiovascular data up through the February 10, 2000 reporting cut-off date, in June 2000. In February 2001, the FDA convened an Advisory Committee to review, among other things, results of the VIGOR Trial. The FDA medical reviewers involved in the label negotiations did not agree with Merck that the VIGOR Trial cardiovascular data could be explained simply by a cardioprotective effect of naproxen, noting that no such protective effect of naproxen had been demonstrated in any prospectively designed clinical trial. The FDA medical reviewers tasked with reviewing data from the VIGOR Trial and other Merck clinical trials did not think that the existing data were sufficient to show that Vioxx did not increase cardiovascular risk. When Merck and the FDA in April 2002 reached agreement on changes to the Vioxx label to reflect data from the VIGOR

Trial, the revised label included cardiovascular information in the "Precaution" section, but not in the "Warning" section, and did not make reference to naproxen cardioprotection as an explanation for the VIGOR Trial cardiovascular results.

From March 2000 through September 2004, the scientific community debated the meaning and importance of the VIGOR Trial cardiovascular data. Scientists, including MRL scientists, conducted a number of epidemiological (or observational) studies regarding the cardiovascular profiles of Vioxx and naproxen. These studies generated inconsistent results. MRL scientists continued to analyze pooled cardiovascular data from the Vioxx clinical program, which they believed confirmed that Vioxx did not pose a cardiovascular risk and that the cardiovascular differential seen in the VIGOR Trial was attributable to a protective effect of naproxen.

In late 2002, Merck instituted a study called Protocol 203 that would combine and analyze cardiovascular data from three placebo-controlled clinical trials – the Adenomatous Polyp Prevention on Vioxx trial (the "APPROVe Trial"), the Vioxx Prostate Cancer Prevention trial (the "ViP Trial") and the Vioxx Colorectal Cancer Therapy Optimal Regime trial (the "VICTOR Trial") – that were designed to test the efficacy of Vioxx in preventing certain cancers. In September 2004, the External Safety Monitoring Board for the APPROVe Trial noted that the difference in the incidence of cardiovascular events between the Vioxx and placebo arms of the study, which the Board members had been monitoring for some time, was statistically significant. Although the APPROVe Trial, which had enrolled patients for a 36-month period, was just weeks from completion, the External Safety Monitoring Board recommended, based on the

cardiovascular data, that the study be stopped and that MRL scientists be unblinded to the data.

After reviewing the cardiovascular data from the APPROVe Trial, Dr. Peter Kim, who became the President of MRL in 2002, recommended that Vioxx be withdrawn from the worldwide market, a conclusion that Merck's Management Committee and Board of Directors endorsed.

These events have given rise to a host of criticisms of and allegations against the Company and its senior management. In connection with our investigation, Debevoise has collected and reviewed such criticisms, including those expressed in newspapers, in scientific journals, in pleadings filed in personal injury and shareholder litigation, in expert reports, at trials, and by members of Congress.

II.

FORMATION AND MANDATE OF THE SPECIAL COMMITTEE.

Within weeks of Vioxx's withdrawal, the number of personal injury lawsuits filed against Merck soared. In addition, the United States Securities and Exchange Commission ("SEC"), the United States Department of Justice ("DOJ"), the FDA, and three separate Congressional committees began to investigate the cardiovascular risks associated with Vioxx and the Company's development, testing and marketing of the product. On October 29, 2004, Merck's Board of Directors received a letter from a lawyer representing Merck shareholders who demanded that the Board "take legal action against Raymond V. Gilmartin, the Chairman of the Board, Chief Executive Officer and

President of the Company and any other individuals responsible for causing the damage to the Company with respect to any improper marketing of Vioxx."[3]

In light of these developments, on November 23, 2004, Merck's Board of Directors formed a Special Committee of six outside directors to conduct an internal investigation of senior management's conduct with respect to Vioxx.[4] In light of "the Board's responsibility to examine and resolve whether management properly executed its duties with respect to the study and disclosure of the cardiovascular safety profile of Vioxx," the Special Committee was instructed to "make recommendations to the full Board on the appropriate disposition of shareholder demands and other requests to the Board related to Vioxx."[5]

The Board authorized the Special Committee to retain outside counsel and other consultants, as necessary. On December 6, 2004, Judge Martin and Debevoise were retained to conduct a comprehensive investigation of the actions of Merck's senior management prior to Merck's voluntary withdrawal of Vioxx and to provide other legal advice to the Committee.

On May 22, 2006, MRL scientists became aware of an error in an article describing the APPROVe Trial cardiovascular data that had been published in the New

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3 10/29/04 demand letter from J. Abraham* (on behalf of E. Fagin* and J. Fagin*) to the Board of Directors of Merck.

4 The Special Committee is composed of: William G. Bowen (Chairman), Lawrence A. Bossidy, William N. Kelley, Rochelle B. Lazarus, Samuel O. Thier, and Peter C. Wendell.

5 Minutes of 11/23/04 Merck Board of Directors meeting, MRK-MIAA0004155, at 56.

England Journal of Medicine in February 2005. Because the error was potentially relevant to the accuracy of certain of the article's conclusions, it was brought to the attention of the full Board on May 23, 2006 at a regularly scheduled meeting. At that meeting, the Board extended the Special Committee's mandate to include investigation of the error in the APPROVe article and, more broadly, review of post-withdrawal analyses and reporting of cardiovascular data arising from the APPROVe Trial. The Special Committee in turn directed Judge Martin and Debevoise to extend the investigation.

III.

SCOPE AND CONDUCT OF THE INVESTIGATION.

From the outset, the Special Committee's overarching directive to Judge Martin was to conduct a comprehensive, independent and objective investigation. Judge Martin was instructed to evaluate and report on senior management's integrity with regard to the development, testing and marketing of Vioxx and, in particular, to determine whether management acted ethically and with scientific integrity in analyzing cardiovascular-related clinical data, in establishing clinical trials to investigate any cardiovascular risks, in reporting cardiovascular-related data to the FDA, in communicating the cardiovascular data accurately to the public, and in describing the cardiovascular risk in product labeling.

Judge Martin also was instructed to evaluate the accuracy and integrity of Merck's press releases relating to Vioxx's cardiovascular profile, to determine whether senior management inappropriately attempted to influence the Company's scientific beliefs with respect to Vioxx's cardiovascular profile, and to determine whether senior

management's directions to sales and marketing personnel accurately reflected the Company's scientific beliefs at the time.

The Special Committee further instructed Judge Martin and the Debevoise team (i) to collect and review all relevant documents, both from within the Company and in the possession of advisors, counsel and other third parties who might have relevant information,[6] and (ii) to conduct interviews of Company directors, employees and others who might have information relevant to the investigation.

In addition, the Special Committee authorized Debevoise to retain expert consultants to assist in its evaluation and analysis of scientific and regulatory issues. With the advice and consent of the Special Committee, Debevoise retained (i) Dr. R. Wayne Alexander*, a prominent cardiologist who chairs the Department of Medicine at Emory University's School of Medicine; (ii) Nancy L. Buc*, Esq., former Chief Counsel to the FDA, a recognized expert on FDA regulatory matters and a member of the law firm Buc & Beardsley; and (iii) Dr. Ralph B. D'Agostino, Sr.*, a leading biostatistician who is Professor of Mathematics, Statistics and Public Health at Boston University, Director of the Boston University Statistics and Consulting Unit, and co-principal investigator of the Framingham Heart Study contract, with the assistance of Dr. Michael Pencina*, who is Research Assistant Professor of Statistics at Boston University's Statistics and Consulting Unit.

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[6] We have not reviewed any documents that the Company has claimed are protected by the attorney-client privilege or the work product doctrine. The Special Committee retained special counsel to review these documents.

The Special Committee asked to be kept apprised of the progress of the investigation and to be notified immediately of any evidence that appeared to reflect negatively on the integrity of senior management. The Special Committee also asked for and received monthly progress reports. Throughout the investigation, Judge Martin was instructed to report all findings to the Special Committee candidly and objectively without regard to the potential consequences to the Company or any of its current or former directors, officers or employees.

IV.

MATERIALS REVIEWED.

A. Documents Produced by Merck in Products Liability Cases, Shareholder and ERISA Litigation and Government Investigations.

As indicated above, the Special Committee's investigation did not occur in a vacuum: beginning prior to and continuing throughout the investigation, Merck was engaged in products liability and shareholder litigation with thousands of plaintiffs around the country and was the subject of investigations by the SEC, the DOJ, the FDA and three Congressional committees: (i) the Senate Committee on Finance, chaired by Senator Charles E. Grassley*; (ii) the House Committee on Government Reform, chaired by Congressman Tom Davis*; and (iii) the House Committee on Energy and Commerce, chaired by Congressman Joseph L. Barton*.

In responding to discovery requests by civil plaintiffs and to government and Congressional subpoenas, the Company has produced over 23 million pages of documents, computer files and electronic mail, including, but not limited to: Board

materials; files (including electronic mail files) of current and former Merck employees who were principally involved in developing, testing or marketing Vioxx; minutes, notes and other records of all meetings of Merck's cross-disciplinary and departmental committees involved in the development, testing and marketing of Vioxx; FDA submissions and correspondence concerning Vioxx; Vioxx-related marketing and sales materials; press releases and other public statements concerning Vioxx; SEC filings made during the relevant period; published articles, clinical trial protocols, clinical trial data, standard operating procedures, data analysis plans and adverse event reports relating to Vioxx clinical trials; other internal Merck communications concerning the development, testing, marketing and withdrawal of Vioxx; communications concerning the drafting of, and subsequent correction to, the article on the APPROVe Trial published in the New England Journal of Medicine; and Merck's post-withdrawal analysis and reporting of cardiovascular data arising from the APPROVe Trial.

B. Documents Submitted by Merck to the FDA in Connection with Advisory Committee Meetings Related to Vioxx.

Between April 1999 and February 2005, the FDA convened three expert panels, consisting of outside independent experts, to review certain safety issues relating to Vioxx. These panels, called Advisory Committees, provide the FDA with the benefit of receiving outside expert recommendations. In general, the Committees invite pharmaceutical company scientists and FDA reviewers to make written submissions about the issue under review, and then hold public hearings, which are transcribed. The FDA Advisory Committees then make recommendations to the FDA.

The first such Advisory Committee meeting concerning Vioxx was held on April 20, 1999, to discuss the original New Drug Application for Vioxx. The second Advisory Committee meeting was convened on February 8, 2001, to review the data from the VIGOR Trial and Merck's supplemental New Drug Application for Vioxx. The third meeting was held from February 16 through 18, 2005, after Vioxx was withdrawn from the market, for the purpose of reviewing and evaluating the safety of the entire class of selective Cox-2 inhibitors, including whether to recommend that the FDA allow Vioxx to be marketed again.

On February 18, 2005, the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee recommended at a joint meeting by a vote of 17-to-15 that Vioxx be allowed back on the market with appropriate warnings.[7] The findings and recommendations of the joint Advisory Committee were then reviewed by the FDA, which issued a memorandum on April 6, 2005 discussing the results of its review.[8]

Debevoise reviewed all background materials submitted by Merck to the three Advisory Committees, reviewed the hearing transcripts and, in the case of the February 2005 Joint Advisory Committee, attended the hearings and reviewed the findings and position statements.

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[7] Minutes of 2/16/06 – 2/18/06 Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, MRK-AID0012816, at 27-28.

[8] 4/6/05 memorandum from J. Jenkins* and P. Seligman* (FDA Position Paper), MRK-AFK0222697-715.

C. Documents Collected from External Sources.

Debevoise also reviewed Vioxx-related materials collected from sources external to Merck. These materials included (i) scientific literature concerning Vioxx, other selective Cox-2 inhibitors and non-selective NSAIDs, including journal articles published before and during the investigation, (ii) documents produced by third parties in the civil litigation, (iii) press coverage concerning Vioxx, (iv) a large sampling of the personal injury and securities-related complaints filed against Merck in state and federal court, and (v) expert reports filed in connection with civil complaints.

V.

WITNESSES INTERVIEWED AND PRIOR TESTIMONY.

Over the course of the investigation, Debevoise interviewed approximately 115 people, including Merck employees, former employees, directors and outside consultants to Merck, and conducted many follow-up interviews, for a total of over 150 interviews. Exhibit 2 to this Report identifies all persons interviewed by Debevoise.

In addition, Debevoise reviewed the testimony of approximately 70 Merck witnesses who testified at civil depositions, before the FDA or before Congressional committees, and reviewed all exhibits used in connection with such testimony. Debevoise also monitored closely the eight Vioxx-related personal injury trials that occurred during the course of our investigation: Ernst v. Merck (Texas state court); Humeston v. Merck (New Jersey state court); Plunkett v. Merck (federal court in Texas); Garza v. Merck (Texas state court); McDarby/Cona v. Merck (New Jersey state court);

Doherty v. Merck (New Jersey state court); Grossberg v. Merck (California state court); and Barnett v. Merck (federal court in Louisiana).

As is true in any non-governmental investigation, Debevoise did not have subpoena power and therefore was dependent upon the voluntary cooperation of persons with relevant information. Although the vast majority of the people we contacted took the time to speak with us, a small number of former Merck employees, including Drs. Carolyn Cannuscio, Laura Demopolous, Peter DiBattiste, Karen Grosser, Eve Slater and Rhoda Sperling, were not willing to take the time. Although interviewing these witnesses might have enhanced our understanding of certain relevant facts and assisted our investigation, in light of the substantial information and evidence, including documentary evidence, to which Debevoise had access, we believe it unlikely that interviewing any of these former employees would have revealed new or different facts that would materially alter our conclusions.

VI.

THE SCOPE AND FORMAT OF THIS REPORT.

The Special Committee's principal concern was to determine whether senior management of the Company acted with integrity throughout the period that Vioxx was developed and marketed to the public. Thus, the Committee directed Judge Martin and the Debevoise team to focus on whether anyone in senior management believed that Vioxx was prothrombotic, intentionally acted to deceive the FDA or the public concerning the safety of Vioxx, or failed or refused to perform necessary tests or clinical trials in order to avoid disclosing suspected or demonstrated safety risks.

The Committee did not ask us to attempt to second guess decisions concerning the development or marketing of Vioxx that were made in good faith. This Report will not attempt, therefore, to pass judgment on the wisdom of each of the actions that Merck employees took in the course of the development and marketing of Vioxx.

We should note also that our investigation has focused on the issue of intentional wrongdoing and that we have not attempted to answer the question whether the conduct of Merck's employees should give rise to civil liability. As the results in the Vioxx civil litigation have demonstrated, different juries under different legal instructions have reached, and may continue to reach, different conclusions concerning the same conduct.

We have set forth in exhaustive detail in the twenty Appendices to this Report all of the relevant events in the development and marketing of Vioxx for two important reasons: First, in judging whether Merck's senior management acted with integrity with respect to any particular matter, it was important to understand the overall factual context in which they were operating. For example, in determining whether someone deliberately attempted to hide a critical fact when that fact was not disclosed in a particular document, it is important to know whether that same person disclosed that fact in another document or in other contexts. Similarly, whether a person's statement of an opinion was intended to deceive may depend upon the extent to which the person making the statement disclosed all of the data necessary to evaluate that opinion.

Second, and perhaps most important, we recognize that given the extensive controversy that has developed concerning Merck's actions with respect to Vioxx, the Board may determine to release our Report to the shareholders and the public. The

authors of this Report have had enough experience in dealing with matters of public concern to know that the mere fact that a particular lawyer or group of lawyers has come to a conclusion will not put to rest the public's concern about a particular controversy. Thus, it is important for the public to have as extensive a record as possible against which it can judge the conclusions we reach herein. It is our hope that by providing a very detailed set of Appendices, we will enable all of those who have serious questions about the conduct of Merck's management to draw their own conclusions based on the facts as we have set them forth. We obviously hope that they will agree with our conclusions, but, at a minimum, we hope that they will agree that we have engaged in a rigorous and comprehensive review of the facts and have set forth those facts in an unbiased manner that will allow others to formulate their own conclusions.

OUR FINDINGS

VII.

THE OVERARCHING ISSUES.

The leitmotif of Merck's critics is that MRL scientists knew that Vioxx was prothrombotic, or, at the very least, that there was a substantial likelihood that it was prothrombotic, and hid that fact from the public until the drug's withdrawal in September 2004. Critics contend that senior officials at Merck knowingly put patients at risk of cardiovascular events rather than jeopardize the profits that Merck generated from the sale of Vioxx. After an exhaustive investigation, we have concluded that there is no basis for such a claim.

In September 2004, when Dr. Peter Kim, the head of MRL, first informed Mr. Raymond Gilmartin, Merck's Chairman, that preliminary results from the APPROVe Trial indicated that Vioxx might be prothrombotic and that he was convening a group of scientists and outside advisors to review the data, Mr. Gilmartin's response was that Merck would put patient safety first, whatever the results. A few days later, on the recommendation of Dr. Kim, Mr. Gilmartin endorsed the decision to withdraw Vioxx from the market, even though some outside scientific advisors recommended keeping it on the market with a stronger cardiovascular warning. The Board of Directors ratified this decision on September 28, 2004, and Vioxx was withdrawn from the worldwide market on September 30, 2004.

In large measure, the most dramatic evidence cited by Merck's critics in support of the claim that MRL scientists knew that Vioxx was prothrombotic consists of statements by MRL scientists taken out of context. For example, newspaper articles have quoted repeatedly from an email sent by Dr. Scolnick (the head of MRL until 2002) on March 9, 2000, the same day that he received the initial results of the VIGOR Trial, in which he stated: "The CV events are clearly there. . . . It is a shame but it is a low incidence and it is mechanism based as we worried it was . . . . [T]here is always a hazard."[9] Indeed, Dr. Scolnick has testified that his immediate reaction to the VIGOR Trial results was that the entire class of selective Cox-2 inhibitors then on the market might be prothrombotic.

By the end of March 2000, however, after reviewing and analyzing a substantial amount of information, including data from other Merck trials, Dr. Scolnick and other MRL scientists became comfortable that the between-treatment difference in cardiovascular events in the VIGOR Trial was most likely caused by the cardioprotective effects of naproxen. Nonetheless, Dr. Scolnick continued to consider the meaning of the data. On April 12, 2000, he wrote to another MRL scientist, "I will tell you my worry quotient is high. I actaully [sic] am in minor agony." In the email, Dr. Scolnick suggested doing a large outcomes study with a "safety first primary endpoint . . . . WE

[9] 3/9/00 email from E. Scolnick to D. Shapiro, A. Reicin and A. Nies, MRK-ABH0016220.

WILL NOT KNOW FOR SURE WHAT IS GOING ON UNTIL WE DO THIS STUDY."[10]

Critics who have focused on Dr. Scolnick's March 9, 2000 email have tended to ignore his subsequent emails reflecting his belief based on additional data and analysis that Vioxx was not prothrombotic. For example, on April 14, 2000, two days after writing the above-quoted email and reviewing additional data suggesting that a disproportionate number of the cardiovascular adverse events occurred in high-risk patients who should have been taking low-dose aspirin to help prevent such events, he wrote:

> READ IT! This is the latest adjudicated events tabulation. My anxiety level about the drug and the class is much allevaited [sic] by this data. It shows that the major major [sic] difference in events between Vioxx and naproxen is in patients who by FDA definition should have been on low dose aspirin!!!. . . . With this analysis we can stem the tide and save the class/ ED Scolnick[11]

In February 2001, during preparations for the FDA Advisory Committee Meeting to review the Vioxx supplemental New Drug Application that included data from the VIGOR Trial, Dr. Scolnick sent an email to colleagues that reflected his view of Vioxx and its cardiovascular safety as of that time:

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[10] 4/12/00 email from E. Scolnick to A. Reicin, MRK-ABC0033809 (emphasis in original).

[11] 4/14/00 email from E. Scolnick to R. Gilmartin, D. Anstice, M. McGlynn, K. Frazier, P. Wold-Olsen and J. Lewent, MRK-ADI0006059. As set forth below at pages 69 and 70 and page 77, as events developed, the subgroup analysis that Dr. Scolnick reviewed was called into question. However, the email evidences Dr. Scolnick's state of mind at the time about the safety profile of Vioxx.

> We all worried to death about the CV events last Spring. Merck is of course always an issue. But I was sick at the thought we might be doing harm to patients. I KNOW each of you well enough to know you felt the same way. with [sic] the data now available I am no longer worried.[12]

The strength of Dr. Scolnick's belief that Vioxx was not prothrombotic also is reflected in an internal email he sent to MRL scientists on November 8, 2001 concerning a proposed label received from the FDA that included a cardiovascular warning for Vioxx:

> twice in my life i have had to say to the FDA "That label is unacceptable, we will not under any circumstances accept it." . . . You WILL have to do that on the cardiac warning for Vioxx. . . . And i assure you i will NOT sign off on any lable [sic] that had a cardiac warning. the data review yesterday convinces me that we do not have an unsafe drug and I am willing if needed to spend several hours one on one with anyone at the FDA going through the data until they in fact get it[.][13]

Those who argue that MRL scientists did not truly believe that the VIGOR Trial cardiovascular risk ratio was a result of the cardioprotective qualities of naproxen often point to a memorandum prepared by Dr. Thomas Musliner, an MRL scientist, more than three years before the VIGOR Trial data were unblinded (the "Musliner Memorandum"). In that memorandum, Dr. Musliner hypothesized that in any study that tested Vioxx against a traditional non-selective NSAID there would be "a substantial chance that significantly higher rates of CV [Adverse Experience] events . . . will be observed in the

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[12] 2/4/01 email from E. Scolnick to A. Nies, A. Reicin and H. Guess, MRK-ACT0009918.

[13] 11/8/01 email from E. Scolnick to D. Greene, A. Nies and B. Goldmann, MRK-ACR0009287.

selective Cox-2 group . . . ."[14] What these critics often omit from their discussion is that Dr. Musliner's hypothesis was explicitly based on the assumptions that Vioxx was cardio-neutral and would have no effect on cardiovascular events and that traditional NSAIDs like naproxen, because they block platelet aggregation, might well be cardioprotective. Accordingly, internal documents such as the Musliner Memorandum establish simply that the theory that NSAIDs like naproxen might have cardioprotective qualities was recognized years before cardiovascular data from the VIGOR Trial were received and was not simply an after-the-fact creation to explain potentially damaging data.

On the basis of our exhaustive review of the record, we have concluded that, prior to receipt of the APPROVe Trial cardiovascular results, none of the senior scientists at MRL believed that Vioxx was prothrombotic. Indeed, we were told by numerous witnesses, including Dr. Scolnick, Dr. Kim and Mr. Gilmartin, that they, or their family members, were taking Vioxx up until the day that it was withdrawn from the market.

To say that no senior scientists at Merck believed that Vioxx was prothrombotic before receiving cardiovascular data from the APPROVe Trial is not to endorse every action that Merck employees took with respect to Vioxx. For example, as explained in Appendix K, in January 2001, Merck senior management received a letter from an academic scientist who criticized the manner in which Merck employees had treated other academic scientists who were critical of Merck and Vioxx. Merck senior

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[14] 11/21/96 memorandum from T. Musliner to B. Friedman et al., MRK-AAX0002413, at 17.

management investigated the alleged conduct of the Merck official and took steps to ensure that it would not be repeated.[15]

Before Vioxx was launched, certain employees in the Marketing and Sales Departments sought to garner support for the drug among important clinicians who might prescribe the drug and thought leaders who might influence others about the benefits of Vioxx. Documents prepared in connection with their efforts refer to "neutralizing" physicians who were critical of Merck or Vioxx by offering grants or other incentives. As discussed later in the Report and more fully in Appendix K, we found no evidence that senior management endorsed such activities. In addition, in late 2001 Merck undertook, on its own initiative, a comprehensive review of sales and marketing practices throughout the Company. As a result, it implemented enhanced policies concerning compliance, known internally as the "Culture of Compliance." This initiative, which enforced and underscored Merck's commitment to its existing policies regarding promotional activities and physician education and training was not Vioxx-specific. It did, however, reinforce policies and procedures to enhance accountability and transparency and ensure that all interactions between representatives of Merck and physicians were appropriate.[16]

We also note that certain of the press releases that Merck issued concerning Vioxx – including the March 27, 2000 release (announcing the preliminary VIGOR Trial

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[15] See Appendix K.

[16] See Appendix K.

results), the May 11, 2006 release (announcing preliminary results of a follow-up study on cardiovascular data from the APPROVe Trial) and the May 30, 2006 press release (correcting an error in the article published in the New England Journal of Medicine in February 2005 about the APPROVe Trial cardiovascular data) – did not provide as much context about the issues presented as might have been desirable, and the May 2006 press releases regarding the APPROVe Trial were not as clear as they could have been.[17]

Similarly, as we explain below and in Appendix G, a promotional aid called the Cardiovascular Card that was used by sales representatives with physicians after the VIGOR Trial cardiovascular data were unblinded did not, standing alone, provide all of the cardiovascular data on Vioxx. Although used in response to questions from physicians about the cardiovascular safety of Vioxx, the Card did not include data from the VIGOR Trial. The Company, however, separately provided a letter describing the VIGOR Trial data to physicians who asked questions about them. Finally, the Card included data from prior clinical trials that were reflected in the label but that – like the VIGOR Trial – were not designed to assess cardiovascular risk.

The actions of Merck's employees with respect to the development and marketing of Vioxx must be evaluated with a recognition of three overarching facts: (i) their belief that Vioxx was an important drug that conferred significant clinical benefits on patients by substantially reducing the risk of serious and sometimes fatal gastrointestinal

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[17] Shortly after issuing the May 11, 2006 press release, the Company posted on its website a 137-page report that it had submitted to the FDA containing data and detailed analyses from the follow-up study, as described below.

complications associated with traditional NSAID therapy; (ii) their belief until the APPROVe Trial data were unblinded that Vioxx was not prothrombotic; and (iii) their decision to withdraw Vioxx based on their views that the APPROVe Trial cardiovascular data reflected an increased relative risk on Vioxx versus placebo. The convictions of Merck personnel concerning the safety of Vioxx are underscored in some instances by their personal use of the drug right up until the day that it was withdrawn. At the same time, MRL scientists understood that, given that the science was new and developing, it was impossible to know with certainty that Vioxx (or any selective Cox-2 inhibitor) posed no cardiovascular risk.

It is in this context that one must evaluate the interaction of MRL scientists with Vioxx's scientific critics and the FDA, and the Company's marketing practices. Whether these beliefs led certain Merck officials to overreact to criticism or to ignore prudent scientific or marketing practices may be the subject of legitimate debate. However, the extensive evidence we have reviewed has convinced us that, during the period that Vioxx was marketed, no member of Merck's senior management believed that Vioxx was prothrombotic and attempted to mislead the scientific or consuming communities.

VIII.

REVIEW OF SPECIFIC CRITICISMS OF MERCK'S CONDUCT.

The allegations that have been made against the Company and its senior management in connection with the development and marketing of Vioxx can be broadly grouped into four categories:

- Merck's knowledge of the cardiovascular risk profile of Vioxx before Vioxx was approved by the FDA in May 1999;
- Merck's scientific response to cardiovascular data from the VIGOR Trial;
- Merck's marketing efforts; and
- Merck's analysis and reporting of cardiovascular data arising from the APPROVe Trial.

While we do not recite all of the allegations that have been made, we set forth below each of the major criticisms within these categories followed by our findings and conclusions with respect to each criticism.

A. Summary of Principal Criticisms and Findings Concerning Merck's Pre-approval Knowledge.

Central to the criticisms of Merck's conduct with respect to Vioxx is the allegation that the Company knew, before Vioxx was approved by the FDA, that the drug posed a serious cardiovascular risk to patients and deliberately failed to disclose that risk to the public, the scientific community and the FDA.

Our findings regarding the allegations concerning Merck's alleged pre-approval knowledge about the cardiovascular risks of Vioxx focus on the comprehensiveness of

Merck's pre-clinical and clinical testing of Vioxx and Merck's response to the FitzGerald prostacyclin hypothesis.

1. Allegation No. 1: Merck Rushed Vioxx to Market Without Adequate Testing.

a. Summary of Allegation.

The argument is made that "[i]n the late 1990s Merck was facing the loss of patent protection on several top drugs and needed a big hit."[18] According to Merck's 1996 profit plan, Merck needed to start marketing Vioxx by the fourth quarter of 1998, after only four years of tests. To meet that deadline, it is argued that Merck compressed significantly the normal period for clinical trials and deliberately failed to test adequately the cardiovascular safety of Vioxx.

b. Our Findings and Conclusions.

While it is true that Merck lost patent protection on some of its major drugs in 2000 and 2001, we found no evidence to suggest that Merck propelled Vioxx to market without conducting necessary testing in order to replace anticipated lost profits.

All new drugs at Merck (and in the pharmaceutical industry in general) undergo rigorous testing, beginning with a series of tolerability studies in animals, that, if successful, are followed by Phase I through III clinical testing in humans. These test results must be presented to the FDA, which must be satisfied that sufficient testing has been performed to establish both the efficacy and the safety of the drug. There is no basis

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[18] Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1, 2004, at A1.

to conclude that Merck attempted to shortcut the necessary testing or that the FDA did not carefully review Merck's testing before permitting Merck to market Vioxx.

Merck's New Drug Application for Vioxx was one of the largest New Drug Applications that Merck had ever filed – in terms of both the number of patients who participated in Merck's clinical studies for Vioxx and the duration of their treatment with Vioxx.[19] The application included data from numerous trials designed to test the efficacy and gastrointestinal safety of Vioxx, which MRL scientists and regulatory liaisons believed supported Merck's primary regulatory goal: to market Vioxx without the standard NSAID-class gastrointestinal warning. The FDA approved Vioxx for sale in the United States but did not agree that data included in the application supported removal of the standard NSAID-class gastrointestinal warning.

Merck's New Drug Application also provided data about Vioxx's effects on other body systems. The New Drug Application included analyses of (i) cardiovascular adverse events that were "serious" (i.e., resulted in death or other serious clinical outcome, such as hospitalization) in the Phase II/III osteoarthritis studies, and (ii) all thromboembolic cardiovascular adverse events (including events pertaining to cardiac, central nervous and peripheral systems) in the same group of studies. These analyses showed that (i) the incidence rates of serious cardiovascular adverse events were not

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[19] In this regard, the application exceeded by far the requirements for a new drug application of the International Conference on Harmonisation Guidances (developed by the FDA and regulators in Japan and the European Union), as the FDA medical reviewer who reviewed Merck's New Drug Application acknowledged. Transcript of 2/16/05 – 2/18/05 Joint Meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, MRK-AIU0185869, at 6106 (statement of M. L. Villalba*).

statistically different between Vioxx, NSAID comparators and placebo, and (ii) the incidence rates of all thromboembolic cardiovascular adverse experiences were similar among the treatment groups.

The FDA medical reviewer who reviewed Merck's New Drug Application for Vioxx has stated that she was aware of the FitzGerald prostacyclin hypothesis at the time she reviewed the application but that there was no evidence that the hypothesis had any clinical impact on cardiovascular risk (either from Vioxx or Celebrex, which the FDA already had approved). The reviewer acknowledged that post-marketing data would provide the only basis on which to answer any hypothetical question about the cardiovascular safety of Vioxx. The FDA did not request that Merck furnish additional data to support its application for approval to market Vioxx, which is something the FDA presumably would have done had there been any doubt at that time about the completeness of the application or the safety of Vioxx.

2. Allegation No. 2: Merck Knew in 1996 that Vioxx Was Dangerous to the Heart.

a. Summary of Allegation.

Some have argued that Merck did not investigate fully during the clinical development phase the serious cardiovascular problems that Vioxx could cause despite the fact, it is argued, that the Musliner Memorandum mentioned above shows that by

November 1996, MRL scientists were actively discussing Vioxx's potential cardiovascular risks.[20]

b. Our Findings and Conclusions.

The Musliner Memorandum was generated in the context of discussions among MRL scientists about the design of a large gastrointestinal clinical trial to test the primary hypothesis that patients taking Vioxx would experience fewer gastrointestinal events than patients taking traditional, non-selective NSAIDs. Documents and interviews make clear that MRL scientists confronted difficult design issues in planning that proposed trial, including what drug or agent Vioxx should be tested against, but that they did not at any point in the design process conclude that, or even consider whether, Vioxx was prothombotic. Rather, their entire discussion was predicated on the assumption – expressly set forth in the Musliner Memorandum – that Vioxx was cardio-neutral.

The record makes clear that MRL scientists did not believe that it was ethical or feasible to deny pain relief to patients with osteoarthritis for a lengthy period (the trial was being planned to last approximately twelve months), so a trial testing Vioxx versus a placebo was not an option. In addition, a number of MRL scientists believed that, as stated in the Musliner Memorandum, testing Vioxx against a traditional non-selective NSAID comparator had the potential to yield a between-treatment differential in cardiovascular events favoring the comparator because non-selective NSAIDs had antiplatelet effects and could, by virtue of those effects, provide cardioprotection to

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[20] Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1, 2004, at A1.

patients in the NSAID arm of the trial. Thus, these scientists expressed concern that testing Vioxx against a traditional NSAID comparator created the theoretical risk that patients in the NSAID arm would experience fewer cardiovascular events than those in the Vioxx arm, a result that they speculated might be misconstrued to suggest that Vioxx had caused a higher number of cardiovascular events.

MRL scientists also discussed internally and with external experts whether or not patients in the trial should be permitted to take low-dose aspirin. The evidence reflects that those involved in the discussions carefully weighed competing design considerations. The benefits of allowing low-dose aspirin use in both the NSAID and Vioxx arms would be (i) that it would permit usage by a broad spectrum of patients, including those requiring the use of low-dose aspirin for cardiovascular prophylaxis, and thus would have reflected "real world" usage of Vioxx, and (ii) that allowing all patients who might require cardiovascular prophylaxis to receive it would lessen the likelihood that patients taking Vioxx would have a higher incidence of cardiovascular events as compared to those taking a non-selective NSAID. The problem with allowing patients to take low-dose aspirin, however, was that aspirin was known to cause gastrointestinal problems, which would confound the study results and potentially prevent MRL from proving its primary hypothesis that selective Cox-2 inhibitors do not cause gastrointestinal injury.

Ultimately, MRL settled on a trial design in which 25 mg of Vioxx would be tested against two non-selective NSAIDs, diclofenac and ibuprofen, in patients with osteoarthritis, and in which low-dose aspirin use would not be allowed. Merck cancelled

the proposed trial in August 1997, before the first patient was enrolled. As discussed more fully below at pages 47 and 48 in response to the assertion that MRL cancelled the trial anticipating negative cardiovascular data, the cancellation was based on a number of factors, none of which reflected a concern about cardiovascular risk. Indeed, the evidence concerning the development and design of the gastrointestinal outcomes trial reflects no concern whatsoever that Vioxx might be prothrombotic.

In sum, the evidence cited by Merck's critics to support the claim that MRL scientists believed in 1996 that Vioxx was prothrombotic is based on statements that, taken in context, evidence a belief not that Vioxx would cause heart attacks but rather that a comparator NSAID might reduce the number of heart attacks through its inhibition of Cox-1. Hindsight has demonstrated that the MRL scientists involved in the discussion were prescient in that Merck's critics have construed the VIGOR Trial data exactly as MRL scientists anticipated they might.

3. Allegation No. 3: Merck Ignored Advice From Outside Experts Concerning Possible Prothrombotic Risks of Vioxx.

a. Summary of Allegation.

Merck also has been criticized for allegedly failing to heed the advice of at least two of its outside consultants, Dr. Garret FitzGerald* of the University of Pennsylvania and Dr. John Oates* of Vanderbilt University, both of whom independently urged the Company to investigate further the potential cardiovascular risks of Vioxx even before it was approved by the FDA.

The consultants' recommendations were prompted by the findings of a study, called Protocol 023, sponsored by Merck and conducted by Dr. FitzGerald* in 1996 and 1997. The study showed that Vioxx, like non-selective NSAIDs, suppressed urinary excretion of a metabolite of prostacyclin – a substance in the body that dilates blood vessels and helps to prevent blood clots by inhibiting platelet aggregation. The study further showed that Vioxx, unlike traditional non-selective NSAIDs, did not suppress urinary excretion of a metabolite of thromboxane, a substance in the body that constricts blood vessels and promotes blood clots. Although very little was known at the time about what role, if any, Cox-2 played in the production of prostacyclin in the bloodstream, Dr. FitzGerald* hypothesized that the reduction in prostacyclin metabolite in the urine meant that Vioxx decreased prostacyclin in the bloodstream and that doing so without also decreasing thromboxane could theoretically place patients in a prothrombotic state.

Critics argue that although the study did not prove that patients taking Vioxx would necessarily experience an increase in the number of cardiovascular events due to a decrease of prostacyclin in their blood, the "FitzGerald prostacyclin hypothesis" was, at the very least, cause for immediate concern and follow-up. Critics charge that Merck failed in 1997 to follow up on the implications raised by the study and did not adequately investigate the cardiovascular risks of Vioxx.

It is further alleged that after Merck presented the Fitzgerald prostacyclin hypothesis to its Board of Scientific Advisors in May 1998, the Board examined the hypothesis and advised MRL to conduct further tests on the potential cardiovascular risks

of the drug. The allegation is made that just as Merck had ignored its outside consultants when they suggested additional cardiovascular studies in 1997, Merck ignored the advice of its Board of Scientific Advisors in 1998 and failed to conduct any of the studies suggested by that body of experts for fear that such studies would demonstrate that Vioxx created or enhanced cardiovascular risk.

b. Our Findings and Conclusions.

(1) Protocol 023 Data and Genesis of the FitzGerald Prostacyclin Hypothesis

Protocol 023 was funded by Merck and designed to test the renal (or kidney-related) effects of Vioxx as compared to indomethacin (a non-selective NSAID) in a small, 36-subject trial. Drs. Garret FitzGerald* and Francesca Catella-Lawson* of the University of Pennsylvania conducted the study, which showed, among other things, that Vioxx reduced prostacyclin metabolite (PGI-M) in urine but did not decrease thromboxane metabolite in the urine. From this finding, Dr. FitzGerald* hypothesized (i) that selective Cox-2 inhibition resulted in reduced levels of prostacyclin in the vasculature (although the source of prostacyclin metabolite in urine was not known with any certainty), and therefore (ii) that the selective inhibition of Cox-2, which has no effect on thromboxane, might upset the balance between prostacyclin and thromboxane in the vasculature, which (iii) could put patients in a prothrombotic state.

(2) MRL Reaction to the FitzGerald Prostacyclin Hypothesis

Our investigation revealed that MRL scientists, including senior management, learned the findings of Protocol 023 – and Dr. FitzGerald's* related hypothesis – in October 1997, and had two immediate reactions.

First, they questioned Dr. FitzGerald's* premise that the suppression of the urinary metabolite necessarily signaled a reduction in vascular prostacyclin. If there were no reduction in vascular prostacyclin, MRL scientists believed, there would be no effect on the thromboxane/prostacyclin balance in the vasculature and thus no prothrombotic effect.

Second, they believed that the Fitzgerald prostacyclin hypothesis was undermined by evidence suggesting that Tylenol, a widely used over-the-counter drug with a long clinical history that had been shown to suppress the same prostacyclin metabolite in urine, had never been shown to be prothrombotic.

(3) Merck's Pre-approval Investigation of the Hypothesis

Despite what the evidence suggests were genuine questions within MRL about the premises of Dr. FitzGerald's* hypothesis, Merck took several affirmative steps to investigate the hypothesis before Vioxx was approved for sale, and, in our view, concluded in good faith that Vioxx posed no cardiovascular risk.

First, in response to the Protocol 023 data, Dr. Douglas Watson, an MRL epidemiologist, was tasked in November 1997 with reviewing data from Merck clinical trials to determine if there was any signal that patients on Vioxx experienced more

thrombotic events than those on placebo. Because many of the clinical trials still were blinded at that time and because there were limited data testing Vioxx against placebo, Dr. Watson's analysis compared the overall incidence of cardiovascular events as of December 1997 in the Vioxx clinical program (in the Vioxx and comparator groups combined) against the incidence of cardiovascular events in the placebo arms of clinical trials for two other Merck drugs. This blinded comparison did not signal to MRL scientists that there was an increased cardiovascular risk in the studies that included Vioxx.

After the data from Vioxx trials that were ongoing at the time of Dr. Watson's analysis were unblinded, MRL scientists analyzed the incidence of cardiovascular events on Vioxx versus comparators in the Vioxx development program and found that the cardiovascular incidence rate for Vioxx was similar to the incidence rate for the comparators (non-selective NSAIDs and placebo) in the Vioxx clinical trials to date. On that basis, MRL management believed that there likely was no clinical significance to Dr. FitzGerald's* belief that Vioxx suppressed vascular prostacyclin, even if correct. Although MRL's analysis was not statistically powered to detect a small difference in cardiovascular events between Vioxx and the comparators, MRL scientists were comforted by the results.

Second, Merck Frosst, Merck's basic research facility in Montreal, Canada, conducted an animal study to evaluate the contribution of Cox-2 to prostacyclin production by the aortic tissue, and found that Cox-2 did not play a major role in prostacyclin production in the rabbit aorta. Although this did not rule out the possibility

that Cox-2 might be responsible for the production of prostacyclin elsewhere in the vasculature or in humans, in the minds of MRL scientists it made one of the premises of the FitzGerald prostacyclin hypothesis more doubtful.

Third, Dr. Alan Nies, head of Clinical Pharmacology at MRL, presented the FitzGerald prostacyclin hypothesis at a meeting of Merck's Board of Scientific Advisors in May 1998. This Board of approximately twenty-five outside consultants convened annually to review and discuss with MRL scientists and Merck senior management Merck's clinical drug program. The evidence reflects that the Board of outside experts, which included Dr. John Oates*, a world-renowned expert on platelets and prostanoids (including prostacyclin and thromboxane), took the FitzGerald prostacyclin hypothesis seriously, but did not believe that it should prevent or delay the commercial distribution of Vioxx given that Merck's unblinded clinical data did not reveal any cardiovascular risk. In its written report, the Board of Scientific Advisors, which had considered the "hypothetical adverse effects" of Vioxx, concluded:

> The gain in safety achieved by the elimination of serious and fatal gastrointestinal toxicity will free patients from one of the most serious adverse effects in current drug therapy. Thus, there is a strong mandate for introduction of Vioxx into medical practice as soon as is feasible.[21]

In light of the FitzGerald prostacyclin hypothesis, and, to a lesser extent, an alternative hypothesis endorsed by some members of the Board of Scientific Advisors that Vioxx's anti-inflammatory properties might provide a cardiovascular benefit to

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[21] 5/98 "Programmatic Review: Vioxx Program," MRK-AEI0002734, at 742.

certain patients, the Board of Scientific Advisors recommended that Merck develop a uniform set of criteria to collect and evaluate cardiovascular events for future analysis. In response, MRL implemented a Cardiovascular Adjudication Standard Operating Procedure (the "Cardiovascular Adjudication SOP") requiring that all cardiovascular events occurring in the Vioxx clinical program be collected in a uniform manner and assessed for a second time by an independent, blinded expert committee to ensure consistency across diagnoses.

Merck took several additional steps to investigate the FitzGerald prostacyclin hypothesis after Vioxx had been approved by the FDA. When Dr. Peter Kim, now President of MRL, joined Merck in early 2001, he established a "Coxib Task Force" to focus on important issues in the Vioxx and Arcoxia programs.[22] After hearing about Dr. FitzGerald's* prostacyclin hypothesis and reviewing the research that Merck had conducted in response to it, Dr. Kim directed Merck scientists to research what Dr. Kim identified as the basic unconfirmed assumption in the prostacyclin hypothesis: whether prostacyclin formation is catalyzed by Cox-2 in the vasculature. From Dr. Kim's perspective, and that of other senior MRL scientists, a finding that prostacyclin exists side-by-side (or is co-localized) with Cox-2 within cells in the vasculature would lend credence to that assumption and would support Dr. FitzGerald's* hypothesis that inhibition of Cox-2 could create a prothrombotic state by creating an imbalance between

[22] Arcoxia is Merck's second-generation selective Cox-2 inhibitor. It has been marketed outside of the United States, but as of the date of this Report, is not being marketing in the United States. Arcoxia is discussed further in Appendix O.

thromboxane and prostacyclin. On the other hand, a finding that Cox-2 is not co-localized with prostacyclin in the vasculature would cast doubt on Dr. FitzGerald's* assumption that Cox-2 catalyzed production of prostacylin in the vasculature, suggesting that suppression of Cox-2 would not alter the balance between prostacyclin and thromboxane in the vasculature and thus that Vioxx should have no prothrombotic effect.

In 2002, Merck conducted an animal study to investigate this question and found that Cox–1 was co-localized with prostacyclin synthase in the vasculature to a greater extent than Cox-2. This suggested to MRL scientists that inhibition of Cox-2 alone would not increase the risk of thrombotic events through the mechanism proposed in the FitzGerald prostacyclin hypothesis. It also underscored – as we were reminded repeatedly by prominent outside experts we interviewed as well as by MRL scientists – that Cox enzyme-related science was new and evolving during the time period covered by our investigation.

The record makes clear that given the state of the science, Merck's clinical trial data and the various assumptions underlying the FitzGerald prostacyclin hypothesis, it was not unreasonable for MRL to conclude, after considering that hypothesis, that selective inhibition of Cox-2 would not have, or was not likely to have, any clinical cardiovascular implication. It is worth noting that even Dr. FitzGerald*, who believed that his hypothesis applied to all selective Cox-2 inhibitors, including Celebrex, did not believe that FDA approval of selective Cox-2 inhibitors should be delayed on the basis of his hypothesis. A 1999 Philadelphia Inquirer article quoted Dr. FitzGerald* as saying:

"The likelihood is, if this is a risk, it will be a small one because our experience to date does not reveal an excess of cardiovascular events."[23]

(4) Studies That Merck Did Not Conduct

The fact that MRL scientists decided not to conduct certain studies proposed by Drs. FitzGerald* and Oates* does not in our view suggest that Merck scientists did not take reasonable steps to test the validity of Dr. FitzGerald's* hypothesis. The evidence shows that MRL scientists concluded that the studies proposed by Drs. FitzGerald* and Oates* would not answer directly or conclusively the fundamental questions posed by the findings of Protocol 023 – whether Vioxx suppressed prostacyclin production in human vasculature, and, if so, whether Vioxx increased the risk of cardiovascular events in humans – and that the way to answer those questions was by collecting clinical trial data. Moreover, as discussed above, MRL did conduct a number of studies to explore the FitzGerald prostacyclin hypothesis, a fact that cuts against the allegation that MRL failed to conduct certain studies proposed by its outside experts out of fear of what the results would reveal.

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[23] Stacey Burling*, Penn Study Hints at Risks with Cox-2 Painkillers/The New Drugs May Increase a Patient's Chances of Getting a Stroke or a Heart Attack, Phila. Inq., Feb. 1, 1999 (quoting Dr. FitzGerald* as stating that he would "fully endorse [the FDA's] decision not to allow [the FitzGerald prostacyclin hypothesis] to retard their approval of Celebrex").

4. Allegation No. 4: Merck Did Not Publish The FitzGerald Prostacyclin Hypothesis in a Timely Manner and Did Not Disclose it to the FDA.

a. Summary of Allegation.

The results of Protocol 023 – including the data reflecting a decrease in urinary prostacyclin metabolites in patients taking Vioxx – were made available to Merck and its consultants in late 1997 but were not published until May 1999. It is asserted that Merck did not want the FDA to know about the FitzGerald prostacyclin hypothesis at least until Vioxx was approved for sale and was concerned that publication of the article might delay approval. For this reason, it is asserted, Merck also did not address the FitzGerald prostacyclin hypothesis in the New Drug Application it submitted for Vioxx.

b. Our Findings and Conclusions.

We have discovered no evidence to suggest that any members of Merck management sought to conceal the FitzGerald prostacyclin hypothesis from the scientific community or the FDA. Although the New Drug Application, submitted to the FDA on November 23, 1998, did not expressly refer to Dr. FitzGerald's* hypothesis, Merck submitted the data from Protocol 023 on which it was based, including the PGI-M (urinary metabolite) data. The application also stated that the clinical effects of Vioxx's potential suppression of prostacyclin without a counterbalancing inhibition of thromboxane might require further study.

The New Drug Application set forth the view held by MRL scientists about the cardiovascular safety profile of Vioxx, namely, that Vioxx had no effect on platelet

function and that therefore, as compared to non-selective NSAIDs which inhibited platelets, there could be a relatively increased rate of cardiovascular events on Vioxx.

In addition, Merck's Background Package submitted to the FDA for the April 20, 1999 meeting of the FDA Arthritis Advisory Committee stated:

> It had been suggested that specific COX-2 inhibition might increase the risk for cardiovascular events due to the lack of platelet function inhibition. It is clear that rofecoxib does not inhibit platelet aggregation and would not, therefore, convey the cardioprotective properties attributed to low-dose aspirin. While this benefit is not offered by rofecoxib, there is no evidence, preclinically or clinically, to suggest that rofecoxib carries any increased risk for cardiovascular events.[24]

Dr. Maria Lourdes Villalba*, the FDA medical reviewer who evaluated Merck's New Drug Application, has stated that when she reviewed the Vioxx application in 1998, "[t]here were theoretical concerns regarding that inhibition of prostacyclin could induce prothrombotic events" but that "based on these data [in the application], there was not much to say about it." Dr. Villalba* further noted that "Celebrex had recently been approved, in December '98, and Celebrex had not shown anything either."[25] As Dr. Villalba* noted, at the time that the Vioxx New Drug Application was under consideration, the FDA already had reviewed data in support of the Celebrex New Drug

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[24] MRL Background Package for 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ACD0064939, at 5109.

[25] Transcript of 2/16/05 Joint Meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, MRK-AIU0185869, at 6108.

Application, including data from the McAdam study (a study similar to Protocol 023 that Dr. FitzGerald* conducted with Celebrex).

With respect to the article about Protocol 023, the evidence shows that Dr. FitzGerald* and Dr. Catella-Lawson* submitted a draft of the article manuscript for MRL's review in January 1998, as was the protocol for Merck-funded studies. MRL scientists Dr. Barry Gertz and Dr. Briggs Morrison engaged in lengthy discussions with Drs. FitzGerald* and Catella-Lawson* over the meaning of the data and the manner in which it should be presented in the published article. The MRL scientists believed that the article should focus on the primary objective of the trial – assessing the renal effects of Vioxx – and the data relevant to that objective, while Dr. FitzGerald* and his team wanted to feature prominently the FitzGerald prostacyclin hypothesis and its potential implications for selective Cox-2 inhibitors.

As described in detail in Appendix A, although the evidence shows that there were sharp differences in the opinions of the MRL scientists and the outside authors and that, as a result, the negotiations were difficult and at times heated, there is no evidence that Drs. Gertz and Morrison were motivated by a desire to hide data or prevent the dissemination of a hypothesis that they viewed as evidence of an increased cardiovascular risk on Vioxx. MRL signed off on the draft manuscript, which included the prostacyclin hypothesis, in April 1998. The publishing delay was not caused by Merck: the first journal to which the article was submitted, the New England Journal of Medicine, declined to publish the article, and it was thereafter submitted to Journal of Pharmacology

and Experimental Therapeutics in October 1998, accepted in January 1999, and published in May 1999. The published article included the FitzGerald prostacyclin hypothesis.

As discussed above, the FitzGerald prostacyclin hypothesis was the main impetus for the Cardiovascular Adjudication SOP, although the hypotheses that traditional non-selective NSAIDs and/or Vioxx might be cardioprotective influenced the decision as well. Merck submissions to the FDA varied in the extent to which they identified the FitzGerald prostacyclin hypothesis as a primary motivation for the SOP. For instance, Merck's June 2000 submission to the FDA stated that the Cardiovascular Adjudication SOP was developed to "determine whether there [was] a difference in the degree of cardiovascular protection conferred by . . . COX-2 selective inhibitors versus nonselective COX-1/COX-2 inhibitors or placebo."[26] Merck's Background Package for the February 8, 2001 meeting of the FDA Arthritis Advisory Committee, however, stated that the SOP had been established to investigate the hypotheses that Vioxx might be pro-thrombotic or that traditional non-selective NSAIDs might be cardioprotective.[27]

There is no evidence that Merck withheld from the FDA any evidence regarding the metabolite findings of Protocol 023 or the incidence of thrombotic events in Vioxx trials or that anyone at Merck purposefully attempted to mislead the FDA or the public about the reasons for the adjudication procedure. Indeed, Merck notified the FDA in December of 1998 about its intent to adjudicate cardiovascular adverse events in Vioxx

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[26] 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, at 015.

[27] MRL Background Package for 2/8/01 FDA Arthritis Advisory Committee Meeting, MRK-ABK0456845, at 859.

trials and submitted a copy of the Cardiovascular Adjudication SOP (which expressly referred to the FitzGerald prostacyclin hypothesis) to the FDA in May 1999.

5. Allegation No. 5: Merck Cancelled a Gastrointestinal Outcomes Trial in 1997 Because MRL Scientists Feared that the Cardiovascular Results Would Be Unfavorable.

a. Summary of Allegation.

In 1997, as part of Merck's strategy of accelerating FDA approval and the commercial introduction of Vioxx, MRL scientists designed a gastrointestinal outcomes trial to prove that Vioxx caused less gastrointestinal injury than traditional non-selective NSAIDs. Such proof, the Company hoped, would convince the FDA that Vioxx should be marketed without the standard gastrointestinal warning on the label of all traditional non-selective NSAIDs, which in turn would put Vioxx at a marketing advantage over traditional non-selective NSAIDs.

Critics claim, however, that in trying to design that trial MRL scientists recognized that Merck was in a "no win situation" because the study would likely reveal increased cardiovascular events in patients who took Vioxx versus those in the study who took a non-selective NSAID comparator.[28] Critics further allege that MRL scientists tried to design the gastrointestinal outcomes study around this problem by excluding high risk patients from the study in the hope that Vioxx's cardiovascular risks "would not be evident."

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[28] Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1, 2004, at A1.

According to critics, Merck cancelled the planned gastrointestinal trial for fear that it would highlight the cardiovascular risks of Vioxx and, as MRL's Dr. Briggs Morrison stated in an email to Dr. Alise Reicin, "kill [the] drug."[29] Critics further assert that Vioxx likely would not have been approved by the FDA if the study had been conducted.

b. Our Findings and Conclusions.

As discussed above, internal documents from 1996 and 1997 regarding the design of a gastrointestinal outcomes trial do not reflect a belief that Vioxx was, or even might be shown to be, prothrombotic. When read in full and in context, the documents reflect a concern that the results of a trial against a non-selective NSAID with cardioprotective properties might be misinterpreted. We are aware of no evidence indicating that the trial was cancelled in response to a belief that Vioxx might be prothrombotic. The internal correspondence about the trial documents a thoughtful exchange among MRL scientists focused on whether to allow people in the trial to take low-dose aspirin. Read in context, the now-famous "kill the drug" email makes clear that an important consideration in designing the trial was that, because Vioxx did not inhibit Cox-1 as did non-selective NSAIDs, patients in the Vioxx arm would be likely to experience more thrombotic events than the patients who were receiving a non-selective NSAID comparator.[30]

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[29] Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1, 2004, at A1.

[30] As described in Appendix A, in early 1997, MRL scientists Drs. Briggs Morrison, Alise Reicin and Brian Daniels engaged in email correspondence about the design of a gastrointestinal outcomes trial and whether such a trial should exclude low-dose aspirin. Dr. Morrison wrote: I know this has been

The evidence indicates that Merck decided to cancel the trial in August 1997 after FDA representatives suggested to MRL scientists and regulatory officials that even if data from the planned trial were favorable the FDA was unlikely to approve a label for Vioxx without the standard NSAID-class gastrointestinal warning.

B. Summary of Principal Criticisms and Findings Concerning Merck's Scientific Response to VIGOR Trial Cardiovascular Data.

Based on further discussion with the FDA as well as the news that Searle/Pfizer was planning a gastrointestinal outcomes trial for Celebrex, Merck subsequently revisited the decision to conduct a gastrointestinal outcomes trial and planned the VIGOR Trial. The VIGOR Trial was a gastrointestinal outcomes trial designed to prove the Cox-2 hypothesis. Data from the trial were unblinded on March 9, 2000. Although the gastrointestinal results were favorable, the unadjudicated data available at that time showed that among the 4,046 patients in the Vioxx group of the trial, there were 92 serious cardiovascular events, 21 of which were reported as myocardial infarctions (heart attacks) and 15 of which were reported as strokes, and that among the 4,029 patients in the naproxen group, there were 46 serious cardiovascular events, including 9 reported myocardial infarctions and 7 reported strokes. (After the data were adjudicated, there were 20 confirmed myocardial infarctions in patients who took Vioxx, and 4 confirmed

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discussed to death, but real world is everyone is on [low-dose aspirin], so why exclude AND without COX-1 inhibition you will get more thrombotic events and kill drug." 2/25/97 email from B. Morrison to T. Simon, B. Daniels, E. Ehrich, and A. Reicin, MRK-LEH0058311, at 12. Dr. Reicin responded: "Low Dose Aspirin – I HEAR YOU! This is a no win situation! . . . . What about the idea of excluding high risk CV patients- ie those that have already had an MI, CABG, or PTCA? This may decrease the CV event rate so that a difference between the two groups would not be evident. . . ." 2/25/97 email from A. Reicin to T. Simon, B. Daniels, E. Ehrich, and B. Morrison, MRL-LEH0058311, at 11.

myocardial infarctions in patients who took naproxen.) The manner in which MRL scientists came to consensus about the meaning of these cardiovascular data and the follow-up investigations they conducted have been criticized extensively.

Our conclusions with respect to these criticisms are based on our finding that, after analyzing the VIGOR Trial data, MRL scientists developed the view that the between-treatment difference in cardiovascular events most likely was due to the cardioprotective effects of naproxen. Extensive documentary evidence, which is set forth in detail in Appendices E and F, traces the evolution of their beliefs regarding what caused the between-treatment difference as well as the manner in which they continued to investigate the data. While MRL scientists recognized that it was impossible to prove a negative, i.e., that Vioxx posed no cardiovascular risk, the dialogue in many of these internal documents reflects a firm belief in the safety of Vioxx and an equally firm belief that the cardioprotective effects of naproxen best explained the between-treatment difference in the incidence of cardiovascular events in the VIGOR Trial.

6. Allegation No. 6: Merck Tried to Design the VIGOR Trial in the First Instance to Avoid Creating Negative Cardiovascular Data.

a. Summary of Allegation.

It is alleged that Merck attempted to design the VIGOR Trial to avoid generating cardiovascular results that were "statistically significant" by (i) excluding from the study patients over 55 who were more likely to have a heart attack, (ii) including more women who are less heart attack-prone than men, (iii) eliminating from the study anyone with a

prior heart problem, and (iv) eliminating any aspirin users. Critics allege that the VIGOR Trial exposed the danger of Vioxx despite these efforts at concealment.[31]

b. Our Findings and Conclusions.

Based on our review of the record, it is clear that because no one at Merck believed that Vioxx was prothrombotic at the time that the VIGOR Trial was planned, scientists involved in the trial design were not concerned that a large clinical trial would unmask a cardiovascular risk.

The evidence shows that certain design decisions dictated to a large extent the VIGOR Trial's patient population. For example, the FDA recommended that Merck test Vioxx's gastrointestinal effects at a high dose because if the gastrointestinal outcomes data were favorable at a high dose, they were likely to be even more favorable at the more frequently prescribed lower dosages. The FDA also recommended testing Vioxx at a higher-than-recommended dose out of a concern that patients experiencing pain would take higher-than-recommended doses in an effort to alleviate their pain more quickly and fully – a phenomenon known as dosage creep.

The recommended doses for osteoarthritis, the principal target market for Vioxx, were 12.5 mg and 25 mg.[32] The record reflects that MRL scientists did not think that it would have been ethical to test a higher-than-recommended or necessary dose of Vioxx

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31 7/11/05 transcript of Ernst v. Merck & Co., No. 19961*BH02, Tex. Dist. Ct., at 72-73.

32 After the VIGOR Trial was planned and commenced, Vioxx was in fact approved for the treatment and signs of osteoarthritis. The FDA-approved label for Vioxx stated that the recommended starting dose was 12.5 mg once daily and that "[s]ome [osteoarthritis] patients may receive additional benefit by increasing the dose to 25 mg once daily."

in that population. In addition, MRL scientists believed (although the FDA was not convinced) that it already had proved the Cox-2 hypothesis in osteoarthritis patients.

Merck planned to seek a future indication for rheumatoid arthritis patients, and MRL scientists and external consultants agreed that it made sense to conduct the trial in such patients. The dosage for such patients had not been determined at the time the trial was being designed but was thought to be at least 25 mg, so conducting the trial with a 50 mg dose of Vioxx did not present an ethical concern.

According to Dr. Alise Reicin, the MRL scientist who drafted the VIGOR Trial protocol, the decision made in 1997 to exclude low-dose aspirin from the trial so that the anticipated positive gastrointestinal results would not be confounded, was equally valid for the VIGOR Trial, which was a gastrointestinal outcomes trial. MRL scientists also decided to exclude from the trial patients with a recent history of cardiovascular disease (e.g., stroke within the past two years, coronary artery surgery or heart attack within the past year, or uncontrolled hypertension) because such patients, under FDA guidelines, should take low-dose aspirin for cardiovascular prophylaxis.

7. Allegation No. 7: The Head of MRL Acknowledged the Cardiovascular Danger of Vioxx.

a. Summary of Allegation.

To support their claim that MRL scientists knew that the VIGOR Trial cardiovascular data proved that Vioxx was prothrombotic, Merck's critics point to an email that Dr. Edward Scolnick, the head of MRL, sent shortly after he received the VIGOR Trial data in which he stated: "the [cardiovascular] events are clearly there. . . .

it is a shame, but it is a low incidence and it is mechanism-based as we worried it was."[33] Dr. Scolnick's March 9, 2000 email has been interpreted in the Vioxx tort litigation as reflecting his understanding that the "mechanism-based" effect in the VIGOR Trial had confirmed the FitzGerald prostacyclin hypothesis, which is why he told other MRL scientists that he wanted to make "clear to the world" that this was an effect of the entire class of selective Cox-2 inhibitors, not just Vioxx.[34]

b. Our Findings and Conclusions.

The most compelling evidence as to whether Dr. Scolnick believed that Vioxx was prothrombotic are his own words, written after MRL scientists had analyzed the VIGOR Trial data and after cardiovascular data from the placebo-controlled Alzheimer's trials were unblinded. Although Dr. Scolnick has testified that his first reaction to the VIGOR Trial data – as reflected in his March 9, 2000 email – was that Vioxx was prothrombotic,[35] the internal emails quoted above at pages 21 and 22 reflect that Dr. Scolnick quickly came to the view that the totality of the data did not support that

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33 3/9/00 email from E. Scolnick to D. Shapiro, A. Reicin, and A. Nies, MRK-ABH0016220 (quoted in Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1, 2004, at A1); see also 9/14/05 transcript of Humeston v. Merck & Co., ATL-L-2272-03 MT, N.J. Super. Ct. Law Div., at 42-43.

34 3/9/00 email from E. Scolnick to D. Shapiro, A. Reicin, and A. Nies, MRK-ABH0016220 (quoted in Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1, 2004, at A1).

35 It should be noted that Dr. Scolnick was not among the MRL scientists to whom the Musliner Memorandum was circulated.

conclusion. In a late 2001 internal email, he was emphatic that the data did not support a cardiovascular warning for Vioxx because Vioxx was not unsafe.[36]

In addition to contemporaneous documents, we also reviewed numerous transcripts of Dr. Scolnick's deposition testimony and interviewed Dr. Scolnick for approximately ten hours. On the basis of this substantial body of information, we are persuaded that Dr. Scolnick concluded shortly after the VIGOR Trial unblinding that the most likely explanation for the cardiovascular results was that naproxen had provided cardioprotection. We also interviewed numerous MRL scientists who worked with Dr. Scolnick. While many of them indicated that Dr. Scolnick was highly demanding and sometimes difficult to work with, they were unanimous in the view that he was "data driven." Not a single MRL witness expressed any doubt about Dr. Scolnick's conviction that Vioxx was safe; indeed, not a single MRL witness believed that Vioxx was prothrombotic before the APPROVe Trial cardiovascular data were unblinded, which led to the withdrawal of Vioxx.

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[36] 11/8/01 email from E. Scolnick to D. Greene, A. Nies, and B. Goldmann, MRK-ACR0009287.

8. Allegation No. 8: Merck's Naproxen Cardioprotection Hypothesis Was an Implausible Explanation for the VIGOR Trial Cardiovascular Data that the Scientific Community – and Even Some MRL Scientists – Recognized Did Not Explain the Between-Treatment Difference in Cardiovascular Events.

a. Summary of Allegation.

Merck did not acknowledge that Vioxx caused the cardiovascular events in the Vioxx arm of the VIGOR Trial and instead publicly stated that the most likely explanation for the between-treatment difference in the incidence of cardiovascular events was that the other agent in the study, naproxen, was cardioprotective. It has been argued that this "naproxen cardioprotection hypothesis" was not a plausible scientific explanation and that MRL should not have propounded the theory in the first instance or continued to adhere to it after its own data disproved it. The following reasons have been offered in support of such criticisms:

First, critics claim that there was no hard clinical evidence to support the naproxen cardioprotection hypothesis.

Second, critics allege that MRL's outside consultants told MRL senior management that the VIGOR Trial cardiovascular data also could be explained by Vioxx's prothrombotic properties, or by chance, and that "[m]any scientists outside the company found [Merck's naproxen cardioprotection] theory implausible. . . ."[37]

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[37] Alex Berenson*, Gardiner Harris*, Barry Meier* & Andrew Pollack*, Despite Warnings, Drug Giant Took Long Path to Vioxx Recall, N.Y. Times, Nov. 14, 2004, at A1; see also 7/14/05 transcript of Ernst v. Merck & Co., No. 19961*BH02, Tex. Dist. Ct., at 76-78.

Third, it is argued that the makers of naproxen never touted any alleged cardioprotective effects of the drug, which is something they surely would have done had it been true.[38]

Fourth, it is alleged that even scientists at MRL conceded that the alleged cardioprotective effect of naproxen could not account for the magnitude of the difference in the incidence of cardiovascular events between the naproxen and Vioxx arms of the study: the difference was even greater than would have been anticipated had the patients in the naproxen arm been taking low-dose aspirin for cardiovascular prophylaxis, which is the recognized gold standard for preventing blood clots.

Fifth, critics argue that a post-hoc subgroup analysis that Merck scientists performed to support the naproxen cardioprotection hypothesis was of questionable validity and allegedly failed to support the hypothesis. Based on a review that they conducted in mid-April 2000, MRL scientists determined that 4% of the patients enrolled in the VIGOR Trial should have been taking low-dose aspirin for cardiovascular prophylaxis based on FDA-approved criteria. Critics allege that separating out these patients conveyed the false impression that the between-treatment difference in the incidence of cardiovascular events in the VIGOR Trial was limited to patients in the 4% subgroup who needed cardiovascular protection and that those patients had received the needed cardioprotection from naproxen. In addition, it is alleged that when all the data were available, the between-treatment difference in cardiovascular events was not

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[38] 7/14/05 transcript of Ernst v. Merck & Co., No. 19961*BH02, Tex. Dist. Ct., at 75.

confined to this sub-group, so Merck's reliance on the analysis was misplaced and misleading.

Sixth, critics assert that, as noted above, Dr. Scolnick recognized that the cardiovascular events were "mechanism-based," that is, that they were caused by Vioxx's selective blocking of the Cox-2 enzyme and prostacyclin. Thus, there was not a "lower" incidence of cardiovascular events in the naproxen arm of the trial, but a "higher" incidence in the Vioxx arm.

Finally, it is alleged that given the uncertainty about the cause of the difference in event rates, the press release that Merck issued on March 27, 2000 announcing the results of the VIGOR Trial should have identified other possibilities for the findings – including the possibility that Vioxx was prothrombotic – and should not have focused exclusively on Merck's naproxen cardioprotection hypothesis.

b. Our Findings and Conclusions.

As explained in the Introduction, the focus of our investigation was whether senior management acted in bad faith, intentionally failed to investigate the cardiovascular risks of Vioxx, or otherwise intentionally sought to mislead the scientific community and general public with regard to the cardiovascular risks of Vioxx. Thus, it is not our role to opine on whether the naproxen cardioprotection hypothesis was, or was not, the best hypothesis to explain the VIGOR Trial cardiovascular results.

We investigated how MRL scientists analyzed the VIGOR Trial data, how they arrived at (and maintained their belief in) the naproxen cardioprotection hypothesis, and whether they did so in good faith. Based on the considerable evidence we reviewed, we

believe MRL scientists and management genuinely believed that the naproxen cardioprotection hypothesis was the most likely explanation for the VIGOR Trial cardiovascular results.

(1) Overview of Post-VIGOR Analyses That Led MRL Scientists to Conclude That Naproxen Cardioprotection Was the Most Likely Explanation for the VIGOR Trial Results

Between March 9, 2000, when the VIGOR Trial data were first unblinded, and March 27, 2000, when Merck issued a press release about the VIGOR Trial and the cardiovascular results and publicly put forth the naproxen cardioprotection hypothesis, MRL scientists performed numerous analyses to investigate the meaning of the data. During this period, MRL's team of unblinded scientists gathered information relating to the potential cardiovascular implications of the three central components of the VIGOR Trial: (i) Vioxx generally and the 50 mg dosage used in the VIGOR Trial, in particular; (ii) the study population – rheumatoid arthritis patients; and (iii) the comparator drug – naproxen.

(a) Review of Vioxx Cardiovascular Data

With respect to the first component, the unblinded MRL scientists examined cardiovascular data from other clinical trials that had included Vioxx, including the Phase IIb/III osteoarthritis trials and two trials conducted to test the efficacy of Vioxx in preventing or slowing the progression of Alzheimer's disease.

(i) Review of unblinded data from osteoarthritis trials

After the VIGOR Trial unblinding, MRL scientists re-analyzed the then-unblinded data from the Phase IIb/III osteoarthritis trials, which reflected no statistically significant difference (and very little numerical difference) in the rate of serious cardiovascular thrombotic events between Vioxx (all doses) and the comparator non-selective NSAIDs as a group. The unblinded team also noted that "the absolute rate of serious thromboembolic events was similar in patients treated with rofecoxib in both the Phase III OA combined analyses [2.05/100 PYR] and VIGOR [2.12/100 PYR]," while the rate of serious thrombotic events for patients on naproxen in the VIGOR Trial was much lower (1.13/100 PYR).[39] These data suggested to MRL scientists "that the difference between rofecoxib and naproxen in VIGOR was driven by a reduction in events in the naproxen group."[40]

(ii) Review of placebo-controlled data from Alzheimer's trials

Merck's Protocol 078 tested the efficacy of Vioxx in preventing the conversion of mild cognitive impairment into Alzheimer's disease, and Protocol 091 tested the efficacy of Vioxx in slowing the progression of the symptoms of Alzheimer's disease. These

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[39] 3/23/00 preliminary VIGOR report to FDA, MRK-ABK0460838, at 47, 51, 63. ("PYR" means patient years at risk.) Some Merck documents refer to certain cardiovascular events as "thrombotic" and other Merck documents refer to these same events as "thromboembolic." Although there is a clinical difference, witnesses and Merck internal documents used these terms interchangeably to refer to cardiovascular events caused by a clot, such as a myocardial infarction or stroke. We use the term "thrombotic" throughout this Report.

[40] 3/23/00 preliminary VIGOR report to FDA, MRK-ABK0460838, at 63.

trials (collectively, the "Alzheimer's trials"), which were still blinded in March 2000, contained a large number of patients (over 2000) who had been on either Vioxx 25 mg or placebo for, at that point, an average of nine months.[41]

After the VIGOR Trial unblinding, the decision quickly was made to partially unblind the serious cardiovascular event data from these two ongoing trials into "Treatment Group A" and "Treatment Group B" (without disclosure of treatment type) in order to obtain placebo-controlled data on the cardiovascular effects of Vioxx. Then, if an imbalance were found between the treatment groups, Merck would totally unblind the data and see if there was evidence against placebo that Vioxx was prothrombotic.

There were 26 patients with serious thrombotic cardiovascular events in group A versus 32 patients with such events in group B, approximately a 20% difference, though not a statistically significant one. However, the number of events characterized by investigators as either "myocardial infarctions" or "acute myocardial infarctions" was equal between the two groups (eight in each arm) as was the number of events investigators labeled "cerebrovascular accidents," i.e., strokes (five in each arm).[42] As a result, Dr. Scolnick felt comfortable that the data did not show an overall imbalance between the two groups or a prothrombotic effect in one arm, and he did not ask for the

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41 Cardiovascular events from these trials were being collected pursuant to normal procedures for reporting and collecting all adverse events and, under the Cardiovascular Adjudication SOP discussed above, were being sent to an external adjudication committee.

42 3/23/00 preliminary VIGOR report to FDA, MRK-ABK0460838, at 55.

data to be fully unblinded to reveal which group was which.[43] Unblinding as to treatment group would have revealed that the group with the lower total number of patients with events, group A, was the Vioxx treatment group.

The cardiovascular data from the Alzheimer's trials were extremely important to MRL's understanding of the VIGOR Trial cardiovascular data. Several MRL scientists, including Dr. Scolnick, recalled that it convinced them that the cardiovascular event differential in the VIGOR Trial was caused by naproxen's cardioprotective effects and not any prothrombotic effect of Vioxx.

(iii) Dr. Barr's analysis

Dr. Eliav Barr, an MRL antiplatelet expert working in the Vaccines division who was tapped by Dr. Scolnick to help investigate the VIGOR Trial cardiovascular data, requested additional information so that he could begin an in-depth review of the cardiovascular events in the VIGOR Trial that had been reported as of March 9, 2000. He requested adjudication packages for the adjudicated cardiovascular events and reports from the Worldwide Adverse Event System for all reported cardiovascular adverse events in the VIGOR Trial (including, but not limited to, those that had been or were to be adjudicated). He also requested background patient demographic data. Dr. Barr examined adverse event data on epistaxis (nose bleeds), a common side effect of antiplatelet treatment, and found significantly more nose bleeds in the naproxen arm (27)

[43] 3/21/05 Open Letter from E. Scolnick, "Vioxx: Scientific Review," MRK-AFO0288987, at 993-94. The decision not to fully unblind the data was influenced by the fact that once a trial is unblinded, the trial may be considered compromised. For that reason, during the pendency of a clinical trial, every effort is made to keep the data blinded.

than in the Vioxx arm (7).[44] He found these data particularly compelling because they suggested that the antiplatelet properties of naproxen had a clinical effect in the VIGOR Trial patients, rendering them more susceptible to bleeding, as would a low-dose aspirin regimen.

Dr. Barr also requested subgroup analyses of the VIGOR Trial cardiovascular data based on patient demographics and cardiovascular risk factors, such as age, gender, history of cardiovascular disease, smoking habits and hormone replacement therapy. These analyses showed that, regardless of treatment group, patients with more cardiovascular risk factors experienced more cardiovascular events. These analyses left open the issue of whether it was Vioxx that was increasing the risk, naproxen that was decreasing it, chance, or some combination of the three.

(iv) Review of post-marketing data

Merck's Worldwide Product Safety and Epidemiology Department tracks adverse event reports for Merck drugs – both adverse event reports from clinical trials and those spontaneously submitted by doctors or patients "post-marketing" (i.e., after a drug has been released onto the market). Soon after unblinding, senior members of the Worldwide Product Safety and Epidemiology Department provided the team of unblinded scientists who were analyzing the VIGOR Trial data with a list and descriptions of all spontaneously reported post-marketing cardiovascular adverse experiences with Vioxx

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[44] 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, at 43-44.

and attempted to evaluate whether the absolute incidence of such reported events indicated a safety signal.

Spontaneously reported post-marketing adverse experience data are difficult to interpret, because there are so many potentially confounding unidentifiable background variables and there is no way accurately to determine the "denominator" (that is, the total number of patients on Vioxx during the relevant period). These issues create especially substantial problems in the case of relatively common adverse experiences (such as myocardial infarctions), because it is difficult to differentiate a drug effect from the normal background incidence of such events in the patient population, especially given uneven rates of spontaneous reporting of adverse events. Based on an examination of the total numbers of spontaneously reported cardiovascular adverse events on Vioxx, MRL scientists concluded that the numbers were not "disproportionate to the numbers reported with other products which have no known associated cardiovascular risks and are indicated for treatment populations with similar age structures as VIOXX."[45]

(b) Naproxen Cardioprotection

With regard to the second component of the VIGOR Trial that MRL scientists investigated – whether naproxen conferred cardioprotection to patients in the naproxen arm of the trial – MRL scientists came to believe, after reviewing the relevant literature and existing clinical data on aspirin and certain other non-selective NSAIDs as well as pharmacological data on naproxen, that a cardioprotective effect of naproxen was the

[45] 3/13/00 memorandum from P. Gruer to A. Reicin, MRK-00420018281, at 83.

most likely cause of the difference in the incidence of cardiovascular events in the VIGOR Trial.

First, as discussed above, MRL scientists knew that aspirin, a traditional non-selective NSAID, was cardioprotective. MRL scientists also knew that aspirin was the only traditional non-selective NSAID conclusively proven to be cardioprotective. MRL scientists were aware, however, that, in several small clinical trials, use of two non-aspirin non-selective NSAIDs (indobufen and flurbiprofen) was associated with a decreased risk of cardiovascular events, suggesting that non-aspirin, non-selective NSAIDs also might be cardioprotective.

Second, MRL scientists were aware that the mechanism for aspirin's cardioprotective effect was its suppression of the Cox-1 enzyme and its irreversible inhibition of platelet aggregation (or blood clotting) throughout the life of a platelet. MRL scientists also were aware that non-aspirin, non-selective NSAIDs (such as naproxen) inhibited Cox-1 and platelet aggregation, but did so reversibly, meaning that the effect ceased once the drug wore off. MRL scientists thus noted that there was a mechanistic basis for the hypothesis that non-aspirin NSAIDs might be cardioprotective if taken often and regularly enough to sustain their effects. (MRL scientists also knew that Vioxx, on the other hand, had no effect on Cox-1 and platelet aggregation and therefore would not be expected to confer a cardioprotective effect through such a mechanism.)

One of the questions MRL scientists asked was why, if traditional non-selective NSAIDs were cardioprotective by virtue of Cox-1 inhibition, such an effect was not

evident in the pre-New Drug Application osteoarthritis studies that tested Vioxx against the non-selective NSAIDs ibuprofen, diclofenac, and nabumetone. In reviewing the results of a pre-New Drug Application pharmacological study assessing the effect of several NSAIDs (including diclofenac, ibuprofen and naproxen) on Cox-1 and platelet aggregation, MRL scientists noted that naproxen was the only tested non-aspirin NSAID that inhibited platelet aggregation to a relatively high degree throughout its dosing interval. This observation suggested to them that, if taken regularly at the recommended dosing interval, naproxen (but not diclofenac and ibuprofen) would sustain its antiplatelet effect and might mimic aspirin's irreversible inhibition of platelet aggregation and therefore its cardioprotective effect.

(c) Rheumatoid Arthritis Patient Population

MRL scientists also investigated the extent to which the patient population might have influenced the cardiovascular results in the VIGOR Trial. Their research revealed that rheumatoid arthritis patients are at increased risk for cardiovascular events generally and have preexisting high levels of thromboxane. Thus, rheumatoid arthritis patients could be more susceptible to the potential cardioprotective effects of naproxen's inhibition of thromboxane and platelet aggregation. However, to the extent that Vioxx caused a decrease in prostacyclin in the vasculature, such patients might be more susceptible to a prothrombotic effect caused by an imbalance between thromboxane and prostacyclin.

(2) Summary of Our Findings and Conclusions

Following are our findings with respect to the arguments that have been made to support the claim that the naproxen cardioprotection hypothesis cannot explain the data, and therefore, that MRL scientists must have adopted it in bad faith.

First, although it is true that naproxen's cardioprotective qualities had not been directly tested in any large clinical outcomes trial, there was pharmacological evidence that naproxen inhibited platelet aggregation to a relatively high degree throughout its dosing interval as well as limited clinical evidence for the more general proposition that non-selective NSAIDs other than aspirin may provide cardioprotection, as described above. While MRL scientists recognized that these data standing alone did not definitively establish that naproxen was cardioprotective, MRL scientists believed that they provided a reasonable basis for the naproxen cardioprotection hypothesis and, given the absence of any significant between-treatment cardiovascular differential in Merck's other Vioxx trials, that naproxen cardioprotection was the most likely explanation for the VIGOR Trial results.

Second, critics rely on the reaction of Dr. Carlo Patrono*, a prostaglandin expert and external consultant to MRL, to support their claim that outside scientists did not agree with the naproxen cardioprotection hypothesis. The evidence demonstrates that Dr. Patrono* initially believed, and so advised Merck, that the cardiovascular results of the VIGOR Trial were due to chance: He did not believe that the data supported the conclusion that Vioxx was prothrombotic or that naproxen had a cardioprotective effect. Dr. Patrono*, however, later changed his view regarding naproxen cardioprotection (and

its role in the VIGOR Trial) after conducting his own clinical pharmacological study that showed that 500 mg of naproxen given twice daily could mirror the antiplatelet effect of aspirin.

In addition, MRL convened three meetings in the fall of 2000 with outside consultants – one with cardiologists, one with prostaglandin experts and one with a mixed group of experts, including rheumatologists, statisticians and nephrologists – at which cardiovascular data from the VIGOR Trial were discussed. Although external consultants recognized that without a placebo arm it was impossible to determine the cause of the disparity in the incidence of cardiovascular events between the two arms of the study, most agreed that naproxen cardioprotection was a plausible cause. They were influenced in particular, as MRL scientists had been, by the fact that there was no difference in the incidence of cardiovascular events between Vioxx and placebo or non-naproxen NSAIDs in prior and ongoing clinical trials.

Because MRL scientists and the VIGOR Trial investigators were blinded to the data throughout the trial, the trial had been monitored by a Data Safety and Monitoring Board – an external board of scientists who periodically reviewed safety data, including cardiovascular data, from the trial on a partially or fully unblinded basis – to protect patient safety. It is noteworthy that the Data Safety and Monitoring Board recognized even as data were accruing that "there is no ability in this trial to distinguish between a potentially harmful effect of Treatment A [Vioxx] and a cardiovascular protective effect

of Treatment B [naproxen] due to its antiplatelet effects."[46] The Monitoring Board members thus believed that the naproxen cardioprotection hypothesis was plausible, even though they did not have the benefit of reviewing cardiovascular data from the VIGOR Trial in the context of data from other trials.

Third, the fact that the naproxen label makes no claim that naproxen is cardioprotective is not surprising given the lack of economic incentive for the makers of naproxen to pursue such a claim and reflects nothing one way or the other about whether naproxen may provide cardioprotection. There are several factors that may explain why no large outcomes study had been conducted to test the cardioprotective effects of naproxen: (i) it would have been very costly to conduct a clinical trial of the size necessary to produce data to support a claim of cardioprotection in the naproxen label; (ii) aspirin, which was available in inexpensive generic formulations, had long been believed to provide cardioprotection and was proven to do so in the early 1990s, shortly before naproxen's patent was set to expire; (iii) aspirin was known to be the only non-selective NSAID that irreversibly inhibited Cox-1 throughout the life of the platelet, whereas any cardioprotective effect of naproxen would require regular dosing and a high degree of patient compliance; (iv) naproxen is known to cause gastrointestinal injury to a greater extent than low-dose aspirin, making patient retention in a clinical trial more difficult and making naproxen compare unfavorably to low-dose aspirin as a theoretical

[46] Minutes of 11/17/99 Data Safety and Monitoring Board meeting, MRK-AFL0000891, at 91-92.

source of cardioprotection; and (v) as a result, there was no economic incentive for the makers of naproxen to sponsor a costly trial.

Fourth, with respect to the argument that MRL scientists recognized that naproxen cardioprotection could not account for the magnitude of the difference in the incidence of cardiovascular events between the Vioxx and naproxen treatment arms in the VIGOR Trial, the record reflects that MRL scientists investigated (and discussed with the external consultants) potential reasons for the magnitude of the difference. The evidence shows that they recognized that the differential might be explained by chance or by characteristics of the rheumatoid arthritis patient population tested in the VIGOR Trial that may have made them more susceptible to the cardioprotective effects of naproxen. All of the relevant data were given to the FDA.

Fifth, even after MRL scientists had concluded that naproxen cardioprotection best explained the between-treatment difference in the incidence of cardiovascular events and Merck issued a press release about the study, MRL scientists continued to analyze the data. In April 2000, MRL scientists determined that based on FDA-approved criteria (as reflected in the aspirin product circular[47]), 4% of the patient population enrolled in the VIGOR Trial should have been taking low-dose aspirin for cardiovascular prophylaxis, and thus should not have been enrolled in the trial because it was designed to exclude

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[47] The United States product circular for aspirin states that aspirin is indicated for patients with a history of ischemic stroke, transient ischemic attack, myocardial infarction, unstable angina, and chronic stable angina. Physicians' Desk Reference. 60th ed. Montvale, NJ: Thomson PDR; 2006:1627-29 (entry for ECOTRIN®: enteric-coated aspirin); see also 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, at 022 (citing U.S. product circular for aspirin).

patients taking (or who should be taking) low-dose aspirin for cardiovascular prophylaxis.

An analysis conducted on April 14, 2000 with all cardiovascular event data that had been adjudicated to date revealed that 31% of the cardiovascular events (including 38% of the heart attacks) observed in the VIGOR Trial occurred in these 4% of patients. When these "aspirin-indicated" patients were excluded from the analysis, the difference in the incidence of cardiovascular events between the remainder of the Vioxx and naproxen groups was not statistically significant. In the 4% of patients who were aspirin-indicated, on the other hand, the incidence of cardiovascular events was significantly higher in patients taking Vioxx than in those taking naproxen. MRL scientists felt that this analysis supported the hypothesis that, in the VIGOR Trial, naproxen had acted like aspirin and conferred cardioprotection to those patients who should have been on aspirin, while Vioxx had simply not provided such protection.

This analysis was reassuring to MRL scientists, and to Dr. Scolnick in particular. However, the analysis was repeated on April 21 and again on July 5 as additional cardiovascular events were adjudicated, and, with the addition of new data, became less compelling. After the July 5, 2000 iteration, there was a statistically significant between-treatment difference in overall cardiovascular events and a nearly significant difference in myocardial infarctions in the non-aspirin-indicated patients. As discussed in Appendix N, based on these additional data, Merck opposed inclusion of references to the aspirin-indicated subgroup analysis in its negotiations with the FDA concerning the contents of the post-VIGOR label.

Still, even with the additional data, the aspirin-indicated subgroup analysis was not in conflict with the hypothesis that naproxen cardioprotection accounted for the cardiovascular event differential in the VIGOR Trial. It remained the case that of the eight myocardial infarctions that occurred in the aspirin-indicated 4% subgroup, none were experienced by patients taking naproxen.

Sixth, we already have addressed the argument that has been made that MRL scientists, including Dr. Scolnick, did not believe the naproxen cardioprotection hypothesis. As indicated above, Dr. Scolnick believed in the cardiovascular safety of the drug and we found no senior Merck scientist who disagreed with this view. In fact, immediately upon seeing the cardiovascular data from the VIGOR Trial, Dr. Eliav Barr remarked that MRL had just successfully completed a placebo-controlled trial that demonstrated the cardioprotective effects of naproxen. Dr. Barr believed that because Vioxx had no antiplatelet effect, it was cardio-neutral, and that the other agent in the study, naproxen, which he believed had a potent antiplatelet effect, was the cause of the reduction in thrombotic events.

Finally, as explained above, although MRL scientists could not definitively rule out other reasons for the between-treatment event rate differential, over the course of a few weeks they became comfortable that naproxen's anti-platelet effects had conferred cardioprotection to patients in the naproxen arm of the VIGOR Trial. While it might have been desirable to have included in the release other possible explanations for the difference – including, for example, that the population studied may have been more susceptible to either a prothrombotic effect of Vioxx or a cardioprotective effect of

naproxen – the press release that was issued on March 27, 2000 set forth the consensus view within MRL: the observed effect likely was caused by naproxen's antiplatelet effects.

For all of these reasons, we have concluded that MRL scientists genuinely believed that the naproxen cardioprotection hypothesis was the best explanation for the between-treatment difference in the incidence of cardiovascular events in the VIGOR Trial.

9. Allegation No. 9: The Published VIGOR Trial Results Intentionally Omitted Important Cardiovascular Risk Information.

a. Summary of Allegation.

The allegation is made that the authors of the VIGOR Trial article that was published in the New England Journal of Medicine in November 2000 intentionally excluded important data in an effort to minimize or misrepresent the cardiovascular risk exposed by the VIGOR Trial. It is argued that the article included all gastrointestinal adverse events that occurred through the end of the trial on March 9, 2000 but included only cardiovascular adverse events reported by February 10, 2000, and that the article concealed this discrepancy.

It is further argued that, before the article was published, Merck had obtained updated cardiovascular data including all cardiovascular adverse events that occurred through March 9, 2000 but purposefully did not include them in the article. Instead, Merck relied on cardiovascular data available only through February 10, 2000, and on the basis of those incomplete data, conducted a sub-group analysis of the incidence of

myocardial infarctions among the 4% of VIGOR Trial patients who should have been taking low-dose aspirin for cardiovascular prophylaxis. Merck then included this sub-group analysis in the article, allegedly to convey the impression that "the patients who suffered heart attacks were at high risk of heart disease to begin with,"[48] and thus to make Vioxx appear to be safe in patients not indicated for low-dose aspirin use. Had Merck included the updated data, the argument goes, this "aspirin-indicated" subgroup analysis and the article's discussion of the VIGOR Trial cardiovascular results would have been materially altered.

Finally, it is argued that, before submitting the manuscript for publication, the authors deleted a table that contained relevant cardiovascular data to conceal those data from publication.

In November 2005, the editors of the New England Journal of Medicine published an editorial about the VIGOR Trial article that raised three principal criticisms: (i) the article did not include the updated cardiovascular data, specifically, three heart attacks that occurred in the Vioxx group of non-aspirin-indicated patients; (ii) as a result, calculations in the article (i.e., the incidence of heart attacks overall and in the non-aspirin-indicated subgroup) were incorrect and presented a misleading view of the difference in risk between Vioxx and naproxen; and (iii) cardiovascular data were deleted from the article before submission. The editors renewed their criticisms in an "Expression of Concern Reaffirmed," which the New England Journal of Medicine

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[48] Roni Rabin*, Vioxx Was Long Under Research Microscope, Newsday, Oct. 12, 2004, at B47.

published in March 2006. The same March edition also carried a "Response to Expression of Concern Regarding VIGOR Study" by the non-Merck authors of the VIGOR Trial article.

In sum, according to critics, the VIGOR Trial article did not present a scientifically honest view of the cardiovascular data, or the risks of Vioxx.

b. Our Findings and Conclusions.

The article on the VIGOR Trial, which was authored by 11 non-Merck members of the VIGOR Trial Steering Committee and two MRL scientists, Dr. Alise Reicin and Dr. Deborah Shapiro, was published in the New England Journal of Medicine in November 2000. The lead author of the article was Dr. Claire Bombardier*, a rheumatologist at the University Health Network in Toronto, Canada. Dr. Loren Laine*, a gastroenterologist from the University of Southern California School of Medicine in Los Angeles, California, also assumed a principal role in drafting the article, along with Dr. Reicin. The article, entitled "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," focused on the gastrointestinal results of the VIGOR Trial, which was designed to focus on gastrointestinal outcomes, not on cardiovascular risks.

With respect to cardiovascular data, the article included percentages of patients in each group who experienced cardiovascular events, including myocardial infarctions, and set forth the 4% aspirin-indicated subgroup analysis:

> The rate of death from cardiovascular causes was 0.2 percent in both groups. Ischemic cerebrovascular events occurred in 0.2 percent of the patients in each group.

> Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent, 95 percent confidence interval for the difference, 0.1 to 0.6 percent; relative risk, 0.2, 95 percent confidence interval, 0.1 to 0.7). Four percent of the study subjects met the criteria of the Food and Drug Administration (FDA) for the use of aspirin for secondary cardiovascular prophylaxis (presence of a history of myocardial infarction, angina, cerebrovascular accidence, transient ischemic attack, angioplasty, or coronary bypass) but were not taking low-dose aspirin therapy. These patients accounted for 38 percent of the patients in the study who had myocardial infarctions. In the other patients the difference in the rate of myocardial infarction between groups was not significant (0.2 percent in the rofecoxib group and 0.1 percent in the naproxen group). When the data showing a reduction in the rate of myocardial infarction in the naproxen group became available after the completion of this trial, Merck, the manufacturer of rofecoxib, notified all investigators in ongoing studies of a change in the exclusion criteria to allow patients to use low-dose aspirin. There was no association between hypertension and myocardial infarction; only a single patient (in the rofecoxib group) had both hypertension and a myocardial infarction as adverse events.[49]

The article also stated:

> The rate of myocardial infarction was significantly lower in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent). This difference was primarily accounted for by the high rate of myocardial infarction among the 4 percent of the study population with the highest risk of a myocardial infarction, for whom low-dose aspirin is indicated. The difference in the rates of myocardial infarction between the rofecoxib and naproxen groups was not significant among the patients without indications for aspirin therapy as secondary prophylaxis.

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[49] Bombardier* C, Laine* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 1523.

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> [O]ur results are consistent with the theory that naproxen has a coronary protective effect and highlight the fact that rofecoxib does not provide this type of protection owing to its selective inhibition of [Cox-2] at its therapeutic dose and at higher doses. The finding that naproxen therapy was associated with a lower rate of myocardial infarction needs further confirmation in larger studies.[50]

The percentages included in the article reflected data reported before February 10, 2000 – a cut-off date that MRL scientists had set before the VIGOR Trial data were unblinded. The Merck authors of the VIGOR article did not discuss with the non-Merck authors of the article or with the New England Journal of Medicine editors the fact that the cardiovascular data presented in the article were based on a pre-specified reporting cut-off date of February 10, 2000 while the pre-specified reporting cut-off date for gastrointestinal events was March 9, 2000. While it may have been prudent to state that fact in the article, we have found no evidence that the failure to do so was motivated by an intent to deceive. In addition, the facts that (i) the article as published reported a statistically significant difference in the incidence of cardiovascular events between Vioxx and naproxen, and (ii) beginning in February 2001, Merck circulated reprints of the article with a cover letter disclosing the post-cut-off data, indicate to us that the presentation of the cardiovascular data in the VIGOR article was not intended to mislead.

The documentary evidence provides a rationale for why and how the February 10 reporting cut-off date for cardiovascular events was selected and demonstrates that it was

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[50] Bombardier* C, Laine* L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med. 2000;343:1520-28, at 1526-27.

chosen before anyone at Merck had been unblinded to the VIGOR Trial results. In brief, MRL scientists fixed the February 10 cut-off date after the Data Safety and Monitoring Board for the VIGOR Trial (a group of five external scientists) asked Merck to create and implement a plan specifically to analyze the cardiovascular data from the VIGOR Trial (in addition to analyzing them as part of a future pooled analysis of Vioxx cardiovascular data from several studies). Although all adverse event data were routinely analyzed in clinical trials, pre-specified detailed analysis plans for specific adverse events were not the norm. Because the VIGOR Trial was a gastrointestinal safety trial, the VIGOR Trial Data Analysis Plan pre-specified an analysis plan for gastrointestinal events but there was no pre-specified plan for analyzing cardiovascular data, nor were adjudications of cardiovascular events proceeding at the same pace as adjudications of gastrointestinal events. In order to satisfy the Data Safety and Monitoring Board's request and still meet the internal deadline that Merck had set for submitting to the FDA the supplemental New Drug Application in support of its request for a label change, Merck set a reporting cut-off of February 10, 2000 for cardiovascular adverse events. This meant that all cardiovascular events reported by the cut-off would be adjudicated, analyzed, and included in the FDA submission, set for June 2000. Merck would still adjudicate and report to the FDA in periodic Safety Update Reports any cardiovascular adverse events reported after the cut-off.

When the authors of the VIGOR article first submitted a manuscript to the New England Journal of Medicine on May 18, 2000, they used the cardiovascular data reported prior to the February 10, 2000 cut-off date – the same data that Merck had used

in its cardiovascular analysis submitted to the FDA in support of the supplemental New Drug Application. By July 5, 2000, the cardiovascular events reported after the February 10 reporting cut-off date had been adjudicated and analyzed, and included three additional myocardial infarctions, all on Vioxx and all in patients not indicated for low-dose aspirin cardiovascular prophylaxis (the "non-aspirin-indicated" subgroup).

Based on the additional data, the percentage of patients in the Vioxx arm who experienced myocardial infarctions rose from 0.4% (17) to 0.5% (20) overall, whereas the percentage of patients in the naproxen arm who experienced myocardial infarctions remained the same. In addition, since all of the additional myocardial infarctions occurred among Vioxx patients in the non-aspirin-indicated subgroup, the between-treatment difference in myocardial infarctions in that subgroup increased from a two-fold to a three-fold difference. Still, the article's statement that there was not a statistically significant between-treatment difference in myocardial infarctions in the non-aspirin-indicated subgroup remained accurate.

The authors of the VIGOR article sent their first revised manuscript back to the New England Journal of Medicine on July 17, 2000 and continued revising the manuscript in conjunction with the New England Journal of Medicine editors through early October without, as indicated above, including the additional adjudicated data.

According to Dr. Alise Reicin, an MRL scientist and one of the two Merck authors of the VIGOR article, the cardiovascular data reported and adjudicated after the February 10 cut-off did not materially affect the conclusions stated in the article. Because she believed that the post-February data did not make a material difference to

the conclusion, and because the set of data presented in the article was based on a reporting cut-off date that was established before data were unblinded, Dr. Reicin did not think it was necessary to advise the other authors of the updated data, and she did not do so.

Finally, we found no evidence to suggest that the authors' decision to delete a table of cardiovascular data before submitting the manuscript was made to mislead. A draft of the manuscript created prior to its submission to the New England Journal of Medicine had included a table of cardiovascular data that listed the raw numbers of total deaths, cardiovascular deaths, myocardial infarctions, and ischemic strokes that occurred in each treatment group, as well as the percentages of the total patients within each treatment group who experienced such events. This table was deleted from the draft manuscript on May 16, 2000, two days prior to its submission to the New England Journal of Medicine. Data on all of the individual endpoints from that table were included in the text of the article in percentage form (from which the raw numbers could be derived mathematically), and none of the underlying data were "hidden." The deleted table did not include data from after the February 10, 2000 reporting cut-off date.

Neither the anonymous peer reviewers nor the editors at the New England Journal of Medicine who received drafts of the manuscript presenting the data in percentages requested that the authors include the raw cardiovascular data or insert a cardiovascular data table. The New England Journal of Medicine editors required the authors to eliminate some of their other tables and figures to meet the Journal's limit of five total tables and figures. One peer reviewer requested inclusion of the relative risk and

confidence interval for myocardial infarctions and these data were included in the revised manuscript and final article.

The non-Merck authors of the article collectively submitted a response on January 16, 2006 to the Journal editors' November 2005 editorial, which was published in the New England Journal of Medicine on March 16, 2006. The non-Merck authors stated that, while they had not been aware that additional adjudicated data were available before the article was published, they stood by the article as published:

> [W]e stand by our original article, which was written in line with basic clinical trial principles, specifying that data must be analyzed according to plans that are determined before unblinding. Thrombotic cardiovascular events were not deleted from the manuscript, and there is no material difference in the conclusion, that arise from the addition of the events reported after the predefined close-out date for cardiovascular events.[51]

It bears mention that had the three myocardial infarctions reported after February 10 been in the naproxen, and not the Vioxx, group, Merck quite likely would have been subject to criticism for altering the conclusions of the article to incorporate new data.

It is also worth noting that the press release that Merck issued on November 23, 2000, the same day as the article was published, did not mention the aspirin-indicated subgroup analysis. The release focused on the gastrointestinal results of the VIGOR Trial, but plainly stated that there were "significantly fewer heart attacks" in the naproxen

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[51] Bombardier* C, Laine* L, Burgos-Vargas* R, et al. Response to expression of concern regarding VIGOR study [letter]. N Engl J Med. 2006;354:1196-98, at 98.

arm of the study than in the Vioxx arm, which, the release stated, was consistent with naproxen's ability to block platelet aggregation due to its suppression of Cox-1.

10. Allegation No. 10: Merck Recognized that Vioxx Was Prothrombotic, and Secretly Tried to Reformulate It.

a. Summary of Allegation.

Merck's critics have argued that despite Merck's public statements that the VIGOR Trial cardiovascular data were explained by the naproxen cardioprotection hypothesis, Merck "privately sought to reformulate Vioxx in 2000 to reduce its cardiovascular side effects."[52] Critics have further alleged that, in fact, Merck submitted a patent application for a reformulated drug while it was denying publicly that Vioxx could cause heart attacks and strokes.[53] According to the Philadelphia Inquirer, an internal company document from 2000 regarding this patent application acknowledged that "the way in which Vioxx reduces pain might also increase cardiovascular problems."[54] It is claimed that Merck executives thus understood the cardiovascular risks of Vioxx and sought a patent "for a method of combining Vioxx with another agent to lessen the risk."[55]

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52 Documents Show Merck Researchers Knew Risks, Miami Herald, June 23, 2005, at 11A.

53 Thomas Ginsberg*, Merck Sought to Trim Vioxx Risk, Phila. Inq., June 23, 2005, at A1.

54 Thomas Ginsberg*, Merck Sought to Trim Vioxx Risk, Phila. Inq., June 23, 2005, at A1.

55 Thomas Ginsberg*, Merck Sought to Trim Vioxx Risk, Phila. Inq., June 23, 2005, at A1.

b. Our Findings and Conclusions.

At various times from 1998 (before Vioxx was approved for sale) through September 2004, when it was withdrawn from the market, Merck, with input from external consultants including Drs. John Oates* and Garret FitzGerald*, considered combining Vioxx with various antiplatelet agents.

Throughout this period, MRL scientists recognized the potential competitive advantage to be gained from combining Vioxx with an antiplatelet agent that would provide aspirin-style cardioprotection to high-risk patients without compromising the gastrointestinal-sparing effect of Vioxx. In addition, following the release of data from the VIGOR Trial, some MRL scientists recognized that, if in fact Vioxx inhibited prostacyclin in the vasculature, such inhibition might have an as-yet unproven clinical impact in certain high-risk patients who had a preexisting imbalance between prostacyclin and thromboxane. MRL scientists theorized that combining Vioxx and an antiplatelet agent into a single drug could potentially correct any preexisting imbalance and eliminate any theoretical cardiovascular risk of Vioxx in these patients.

The Company filed two patent applications – one in 1998 and one in 2000 – covering Vioxx combination therapies, but the Company did not actively pursue the development of either combination therapy option. Rather, beginning in 2002, the Company focused on the possibility of combining Vioxx with drugs that release nitric oxide, a gastroprotective agent. Such a combination, it was hypothesized, would enable patients to take a combination of nitric oxide and Vioxx concomitantly with low-dose aspirin without any gastrointestinal side effects. This combination, if proven to be

effective at eliminating the gastrointestinal risk of concomitant administration of Vioxx plus aspirin, would have provided the Company with a competitive advantage in the market of Vioxx users who were also at high cardiovascular risk.

While the scientists who were involved in attempting to develop a combination therapy were aware of Dr. FitzGerald's* prostacyclin hypothesis and the debate surrounding the VIGOR Trial cardiovascular data, there is no evidence that MRL senior scientists' considerations of combination therapy options arose from an actual belief that Vioxx was prothrombotic. Indeed, an internal memorandum prepared by Dr. Mervyn Turner, the head of Merck's Worldwide Licensing and External Research Department, in September 2002 concerning a possible nitric oxide/Vioxx combination states: "We do not believe that the VIGOR study represents a true prothrombotic property of coxibs."[56]

The evidence establishes that the Merck scientists' objective in pursuing a combination therapy was to develop a new drug with properties superior to those of any other drug, including Vioxx, not to protect against a known prothrombotic effect of Vioxx.

11. Allegation No. 11: Merck's Pooled Analyses Were Flawed.

a. Summary of Allegation.

In an effort to show that the VIGOR Trial was an outlier and that other clinical data did not show that Vioxx presented a cardiovascular risk, Merck conducted a number of "pooled" or meta-analyses of its Vioxx trials. It has been argued that these pooled

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[56] 9/12/02 email from M. Turner to J. Lasota, MRK-AEG0037638, at 38.

analyses are flawed for at least two reasons. First, it allegedly was improper to pool data from Merck's Phase II/III osteoarthritis trials with the VIGOR Trial data because the earlier trials involved different patient populations, involved fewer patients, and were of shorter durations.[57] Second, the composite endpoint that Merck used in its pooled analyses did not focus, as it should have, on the differences in heart attack rates between Vioxx and the comparator drugs or placebo.[58] It is argued that had Merck not used a composite endpoint, Vioxx would have been shown to be worse than the other treatments.[59]

b. Our Findings and Conclusions.

As discussed above, after reviewing the FitzGerald prostacyclin hypothesis and data from Merck's Vioxx clinical development program at its May 1998 meeting, Merck's Board of Scientific Advisors recommended that, although Merck's clinical data did not reveal any cardiovascular risk of Vioxx, Merck should establish a process to monitor, on a program-wide basis, the cardiovascular profile of Vioxx. The Board of Scientific Advisors noted that individual trials of Vioxx would be too small and therefore

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57 4/8/05 expert report of R. Kronmal*, at 15 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

58 Juni* P, Nartey* L, Reichenbach* S, Sterchi* R, Dieppe* PA, Egger* M. Risk of cardiovascular events and rofecoxib: cumulative meta analysis. Lancet. 2004;364:2021-2029, MRK-AJK0010752 (11/4/04 online [in press] copy), at 5.

59 4/8/05 expert report of R. Kronmal*, at 17 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); see also Juni* P, Nartey* L, Reichenbach* S, Sterchi* R, Dieppe* PA, Egger* M. Risk of cardiovascular events and rofecoxib: cumulative meta analysis. Lancet. 2004;364:2021-2029, MRK-AJK0010752 (11/4/04 online [in press] copy), at 5.

underpowered to detect any potential cardiovascular effect.[60] The Board therefore recommended that Merck plan to pool cardiovascular event data from several of its future Vioxx trials to have sufficient power to assess the effect of Vioxx on cardiovascular risk. The Board of Scientific Advisors further advised that Merck should create a uniform set of criteria by which such events would be adjudicated so as to facilitate future pooling. In accordance with these recommendations, MRL scientists devised the Cardiovascular Adjudication Standard Operating Procedure, discussed above.

It was understood that the first pooled analysis would be performed when MRL determined that there was a sufficiently large body of cardiovascular clinical trial data so that such an analysis would be statistically meaningful. In August 2000, after the VIGOR Trial data and data from several other clinical trials of Vioxx had become available, MRL scientists and biostatisticians discussed the logistics and methods for the first pooled analysis. To increase the data pool, MRL scientists determined that the pooled analysis should also include the investigator-reported (unadjudicated) data from the trials that pre-dated the Cardiovascular Adjudication SOP. In the process of devising the plan for the analysis, MRL scientists discussed how to define the endpoints of the analysis.

Two different composite endpoints were considered: (i) the Antiplatelet Trialists' Collaboration ("APTC") composite endpoint; and (ii) a composite endpoint consisting of events enumerated under the Cardiovascular Adjudication SOP (the "confirmed thrombotic endpoint"). The APTC composite endpoint consisted of cardiovascular death,

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[60] The concept of power is discussed in Exhibit 3 to the Report.

myocardial infarction, stroke (both ischemic and hemorrhagic), and death due to unknown cause or due to bleeding. The confirmed thrombotic endpoint included cardiac events (such as acute myocardial infarction), cerebrovascular events (such as ischemic cerebrovascular stroke), as well as peripheral vascular events (such as pulmonary embolism), but did not include unknown cause death.

MRL scientists noted that each endpoint had certain advantages and disadvantages. For example, they noted that the APTC composite endpoint had wide acceptance in the scientific community and consisted of events that had a high confirmation rate in the course of the adjudication process. The fact that it included "hard" endpoints such as myocardial infarction and stroke meant that investigators tended to diagnose these events correctly, which decreased the probability of including in the pooled analyses misdiagnosed events from the trials that pre-dated the Cardiovascular Adjudication SOP. At the same time, however, the APTC composite endpoint included non-thrombotic events, such as hemorrhagic strokes and unknown deaths, that, if included in the analysis, might dilute the power of the analysis to detect a difference in thrombotic events, or, in the case of hemorrhagic strokes, might bias the analysis in favor of Vioxx (which had no antiplatelet effect) as compared to traditional nonselective NSAIDs (which were known to increase bleeding time).

With regard to the confirmed thrombotic endpoint, MRL scientists noted that although it included only thrombotic events (thus directly addressing the issue of whether Vioxx was prothrombotic), it encompassed "soft" events that were misdiagnosed more

frequently by investigators (thus increasing the probability of including in the analysis misdiagnosed events from trials that pre-dated the Cardiovascular Adjudication SOP).

The evidence shows that MRL scientists discussed the pros and cons of each endpoint internally and with external experts. Dr. Carlo Patrono*, an expert on antiplatelet agents and a member of the Antiplatelet Trialists' Collaboration, favored using the APTC composite endpoint. In addition, the APTC composite endpoint was the most commonly accepted endpoint used in trials evaluating antithrombotic agents. MRL scientists chose the APTC composite endpoint as the primary endpoint for the analysis and the confirmed thrombotic endpoint as the secondary endpoint.

MRL submitted the results of its first pooled analysis to the FDA on January 8, 2001. The results of the analysis were also published in an article co-authored by MRL scientists and Dr. Marvin Konstam*, Chief of Cardiology at the New England Medical Center and an MRL consultant, in Circulation on November 6, 2001 (the "Konstam article"). The results of the pooled analysis showed, among other things, that patients on Vioxx had (i) a significantly increased risk of APTC composite endpoint events compared to patients on naproxen (relative risk 1.69; 95% confidence interval, 1.07 to 2.69), and (ii) a similar (and numerically decreased) risk of APTC composite endpoint events compared to patients on non-naproxen NSAIDs (relative risk 0.79; 95% confidence interval, 0.40 to 1.55) as well as to those on placebo (relative risk 0.84; 95% confidence interval 0.51 to 1.38).

Based on the results of the analysis, the Konstam article concluded that "[d]ata from >28,000 patients in 23 studies representing >14,000 patient-years at risk

demonstrated that rofecoxib was not associated with excess CV thrombotic events compared with either placebo or non-naproxen NSAIDs." With regard to naproxen, the article stated that "[t]he data suggest[ed], but [were] insufficient to ascertain, the cardioprotective benefits of naproxen."[61]

The data submitted to the FDA and published in the Konstam article presented the overall results, the results by individual event type, as well as the results for the separate patient populations: patients with osteoarthritis, patients with rheumatoid arthritis and patients with Alzheimer's disease. In addition, Merck provided the data from each of the individual trials broken down by event-type to the FDA in Clinical Study Reports and periodic Safety Update Reports.

As subsequent trials of Vioxx ended and more cardiovascular adverse event data became available, MRL updated its pooled analysis and submitted updated results to the FDA, including on January 19, 2001 (this time, at the FDA's request, excluding from the pooled analysis all studies of fewer than six months), in July 2001, May 2002, and March 2004. Merck published the data from its July 2001 pooled analysis in a 2003 review article by Matthew Weir* et al. (including 1,783 patient-years in addition to the data included in the Konstam article) in The American Heart Journal.[62] The results of

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61 Konstam* MA, Weir* MR, Reicin AR, et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. Circulation. 2001;104:2280, at 87. MRK-ADY0002799.

62 Weir* MR, Sperling RS, Reicin A, Gertz BJ. Selective COX-2 inhibition and cardiovascular effects: a review of the rofecoxib development program. Am Heart J. 2003;146:591-604. MRK-AHN0014891.

these subsequent pooled analyses were consistent with the results of the original pooled analysis submitted to the FDA on January 8, 2001 and published in the Konstam article.

There is no evidence to suggest that the deliberative process that Merck scientists undertook internally and with their external consultants to select a composite endpoint for the analysis was designed to hide any risk. To the contrary, the record is clear that Merck's very purpose in conducting the pooled analyses was to investigate whether Vioxx presented any cardiovascular risk to patients that individual trials were unable to detect.

12. Allegation No. 12: Merck Intentionally Withheld from the FDA a Meta-Analysis of Myocardial Infarctions in the Vioxx Program.

a. Summary of Allegation.

It has been argued that Merck intentionally withheld from the FDA data regarding the cardiovascular safety of Vioxx, including a meta-analysis of the myocardial infarction endpoint. Specifically, critics assert that Merck performed a meta-analysis in late 2000, which they allege demonstrated that Vioxx caused significantly more myocardial infarctions than NSAID comparators and placebo, but did not include it in the "Interim Cardiovascular Meta-analysis" submitted to the FDA on January 8, 2001. That submission, as discussed in response to Allegation No. 11, analyzed only the Antiplatelet Trialists' Collaboration ("APTC") composite cardiovascular endpoint, which allegedly produced more favorable results than the meta-analysis of the myocardial infarction endpoint.

b. Our Findings and Conclusions.

The evidence shows that early internal drafts of the first Vioxx cardiovascular meta-analysis that Merck planned to submit to the FDA had included a section reviewing a meta-analysis of the myocardial infarction endpoint. Neither this section nor any reference to a meta-analysis of myocardial infarctions, however, was included in the "Interim Cardiovascular Meta-analysis" provided to the FDA on January 8, 2001. As discussed above, that meta-analysis included only an analysis of the widely accepted APTC composite endpoint, which included a number of thrombotic and other cardiovascular events.

Both the APTC composite endpoint meta-analysis and the myocardial infarction meta-analysis included analyses of event rates for Vioxx as compared to (i) non-naproxen NSAIDs and placebo combined and (ii) all comparators combined (i.e., any nonselective NSAID, including naproxen, and placebo). With respect to the first comparison, neither the APTC meta-analysis nor the myocardial infarction meta-analysis showed a statistically significant difference in the event rates between Vioxx and the combined comparators, and in fact both meta-analyses showed a small numerical decrease in the event rate on Vioxx.

With respect to the second comparison, however – which included naproxen – the meta-analysis of myocardial infarctions showed a statistically significantly higher event rate on Vioxx, which did not emerge in the APTC composite cardiovascular endpoint analysis that Merck submitted to the FDA. This second comparison (between Vioxx and all comparators combined) was driven to a large extent by the Vioxx-naproxen

component. In addition, according to MRL scientists, the validity of this comparison was subject to question because there was not sufficient homogeneity between the blocks of data from the studies included in the comparison, meaning that they were sufficiently different that it was not appropriate to group naproxen together with all other comparators for meta-analysis purposes. This fact was noted in Merck's FDA submission of the APTC composite endpoint meta-analysis.

We have found no evidence suggesting that MRL scientists failed to include the meta-analysis of myocardial infarctions for the purpose of hiding or misrepresenting data. Rather, the "Interim Cardiovascular Meta-analysis" submitted to the FDA included data broken out by individual events for each pooled comparison (including the number of myocardial infarction events and relevant patient years), which FDA statisticians could have used to conduct a meta-analysis of myocardial infarctions. Although the FDA responded to Merck's meta-analysis of APTC composite endpoint events by asking for several additional analyses, it did not request that Merck provide a meta-analysis of myocardial infarctions.

In addition, after January 2001, Merck provided the FDA with updated meta-analyses and submitted periodic Safety Update Reports with cardiovascular (including myocardial infarction) event data. We are not aware of any evidence that Merck attempted to conceal any cardiovascular data from the FDA.

13. Allegation No. 13: Merck Confirmed the Cardiovascular Safety of Vioxx Through Misleading Promotion.

a. Summary of Allegation.

Throughout 2000 and 2001, it is claimed that "'Merck issued a relentless series of publications reconfirming the drug's safety"[63] and continued to "confirm the safety profile of Vioxx" in press releases[64] and at medical conferences so that the public and physicians prescribing Vioxx would erroneously believe that it was safe. Critics rely on the fact that the FDA's Division of Drug Marketing, Advertising, and Communications (known as DDMAC) sent Merck a Warning Letter in September 2001 criticizing the Company's promotion of Vioxx as misleading and stating that it was "simply incomprehensible" that Merck would claim that Vioxx posed no cardiovascular risk.[65] In addition, DDMAC stated that the "naproxen benefit hypothesis was hypothetical and was not the only reasonable explanation for the VIGOR results."[66]

b. Our Findings and Conclusions.

The September 17, 2001 Warning Letter focused on three sets of events: (i) six promotional audio conferences presented on Merck's behalf by an outside speaker who

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63 Sharon Kirkey*, Vioxx-maker Valued Sales Over Safety, The Gazette (Montreal), Oct. 7, 2004, at A12 (quoting Dr. Eric Topol*).

64 See, e.g., 4/28/00 Merck press release, "Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx®," MRK-ABI0002231-32; 5/22/01 Merck press release, "Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx®," MRK-ABI0003228-30.

65 Barbara Martinez*, Vioxx Lawsuits May Focus on FDA Warning in 2001, Wall St. J., Oct. 15, 2004, at B1.

66 Barbara Martinez*, Vioxx Lawsuits May Focus on FDA Warning in 2001, Wall St. J., Oct. 15, 2004, at B1.

allegedly misrepresented the safety profile of Vioxx; (ii) allegedly misleading oral representations by two sales representatives to FDA officials at two pharmacists' conferences; and (iii) a press release issued on May 22, 2001 that claimed that Vioxx had a "favorable cardiovascular profile."

Specifically, in the September 2001 Warning Letter, DDMAC asserted:

> You have engaged in a promotional campaign for Vioxx that minimized the potentially serious cardiovascular findings that were observed in the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, and thus, misrepresents the safety profile for Vioxx. Specifically, your promotional campaign discounts the fact that in the VIGOR study, patients on Vioxx were observed to have a four to five fold increase in myocardial infarctions (MIs) compared to patients on the comparator non-steroidal anti-inflammatory drug (NSAID), Naprosyn (naproxen).[67]

DDMAC further alleged that Merck's promotional campaign failed "to disclose that [the naproxen cardioprotection hypothesis was] hypothetical, [had] not been demonstrated by substantial evidence, and that there [was] another reasonable explanation, that Vioxx may have pro-thrombotic properties."[68]

As discussed more fully in Appendix G, Merck conducted an investigation of the issues identified in DDMAC's Warning Letter and, on October 1, 2001, Mr. David Anstice, President, Human Health – The Americas, sent DDMAC a written response.[69] Mr. Anstice's letter stated that Merck strongly disagreed with DDMAC's assertion that

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67 9/17/01 FDA Warning Letter from T. Abrams* to R. Gilmartin, MRK-AAF0007777, at 77.

68 9/17/01 FDA Warning Letter from T. Abrams* to R. Gilmartin, MRK-AAF0007777, at 77.

69 10/1/01 letter from D. Anstice to T. Abrams*, MRK-AFT0007691-99.

Merck had "engaged in a promotional campaign for Vioxx that minimized the potentially serious cardiovascular findings that were observed" in the VIGOR Trial and its assertion that Merck's May 22, 2001 press release was false or misleading.

With regard to the six promotional audio conferences discussed in the Warning Letter, Mr. Anstice's response explained that Merck had strict policies, designed to enforce federal regulations, concerning the promotion of its products. He informed DDMAC that all outside speakers were required to sign a contract with Merck in which they agreed that they would not make any off-label claims in their presentations and would provide fair balance. Mr. Anstice acknowledged that the outside speaker cited in the Warning Letter had violated Merck's policies at these audio conferences and informed DDMAC that Merck had discontinued using the speaker.

With respect to the second issue raised in the Warning Letter – Merck's May 22, 2001 press release – Merck's response letter explained that the May 22 press release was issued "in response to media and analyst activity and was not proactively issued to promote the cardiovascular safety profile of Vioxx."[70] As explained in the letter, Merck issued the press release in response to two events: (i) an April 27, 2001 analyst's report by Richard Stover* of Arnhold & S. Bleichroeder, Inc., entitled "Cox-2 Inhibitor Outlook: Cardiovascular Safety Issues Raised in FDA Advisory Committee Meetings," which concluded, in part, that naproxen did not show a cardioprotective effect in the VIGOR Trial, and (ii) a May 22, 2001 article in The New York Times, entitled "Doubts

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[70] 10/1/01 letter from D. Anstice to T. Abrams*, MRK-AFT0007691, at 94.

are Raised on the Safety of 2 Popular Arthritis Drugs," which cited Mr. Stover's* report questioning the cardiovascular safety of both Vioxx and Celebrex and which had been picked up by the television media.[71]

Merck's press release, entitled "Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx," stated that Vioxx had a "favorable cardiovascular safety profile."[72] Mr. Anstice further stated:

> . . . the [Warning] Letter appears to create an affirmative obligation to disclose alternative explanations for data in a communication whose very purpose is to respond to and debate those same alternative explanations. . . [and] does not acknowledge the fact that substantial balance, including the existence of alternative hypotheses, was included in that press release.[73]

Merck argued that "The First Amendment protects Merck's right to respond under these circumstances with information that is truthful and not misleading, as well as the public's right to hear both sides of the story."[74] Merck's subsequent releases regarding Vioxx and the VIGOR Trial, however, were more explicit regarding alternative explanations for the VIGOR Trial results.

With respect to the third issue raised in the Warning Letter – oral representations made by sales representatives at two pharmacists' conferences regarding the

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71 10/1/01 letter from D. Anstice to T. Abrams* attaching documents, MRK-AFT0007691, at 700-40.

72 5/22/01 Merck press release, "Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx®," MRK-ABI0003228, at 28.

73 10/1/01 letter from D. Anstice to T. Abrams*, MRK-AFT0007691, at 94-95.

74 10/1/01 letter from D. Anstice to T. Abrams*, MRK-AFT0007691, at 95.

cardiovascular safety profile of Vioxx – Mr. Anstice advised DDMAC that if Merck's investigation of the allegations revealed that sales representatives acted contrary to the "long-standing written policies that govern the activities of all field-based personnel," Merck would take appropriate disciplinary action.

After consultation with DDMAC, including teleconferences and a meeting in late October of 2001, Merck sent two DDMAC-approved "Dear Healthcare Provider" letters on November 19, 2001 to attendees of the audio and pharmacists' conferences who could have been exposed to the explanations for the VIGOR Trial cardiovascular rates that focused solely on the naproxen cardioprotection hypothesis. The letters stated that DDMAC objected to claims "that the FDA asserts were misleading about the significant cardiovascular findings in the Vioxx Gastrointestinal Outcomes Research ("VIGOR") study."[75] The letters further stated:

> Alternative interpretation[s] have been proposed for the difference in the rates of myocardial infarctions (MI) in the Vioxx treatment group in comparison with the naproxen treatment group. Possible explanations include that Vioxx increased the MI rate or naproxen decreased the MI rate. The underlying reason for the difference has not been established in prospectively designed clinical studies.[76]

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[75] 11/19/01 letter from T. Casola to T. Abrams* attaching Dear Healthcare Provider letters, MRK-AAF0007880, at 82, 89.

[76] 11/19/01 letter from T. Casola to T. Abrams* attaching Dear Healthcare Provider letters, MRK-AAF0007880, at 82, 89.

On January 2, 2002, DDMAC sent Merck a letter stating that based on these corrective actions, it considered the matter "satisfactorily resolved" and "closed."[77] DDMAC did not require Merck to take any corrective action concerning the press release. Merck did not receive any additional warning letters from DDMAC alleging that Merck's promotion of Vioxx was improper. In addition, as discussed at pages 116 and 117 and 120 through 121 below, in late 2001, Merck introduced a Company-wide campaign to underscore the importance of compliance, in part to ensure that Merck product promotion complied with federal regulations as well as Merck policies.

14. Allegation No. 14: Other Merck Studies Showed that Vioxx Was Dangerous, But Merck Ignored or Hid the Results.

a. Summary of Allegation.

It is alleged that cardiovascular data from the VIGOR Trial were not the only data that revealed Vioxx's cardiovascular risk. According to critics, data from other Merck clinical trials – available long before the APPROVe Trial data were unblinded – raised a red flag about the cardiovascular safety of Vioxx, but Merck chose to ignore them. A related criticism is that Merck selectively determined not to publish negative data from these trials.

First, it is argued that two twin studies conducted before Vioxx was approved for sale, Protocol 090 and Protocol 085, revealed an excess incidence of heart attacks in the Vioxx arm, but that Merck discounted the data because the studies were short.

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[77] 1/2/02 letter from L. Governale* to T. Casola, MRK-AAF0007894, at 94.

Second, it has been claimed that Merck's ADVANTAGE Trial likewise revealed an increased cardiovascular risk of Vioxx and that MRL scientist Dr. Alise Reicin tried to minimize these results by asking another MRL scientist, Dr. Eliav Barr, to alter the results to reflect that a certain death in that trial was not a heart attack.[78] In their email exchange, Dr. Reicin is alleged to have "repeatedly urged the researcher to change his views about the death 'so that we don't raise concerns.'"[79]

Third, it is claimed that although two placebo-controlled trials testing the efficacy of Vioxx both in treating and in preventing Alzheimer's disease did not indicate a difference in the incidence of cardiovascular events between the Vioxx and placebo arms, they showed that elderly people taking Vioxx were 4½ times "more likely to die than those in a placebo group."[80] According to Dr. Gurkirpal Singh*, director of the post-marketing drug surveillance program at Stanford University, the reason more patients on Vioxx were dying even though the rate of heart attacks and strokes was not higher was that "[t]hey were dying before they got a heart attack or stroke. . . ."[81] The argument continues that although interim data from the Alzheimer's trials did not reflect a

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78 Alex Berenson*, Evidence in Vioxx Suits Shows Intervention by Merck Officials, N.Y. Times, April 24, 2005; 11/8/00 email from A. Reicin to E. Barr, MRK-NJ0124427, at 27-28.

79 Alex Berenson*, Evidence in Vioxx Suits Shows Intervention by Merck Officials, N.Y. Times, April 24, 2005.

80 Judith Graham*, FDA Knew in 2002 that Vioxx Posed Risk; Agency Chose Not to Warn Doctors, Chicago Trib., February 10, 2005, at C1; see also 9/14/05 transcript of Humeston v. Merck & Co., ATL-L-2272-03 MT, N.J. Super. Ct. Law Div., at 39-40, 70.

81 Judith Graham*, FDA Knew in 2002 that Vioxx Posed Risk; Agency Chose Not to Warn Doctors, Chicago Trib., February 10, 2005, at C1.

cardiovascular risk, the studies revealed an increased incidence of cardiovascular events after 18 months, a fact that MRL scientists attributed – without support – to chance.

b. Our Findings and Conclusions.

The evidence shows that all relevant data with respect to the studies discussed above were submitted on a timely basis to the FDA and that Merck did not "ignore" or try to "hide" allegedly negative data.

Merck's Protocols 090 and 085 were twin 6-week trials that tested the comparative efficacy of Vioxx, placebo and nabumetone (a non-selective NSAID) in relieving the pain and inflammation associated with osteoarthritis. Merck submitted the trial data from these studies – including the cardiovascular data – to the FDA on June 29, 2000 with the supplemental New Drug Application for Vioxx. In the application, Merck highlighted the fact that these trials had included low-dose aspirin to support a claim that Vioxx could be administered concomitantly with aspirin. The trials each included approximately 1,000 patients, randomized among the three arms of the study.

In Protocol 090, of the 978 patients enrolled, investigators reported that 6 patients in the Vioxx arm experienced a serious cardiovascular event (including heart attacks), versus 1 in the placebo group and 2 in the nabumetone group. The difference in the incidence of serious cardiovascular events between treatment groups in Protocol 090 was not statistically significant and MRL scientists believed that the numbers were too small to be meaningful. (After these events were adjudicated, there were 5 serious cardiovascular events in the Vioxx arm, 0 in the placebo arm, and 1 in the nabumetone arm.)

Protocol 085 (the twin study), did not show any imbalance in serious cardiovascular events: there were 2 investigator-reported cardiovascular events in the Vioxx arm, 2 in the nabumetone arm, and 0 in the placebo arm. Dr. Maria Lourdes Villalba*, a medical reviewer at the FDA who reviewed data from Protocols 090 and 085 as well as other Vioxx trials following the VIGOR Trial, did not view these results as significant. In an internal FDA email, she stated:

> the number of events [in Protocol 090] was small and there was a twin study (085) with identical size and duration, conducted at approximately the same time, that showed no difference in CV thrombotic events as compared to placebo and nabumetone.[82]

These cardiovascular data were included in Merck's cardiovascular pooled analysis, which was published in Circulation in 2001. The data also were discussed in an article written by Dr. Eric Topol* of the Cleveland Clinic and published in JAMA in 2001. The efficacy and tolerability data from Protocol 090 (but not the cardiovascular data) were presented on a poster at the American Geriatric Society Conference in May 2001. An article including all of the Protocol 090 data, including cardiovascular data, was published in the Journal of Clinical Rheumatology in February 2006.

Data from the ADVANTAGE Trial (a 12-week trial of Vioxx versus naproxen in osteoarthritis patients that ended in April 2000) were likewise submitted to the FDA in support of Merck's supplemental New Drug Application. Dr. Barr subsequently reviewed all deaths that occurred in the course of the ADVANTAGE Trial to determine

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[82] 11/8/04 email from M. Villalba* to L. Lemley* and J. Woodcock*, FDACDER 023057.

which ones fell within the APTC composite cardiovascular endpoint and should therefore be included in the cardiovascular meta-analysis soon to be submitted to the FDA. Both Dr. Barr and Dr. Reicin agreed that the death at issue should be counted in the meta-analysis. Their disagreement was over whether Dr. Barr should retrospectively characterize a certain death as a heart attack, which, according to Dr. Reicin, would have raised concerns about process because all heart attacks were supposed to have been adjudicated but this event had not been adjudicated since it had not been reported by the investigator as a heart attack. The data were blinded and there is no evidence that either Dr. Barr or Dr. Reicin knew which treatment, Vioxx or naproxen, this patient was taking.

In the end, this death was counted in Merck's cardiovascular meta-analysis and was listed as an "unknown cause of death" in Merck's submission to the FDA. In an article about the ADVANTAGE Trial published in the Annals of Internal Medicine in 2003, the death was included in one composite grouping of cardiovascular events (the APTC composite endpoint analysis), but not in another.[83]

With respect to critics' claims about Merck's lack of transparency with data from the long-term Alzheimer's trials, while Merck had reviewed blinded, and then unblinded, cardiovascular data during the pendency of those trials, it was not until the spring of 2001 that mortality data from Protocol 091, the first of the Alzheimer's trials to end, were examined. The data showed that there was a mortality imbalance between the Vioxx and

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[83] Lisse* JR, Perlman* M, Johannson* G, et al. Gastrointestinal tolerability and effectiveness of robecoxib versus naproxen in the treatment of osteoarthritis: A randomized, controlled trial. Ann Intern Med. 2003;139:539-46.

placebo arms of the trial. The record establishes that based on these data, Merck unblinded mortality data from Protocols 078 and 126 and performed a combined analysis that showed 41 deaths in the Vioxx group and 24 deaths in the placebo group for the three Alzheimer's trials combined.

MRL scientists conducted analyses to investigate the data and determine whether there was a relationship between mortality and cardiovascular adverse events. These analyses showed that (i) there was a relatively equal distribution of cardiovascular events between the Vioxx and placebo groups and (ii) the mortalities were due to numerous causes. Because there was no discernable pattern to the mortalities, MRL scientists concluded that there was no causal nexus between Vioxx and the mortalities. The evidence shows that on July 12, 2001, Merck submitted a periodic Safety Update Report to the FDA, which provided safety data, including mortality data, from Protocols 078, 091 and 126. These data were incorporated into the revised Vioxx product labeling in 2002. Based on the evidence we reviewed, Merck did not hide or prevent dissemination of data from these trials.

The evidence further shows that at the time that final cardiovascular data from the Alzheimer's trials became available, MRL scientists did not believe that there was any significance to the apparent increase in the hazard rate after 18 months because, for the first 18 months, the incidence of cardiovascular events had been lower in the Vioxx group than in the placebo group. The rate of accumulating cardiovascular events in the Vioxx group began to exceed that of the placebo group after 18 months. Throughout the Alzheimer's trials, the difference in the cardiovascular event rate between the two arms

was not statistically significant, and the total incidence of cardiovascular events between Vioxx and placebo was almost exactly even. Therefore, MRL scientists and statisticians viewed the changes in the event rates as simply "noise" around the mean.

In addition to investigating publication of data from these trials specifically, we also reviewed Merck's policy on publishing the results of its clinical studies. The evidence showed that it had always been Merck's policy, as a general matter, to endeavor to publish the results of all Merck-sponsored clinical studies, regardless of outcome, with the exception of hypothesis-generating studies that Merck viewed as proprietary information. This guiding principle, while part of Merck's culture, was formally codified in 1999 and 2000, when Merck drafted and adopted its Code of Conduct for Clinical Trials.[84] This was precipitated by a discussion in the pharmaceutical industry about proper publication practices that arose because of a series of high profile events in the 1990s in which pharmaceutical companies other than Merck had been accused of attempting to block the publication of unfavorable data.[85] The Code of Conduct was a

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[84] See 9/12/01 slide presentation of L. Hirsch, H. Guess, and D. Thompson to CCRC, MRK-NJ0206001, at 06-07 (discussing Merck Clinical Trial Code of Conduct). At around the same time, Merck approved a new guidance on publication practices, which was the product of a joint effort by representatives from Merck, Glaxo Wellcom, AstraZeneca, and Eli Lilly. See id.; 12/99 Guidance Document, "Good Publication Practices: Guidelines for Pharmaceutical Companies," MRK-AGV0043414-18.

[85] See 9/12/01 slide presentation of L. Hirsch, H. Guess, and D. Thompson to CCRC, MRK-NJ0206001, at 05 (mentioning, among others, dispute between Knoll Pharmaceuticals and the University of California, San Francisco regarding synthroid and dispute between Apotex Pharmaceuticals and Dr. Nancy Oliveri regarding deferipone). The Code of Conduct was also a reaction to a series of two articles published in The New York Times in May 1999 that raised questions about the practice of Merck and other pharmaceutical companies paying large sums to clinical investigators and about fraud among the clinical investigators. Kurt Eichenwald* and Gina Kolata*, Drug Trials Hide Conflicts for Doctors, N.Y. Times, May 16, 1999, MRK-ABS0399414-31; Kurt Eichenwald* and

one-page list of key principles governing the ethical and scientific conduct of Merck-sponsored studies that was appended to the back of every study protocol.[86]

In the spring of 2001, a new department – the Medical Communications Department – was created to oversee all publication efforts. A more detailed publication policy, entitled "Merck Guidelines for Publication of Clinical Trials and Related Works," was adopted in September 2003.[87] The 2003 publication guidelines cover not only clinical trials, but also "related works," which include observational studies. The guidelines include detailed guidance on what studies should be published, what data should be included, what constitutes publication, and when studies should be published.[88]

Gina Kolata*, A Doctor's Drug Studies Turn Into Fraud, N.Y. Times, May 16, 1999, MRK-ABS0399398-412.

86 See, e.g., Merck Code of Conduct for Clinical Trials attached to APPROVe Trial Protocol, MRK-ABS0326111, at 185, 197.

87 9/23/03 "Merck Guidelines for Publication of Clinical Trials and Related Works," MRK-AGE0000593-600.

88 Recently, the pharmaceutical industry as a whole has tried to address the problem of selective publication of clinical studies. The National Institute of Health ("NIH") has established a national registry of clinical trials (http://www.clinicaltrials.gov) and the Pharmaceutical Research and Manufacturers of America ("PhRMA") has developed a database where the results of clinical trials can be posted and publicly viewed (http://www.clinicalstudyresults.org). Merck currently registers on the NIH registry all Phase II, III, and post-marketing trials in which treatment has been assigned and has begun posting the results of its hypothesis-testing studies on the PhRMA database as well. Merck Perspective, "Clinical Trials Registries and the Publication of Clinical Trial Results," http://www.merck.com (last updated September 2005).

15. Allegation No. 15: Merck Kept the Cardiovascular Safety Information Out of the Product Label.

a. Summary of Allegation.

Although the VIGOR Trial data were available in March 2000, the Vioxx label was not changed to reflect those data until April 11, 2002. Critics claim that Merck deliberately prolonged negotiations with the FDA over how the VIGOR Trial and ADVANTAGE Trial cardiovascular data should be reported in the label in an effort to forestall disclosure of those data.[89] When the new label finally was approved in April 2002, the cardiovascular risk information was not reported in the "Warning" section of the label but was mentioned only in the "Precaution" section. In addition, it has been argued that Merck, on its own initiative, could have effected a change to the label to make clear the cardiovascular risks of Vioxx.

b. Our Findings and Conclusions.

None of the evidence we have reviewed supports a conclusion that Merck intentionally sought to delay the label negotiations. To the contrary, the record reflects that Merck sought expedited review of its supplemental New Drug Application, which was submitted on June 29, 2000, so that the FDA would approve a label with the VIGOR Trial gastrointestinal data as quickly as possible. The FDA, however, denied expedited review and set an Advisory Committee meeting for February 8, 2001 to review Merck's application.

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[89] Anna Wilde Mathews*, Did FDA Staff Minimize Vioxx's Red Flags?, Wall St. J., November 10, 2004, at B1; Gardiner Harris*, F.D.A. Official Admits 'Lapses' on Vioxx, N.Y. Times, March 2, 2005, at A15.

Negotiations as to how the VIGOR Trial results would be characterized in the label, and where within the label they would be reported, did not begin in earnest until some months after the February 2001 FDA Advisory Committee meeting. On May 21, 2001, Merck submitted its third proposed label to the FDA. The FDA, however, did not counter-propose a label until almost five months later, on October 15, 2001. After this substantial time delay, for which there is no evidence that Merck was responsible, negotiations moved relatively quickly, with each side responding in a timely manner to the other party's proposal. From June 29, 2000 through April 11, 2002, Merck submitted a total of 12 draft label proposals to the FDA. The FDA submitted four counterproposals to Merck.

Importantly, the record reflects that the label negotiations were focused on much more than the presentation of cardiovascular data. Also of great significance to Merck was changing the standard NSAID-class gastrointestinal warning to reflect the positive results of the VIGOR Trial. To be sure, Merck and the FDA negotiated over the presentation of cardiovascular data and where within the label it should be included. MRL scientists and regulatory personnel did not believe that the Vioxx cardiovascular data supported a warning, which Merck believed should be reserved for known adverse effects. MRL scientists took the position that the VIGOR Trial cardiovascular data were explained by the naproxen cardioprotection hypothesis and not by any prothrombotic effect of the drug. The record reflects that MRL scientists, including regulatory personnel, believed that cardiovascular data from the VIGOR Trial and other Vioxx trials should be presented so that physicians could make their own risk/benefit analysis.

The FDA's October 15 counterproposal label with its suggested cardiovascular warning led Dr. Scolnick to write:

> twice in my life i have had to say to the FDA "That label is unacceptable. We will not under any circumstances accept it." . . . You WILL have to do that on the cardiac warning for Vioxx. . . . And i assure you i will NOT sign off on any lable (sic) that had a cardiac warning. the data review yesterday convinces me that we do not have an unsafe drug and i am willing if needed to spend several hours one on one with anyone at the FDA going through the data until they in fact get it[90]

Merck's next proposal, which the FDA accepted, moved the cardiovascular data to the Precautions section of the label, where it remained through the final version of the label.

There is some question whether it would have been possible for Merck to add the cardiovascular data from the VIGOR Trial to the Vioxx label prior to FDA approval in April 2002 through a "changes being effected" supplement. The regulations indicate that unilateral changes may be made at the election of the drug sponsor to add important known risk information to the label in certain situations. However, in the fall of 1999, the FDA denied Merck's use of the "changes being effected" process to add language to the Vioxx label based on post-marketing adverse experience data regarding concurrent administration of Vioxx and the blood-thinning drug warfarin. Moreover, MRL scientists did not believe that Vioxx posed a known cardiovascular risk because their review of the available data persuaded them that the cardiovascular effects seen in the VIGOR Trial were the result of the cardioprotective effect of naproxen.

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[90] 11/8/01 email from E. Scolnick to D. Greene, A. Nies and B. Goldmann, MRK-ACR0009287.

In hindsight, it may well be that the unilateral addition of a cardiovascular warning to the Vioxx label would have been beneficial to Merck in terms of defending against the numerous failure-to-warn products liability cases pending, but there is no basis on which to conclude that pursuing the standard FDA-approved label modification process rather than making changes unilaterally was unreasonable.

16. Allegation No. 16: Merck Announced – Then Cancelled – a Cardiovascular Outcomes Trial to Avoid Revealing That Vioxx Was Prothrombotic.

a. Summary of Allegation.

At the end of 2001, approximately 21 months after the VIGOR Trial data were unblinded, Merck announced that it would conduct a cardiovascular outcomes trial. In early 2002, Merck finally settled on a trial design, which it called the VALOR Trial. Merck established an outside Steering Committee for the VALOR Trial and began to line up investigators and sites at which patients would receive treatment. Then, on the eve of its start in March 2002, the VALOR Trial was cancelled abruptly, and without explanation. The VALOR Trial "was scheduled to produce data by March 2004 but may have provided answers about Vioxx's risks even earlier if patients had shown ill effects."[91]

It is argued that the Company's 21-month delay in scheduling the trial was inexcusable given the known risks of the drug, and that Merck only compounded the problem when it cancelled the study it had committed to conduct.

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[91] Barry Meier*, Merck Canceled an Early Study of Vioxx, N.Y. Times, Feb. 8, 2005, at C1.

b. Our Findings and Conclusions.

The criticism that MRL scientists knew or feared that Vioxx was prothrombotic and canceled the planned cardiovascular outcomes trial to avoid exposing that fact is not supported by the extensive evidence we have reviewed.

The evidence reveals that Merck made a series of efforts to design a cardiovascular outcomes trial that would answer the fundamental question of whether Vioxx was prothrombotic. Following the release of the VIGOR Trial data, MRL scientists immediately began to consider designing and implementing a cardiovascular outcomes trial to answer this question. By May 2000, however, MRL scientists had strengthened their view on the basis of all of the available clinical evidence that Vioxx did not pose a cardiovascular safety problem and had come to see that it would be difficult to design an ethical and feasible cardiovascular outcomes trial. In addition, members of the Marketing Department, who subsequently supported such a trial, had concluded at the time that it was not necessary. Accordingly, MRL decided not to embark on a lengthy and expensive outcomes trial at that time.

In 2001, however, competitors and critics intensified their claims that selective Cox-2 inhibitors in general, and Vioxx in particular, put patients at increased cardiovascular risk. These claims prompted MRL scientists to reconsider conducting a cardiovascular outcomes trial in the hopes that a successful trial would quell critics and prove to the public what MRL scientists already believed to be true: that Vioxx was not prothrombotic. In a September 13, 2001 email, Dr. Scolnick described MRL's

prioritization of clinical studies for the following year: "For Vioxx: Only the Cv outcome study. ONLY ESSENTIAL STUDY!"[92]

By that time, MRL scientists had already begun designing such a trial, and diligent attempts to do so continued throughout the fall of 2001 and early spring of 2002. MRL scientists well understood that the cleanest way to prove that Vioxx was not prothrombotic would be to test it against placebo. FDA policy, however, provides that a placebo-controlled trial must be designed to demonstrate some benefit of the test drug (i.e., a "superiority" hypothesis), rather than that no difference exists between the test drug and the comparator (i.e., a "non-inferiority" hypothesis). Additionally, the FDA generally disfavored placebo-controlled trials testing a non-inferiority hypothesis regarding cardiovascular safety, and enrolling patients in such a trial would not be feasible. Thus, a simple Vioxx versus placebo trial, focused on cardiovascular outcomes, was precluded by FDA guidelines.

MRL scientists and outside consultants developed several other design options involving an active comparator, but the inclusion of another drug in the study design would make it difficult to determine unambiguously whether Vioxx itself was prothrombotic because any differential seen in the results could – like the VIGOR Trial results – be interpreted to have been caused either by Vioxx or by the active comparator.

The evidence shows that around January 2002, Merck decided to conduct the VALOR Trial, which was a slightly more complex version of a placebo-controlled trial,

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92 9/13/01 email from E. Scolnick to D. Anstice et al., MRK-ABW0005624.

administering Vioxx or placebo in a population of high-cardiovascular risk patients, all of whom would take low-dose aspirin. The primary hypothesis was a superiority hypothesis predicated on the notion that, because atherosclerosis was believed to be an inflammatory disease, the anti-inflammatory properties of Vioxx would confer a cardiovascular benefit to patients in the Vioxx arm. The VALOR Trial was set to begin in the second quarter of 2002.

While MRL was still developing the final protocol for the VALOR Trial, Dr. Robert Silverman from MRL Regulatory Affairs met informally with Dr. Lawrence Goldkind*, Deputy Division Director at the FDA's Division of Anti-Inflammatory, Analgesics & Ophthalmic Drug Products, and discussed the proposed trial. Dr. Goldkind* expressed discomfort with the design and objective of the study and noted that any anti-inflammatory benefit Vioxx might provide was speculative and would be outweighed by greater risks. Dr. Silverman communicated Dr. Goldkind's* views to the VALOR Trial team, which prompted further internal discussion of the viability and ethics of such a design.

Dr. Peter Kim, then Executive Vice President for Research and Development at MRL, cancelled the trial in March 2002 for a variety of reasons, including the fact that the superiority claim of the study – that Vioxx might be beneficial to high-cardiovascular risk patients – was not strong enough in his view to justify, ethically, conducting the study. In addition, the inclusion of aspirin in the study would not produce a result that clearly answered the question of whether Vioxx alone had negative cardiovascular effects as compared to non-selective NSAIDs alone or placebo.

By October 2002 Merck had determined that it would combine placebo-controlled data from three long-term cancer prevention studies testing the efficacy of Vioxx in reducing the risk of certain cancers and use these pooled data to further evaluate the cardiovascular profile of Vioxx. This study, called Protocol 203, was viewed by MRL scientists as equivalent to a prospectively designed cardiovascular outcomes trial, and would provide a clean answer to the question of whether Vioxx was prothrombotic, without implicating the ethical concerns raised in the VALOR Trial.

In sum, while the process of designing a cardiovascular outcomes trial was painstaking, there is no evidence that MRL intentionally delayed the process to avoid the results.

17. Allegation No. 17: Merck Ignored Mounting Epidemiological Evidence That Vioxx Was Prothrombotic.

a. Summary of Allegation.

Critics assert that from 2002 until the time that Vioxx was withdrawn from the market, there were numerous epidemiological studies that demonstrated that Vioxx caused increased cardiovascular risk to patients based on data other than from Merck's various clinical trials.

For example, it is alleged that an October 2002 study by Dr. Wayne Ray*, an epidemiologist at Vanderbilt University, found that "Medicaid patients in Tennessee who

were taking high doses of Vioxx . . . had significantly more heart attacks and strokes than similar patients who were not taking high doses."[93]

It also is alleged that even a Merck-sponsored study conducted in 2003 by Dr. Daniel Solomon* of Harvard University "found Vioxx was associated with an elevated relative risk of heart attacks compared to use of Pfizer's Celebrex or no similar painkiller."[94] When Dr. Solomon* refused to change the study's conclusion, Merck removed from the article the name of one of its scientists who had collaborated on the study.[95]

In addition, nearly a year before Merck received the APPROVe Trial results, it received "preliminary results" from a separate, Merck-sponsored epidemiological study – the Ingenix Study – that, according to critics, "apparently indicated that the drug posed cardiovascular risks."[96]

b. Our Findings and Conclusions.

Our review of the record as detailed in Appendix P demonstrates that the epidemiological evidence was by no means clear-cut: some studies found that there was no difference in the incidence rate of cardiovascular events between selective Cox-2

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93 Alex Berenson* et al., Despite Warnings, Drug Giant Took Long Path to Vioxx Recall, N.Y. Times, Nov. 14, 2004, at A1.

94 Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1, 2004, at A1.

95 Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1, 2004, at A1.

96 Barry Meier*, Earlier Merck Study Indicated Risks of Vioxx, N.Y. Times, Nov. 18, 2004, at C1.

inhibitors and non-naproxen NSAIDs; others found that selective Cox-2 inhibitors were associated with a higher rate of cardiovascular events; some studies found that naproxen conferred cardioprotection; other studies found that it did not. In addition, the studies employed widely differing methodologies, some of which were the subject of debate and controversy within the scientific community.

Internal Company documents reflect Merck's view – which is widely held in the scientific community – that controlled clinical trials are the gold standard for studying the efficacy and safety of a drug. Epidemiological studies may be useful to identify a possible safety signal but are by no means definitive. Merck conducted and funded epidemiological studies, some of which produced results in support of naproxen cardioprotection and Vioxx's cardio-neutrality, and some of which did not. In addition, the record underscores that the science was evolving and that the limitations of epidemiological studies were widely recognized. We found no evidence to suggest that anyone at Merck disregarded a signal that he believed to be a reliable indicator that Vioxx was prothrombotic.

18. Allegation No. 18: Merck Withdrew its Application Seeking Approval to Market Arcoxia Because MRL Scientists Knew That it Was Not Safe and Would Invite Further Scrutiny of Vioxx's Cardiovascular Profile.

a. Summary of Allegation.

It has been asserted that Merck withdrew its New Drug Application for Arcoxia, its second-generation selective Cox-2 inhibitor, in 2002 based on negative clinical data

about its cardiovascular safety.[97] According to critics, Merck did not want the FDA scrutinizing these data at an upcoming Advisory Committee meeting because it feared that the Arcoxia data might prompt the Agency to take a harder look at Vioxx's cardiovascular safety and the Company did not want to jeopardize its existing blockbuster.[98]

b. Our Findings and Conclusions.

Although our investigation focused on Vioxx, we also investigated whether Merck's decision to withdraw the Arcoxia New Drug Application was motivated by cardiovascular safety issues with the drug. We did not find any evidence that Merck withdrew the Arcoxia application based on a belief that Arcoxia was prothrombotic or a concern that the Arcoxia application might jeopardize Vioxx.

Merck originally submitted the New Drug Application for Arcoxia in late 2001. By March 2002, there were already three entrants into the domestic selective Cox-2 inhibitor market – Celebrex, Vioxx, and Pfizer's second selective Cox-2 inhibitor, Bextra. According to the Company's March 15, 2002 press release, Merck withdrew the application in order to better position Arcoxia in the marketplace:

> Last month, Merck announced plans to submit an expanded New Drug Application (NDA) for ARCOXIA (etoricoxib) to the FDA to include new efficacy data for ankylosing spondylitis [a rare, but chronically painful, disease of the spine] that will better position the product to compete successfully in the coxib class, where there already are

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97 See Geoff Dyer*, "Merck Revival Hopes Dented," Financial Times (London), March 16, 2002, at 17.

98 Complaint in Kaufman v. Gilmartin, No. 04-5566, D.N.J., at ¶¶ 67-68.

> three entrants. Accordingly Merck announced the withdrawal of the original U.S. NDA for the investigational medicine. Merck believes the new data, along with the data previously submitted, will provide a fuller picture of the product's efficacy and safety and will position it more favorably for approval in the United States.[99]

At the same time, the Company was engaged in discussions with the FDA concerning the safety profile of Arcoxia, which led to the Company's announcement on June 11, 2002 that the FDA had requested "additional cardiovascular safety data for ARCOXIA versus comparators other than naproxen."[100]

Merck resubmitted the Arcoxia New Drug Application on December 30, 2003 and received an approvable letter from the FDA on October 29, 2004, which stated that the application would be approved upon the submission of additional data, including cardiovascular safety data. Merck recently completed a pooled analysis of cardiovascular data from three large clinical trials that tested Arcoxia against diclofenac, a widely used non-selective NSAID. The combined data from all three trials demonstrated similar rates of cardiovascular events among those patients treated with Arcoxia and those treated with diclofenac. The Company has submitted this data to the FDA and has announced its intention to use this data to respond to the FDA's October 2004 approvable letter.[101]

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[99] 4/18/02 Merck press release, "Merck Announces First-Quarter 2002 Earnings Per Share of 71 Cents," MRK-PRL0000251, at 54.

[100] 6/11/02 Merck press release, "Merck Plans to Refile U.S. New Drug Application for ARCOXIA™ in Second Half of 2003," MRK-ADW0081756, at 56.

[101] 8/23/06 Merck press release, "Merck Provides Preliminary Analyses of the Completed MEDAL Program for ARCOXIA™ (Etoricoxib)," MRK-I4640003746-48.

Although the Arcoxia New Drug Application is still pending in the United States, the drug has been approved and is marketed in over 40 foreign countries.

C. Summary of Principal Criticisms and Findings Concerning Merck's Marketing of Vioxx.

Claims that Merck disseminated false information concerning the safety of Vioxx stem from the premise that MRL scientists and Company senior management understood, or at least suspected, that Vioxx caused cardiovascular events. The Company also is criticized for giving the Marketing Department an inappropriate level of influence in the setting of Merck's scientific agenda and for engaging in other improper conduct to "neutralize" Merck's critics.

Our findings regarding claims about Merck's marketing and promotion derive for the most part from our finding that MRL scientists believed that Vioxx was a safe drug. To the extent that such claims focus on the aggressiveness of some in Merck's Marketing Department, we are persuaded that senior management did not condone such conduct and that Senior Management adopted the Culture of Compliance to reinforce Merck's commitment to high ethical standards. Consistent with our mandate, we did not investigate allegations of misconduct by individuals in the Marketing Department who were separated from the Company or who were not part of senior management.

This is not to say that we endorse all of the sales and marketing practices that we reviewed. The evidence establishes that certain individuals within the Marketing and Sales Departments engaged in practices that were inconsistent with Merck's policies and at times proposed neutralizing critics through means that senior management viewed as

unacceptable. Such unacceptable conduct, however, was addressed Company-wide in late 2001 when senior management put in place an enhanced "Culture of Compliance." Although the initiative was not designed to address specifically any of the marketing practices discussed in this Report, the Company's renewed emphasis on compliance and training has curbed promotional activities that Merck deems unacceptable.

19. Allegation No. 19: Merck Attempted to Improve Vioxx's Competitive Position by "Neutralizing" Physicians Who Supported Celebrex or Were Critical of Vioxx.

a. Summary of Allegation.

Merck filed for FDA approval to market Vioxx in the United States on November 23, 1998, knowing that Vioxx's principal competitor, Searle/Pfizer's Celebrex, would be available beginning in early 1999. Even with the fast-track approval Merck hoped it would receive from the FDA, this meant that Merck would have to "play[] [a] game of catch-up" to reduce Celebrex's market lead and to garner support for Vioxx.[102] Critics allege that Merck therefore set out even before Vioxx was approved to "neutralize" a list of "problem" physicians who were pro-Celebrex by "offer[ing] them carrots like clinical trials, posts as consultants or [] grants."[103] Despite Merck's insistence that such activities were "educational," the "standardized form requesting payments to doctors . . . read 'Expected Outcome/Return on Investment,'" which, it is

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[102] Barry Meier* & Stephanie Saul*, Marketing of Vioxx: How Merck Played Game of Catch-Up, N.Y. Times, Feb. 11, 2005, at A1.

[103] Barry Meier* & Stephanie Saul*, Marketing of Vioxx: How Merck Played Game of Catch-Up, N.Y. Times, Feb. 11, 2005, at A1.

asserted, revealed an inappropriate marketing-oriented, rather than educational, purpose.[104]

b. Our Findings and Conclusions.

Our review of the evidence shows that the market competition between Searle/Pfizer and Merck, even before either of their selective Cox-2 inhibitors was approved by the FDA, was intense and that both companies invested tremendous resources in launching their respective drugs.

When Celebrex was introduced to the market in early 1999, Vioxx was still five months away from FDA approval. During this pre-approval period, Merck's Marketing Department worked to help introduce physicians to Vioxx and to develop physicians as advocates for the product. Up until the end of 2001, some of the ways in which Merck developed advocates included: advisory board meetings and consultants' meetings at which various topics concerning Vioxx and the NSAID market generally would be discussed in a focus-group setting; a Merck-sponsored speaker program in which outside speakers would make presentations to a safety monitoring board about Vioxx; a Medical School Grant Program through which physicians could apply for grants to study Vioxx; and sponsorship of Continuing Medical Education programs. The Company also sought to develop advocates by employing physicians as clinical investigators in post-marketing Vioxx trials.

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[104] Barry Meier* & Stephanie Saul*, Marketing of Vioxx: How Merck Played Game of Catch-Up, N.Y. Times, Feb. 11, 2005, at A1.

Merck field sales representatives whose job it was to discuss the anticipated market entry of Vioxx with physicians identified certain physicians whom the field representatives believed were anti-Vioxx (based on their understanding of Vioxx's product profile) or anti-Merck. A member of the Marketing Department compiled these physicians' names in a list of "36 Physicians to Neutralize."[105] Critics point to a column on the "36 Physicians to Neutralize" chart that includes comments regarding the means by which the physician might be converted to an advocate. Included in the column are "show me the money," "continue to support with clinical studies," "Weekend Consultants' meeting in an elegant location (New York, Hawaii) or a 5-day international meeting,"and "offer medical school grant." While we do not condone such practices, we found no evidence that anyone in senior management encouraged or condoned them. Nor did we review evidence that the sales representatives' recommendations for developing the physician into an advocate were followed.

Despite the provocative sound of the word "neutralize," senior management of the Marketing Department reported that they understood the effort to "neutralize" physicians to be one in which Merck scientists would educate these targeted physicians about Vioxx, often through one of the programs mentioned above. Evidence shows that Merck management believed that if physicians were educated about the benefits of selective Cox-2 inhibitors and about Vioxx in particular, they would no longer be "anti-Vioxx" and would be more likely to become proponents of the drug. It is important to note that

[105] List of Physicians to Neutralize, MRK-AFI0004750-96 (attached to 7/23/99 email from S. Baumgartner to S. Johnson, MRK-AF100044569).

throughout the period that Vioxx was marketed, Merck expected all Company representatives to adhere to Merck's policies and procedures, which were designed to ensure compliance with federal regulations and which also, in many instances, went beyond what the law required.

All of the members of senior management in the Marketing Department whom we interviewed were unequivocal that the only travel or entertainment for doctors that was permissible had to be premised on education or market research. Merck policy – both before the Culture of Compliance and after – strictly prohibited offering weekend trips or medical school grants without a bona fide scientific or market research purpose.

Many of the programs discussed above in connection with advocate development and/or neutralizing physicians were revised in connection with the Culture of Compliance. For example, since late 2001, Merck policy has been that advisory boards and consultants' meetings may only be convened when the information sought is not available through other means. In addition, the Marketing and Sales Departments no longer have a voice in determining which physicians should participate in a clinical trial, or which physicians Merck should support through Merck's Medical School Grant Program. In addition, Merck has centralized the education programs, which makes oversight easier.

The Culture of Compliance was initiated proactively by the Company in late 2001 to ensure that all Company employees understood the policies governing marketing and sales practices and to enhance accountability. As part of the broad-based initiative, Mr. David Anstice, President, Human Health – The Americas, established an Office of

Compliance. That office, under the leadership of Ms. Lucine Beauchard, undertook a comprehensive review of all existing Merck Marketing and Sales programs, winnowed down the number of programs (to simplify oversight and compliance and ensure that all programs furthered Merck's legitimate business purposes), clarified the written policies for each approved program, and made structural changes that further separated marketing and selling from medical and scientific activities.

The evidence shows that the initiative was aimed at the marketing and sale of all Merck products and was not specific to Vioxx. In addition, the fact that a program was discontinued or changed pursuant to the initiative did not mean that it was determined to have been abused. Rather, the focus was to underscore Merck's strong commitment to ethical business practices. Notably, the Culture of Compliance was voluntarily initiated in response to internal concerns at Merck and was not in response to any federal or state investigation of sales practices at Merck or in the pharmaceutical industry. While no set of policies can completely eliminate the risk of rogue sales representatives or other sales and marketing personnel engaging in conduct that violates Company policy, the Culture of Compliance reflected a strong desire on the part of the Company to aggressively address any such conduct and to promote high standards of ethical behavior.

20. Allegation No. 20: Merck's Marketing Department Unduly Influenced the Scientific Research Agenda.

a. Summary of Allegation.

It is argued that after the VIGOR Trial data were unblinded, "Merck allowed marketing to trump its scientists"[106] and to determine what Vioxx trials should be conducted. For example, Marketing executives purportedly "rejected pursuing a study focused on Vioxx's cardiovascular risks apparently because [they] feared it could send the wrong signal about the company's . . . confidence in Vioxx. . . ."[107] An internal Marketing presentation to senior executives states: "At present, there is no compelling marketing need for such a study . . . . Data would not be available during the critical period. The implied message is not favorable."[108] It is argued that this emphasis on marketing over science underscored Merck's desire to put profits above patient safety.

b. Our Findings and Conclusions.

The criticism that Merck's Marketing Department dictated the scientific research agenda is not supported by the evidence. To the contrary, documentary and other evidence underscores that all research decisions were made by MRL senior management. When Mr. Gilmartin joined the Company in 1994, he created a number of cross-disciplinary teams, including the Human Health Product Approval Committee.

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106 Christopher Bowe* & Simon London*, The Company's Chief Executive Faces a US Senate Hearing Today, Financial Times (London), Nov. 18, 2004, at 19.

107 Alex Berenson* et al., Despite Warnings, Drug Giant Took Long Path to Vioxx Recall, N.Y. Times, Nov. 14, 2004, at 1.

108 Alex Berenson* et al., Despite Warnings, Drug Giant Took Long Path to Vioxx Recall, N.Y. Times, Nov. 14, 2004, at 1.

Mr. Gilmartin believed that in a company the size of Merck, interaction between various departments was critical to ensure that the Marketing, Public Affairs and other Departments understood the scientific product profiles so that they would be better positioned to address questions and engage in strategic planning. In addition, the Human Health Product Approval Committee allowed MRL scientists to hear from members of the Marketing Department about what doctors in the field were looking for in a drug.

Critics point to a slide presentation from a May 2000 Human Health Product Approval Committee meeting which reflects that the Marketing Department sought approval of a decision not to proceed with a cardiovascular outcomes trial as evidence that the Marketing Department directed the scientific agenda. The record shows that in the immediate aftermath of the VIGOR Trial unblinding, MRL scientists discussed conducting an outcomes trial. As discussed above in response to Allegation No. 8, however, they had concluded by May 2000, based on their review and analysis of cardiovascular data from the Vioxx clinical program, that the difference in the incidence of cardiovascular events between the Vioxx and naproxen groups in the VIGOR Trial most likely was caused by the cardioprotective effect of naproxen and that Vioxx was cardio-neutral. While members of the Marketing Department were invited to express their views, it was MRL that determined that a cardiovascular outcomes trial was not necessary. Members of senior management in both MRL and the Marketing Department were unequivocal that if MRL had believed that it was necessary to conduct an outcomes trial, the views of the Marketing Department would have been irrelevant.

While it is true that at one point in time some people in the Marketing Department thought that announcing a cardiovascular risk study of Vioxx would send a wrong message, at another time Marketing personnel thought that such a study was necessary to put to rest the competition's clam that the VIGOR Trial showed that Vioxx was prothrombotic. In the end it was the MRL scientists who determined what studies should be conducted, and when.

21. Allegation No. 21: Merck Went on the Offensive Against Doctors and Academics who Questioned Vioxx's Cardiovascular Safety.

a. Summary of Allegation.

It is alleged that when academic researchers raised questions about Vioxx's cardiovascular safety, Merck "struck back hard."[109] Merck's approach was first to try and persuade critics to change their views. If that did not work, a Merck executive would threaten and try to discredit critics. A letter to Mr. Gilmartin, Merck's Chairman and Chief Executive Officer, from Dr. James Fries*, a Stanford University Medical School doctor, sums up Merck's tactics in this regard. As explained by Dr. Fries*, Merck's Dr. Louis Sherwood met with academics and threatened them with consequences, financial and reputational, if they were not more favorable to Merck.[110] Dr. Fries'* letter

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[109] Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1, 2004, at A1.

[110] Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1. 2004, at A1.; Thomas Ginsberg*, Threats to Critics of Vioxx Alleged, Phila. Inq., June 5, 2005, at A1.

identified eight academic physicians he alleged were threatened or retaliated against by Dr. Sherwood or other Merck employees.

b. Our Findings and Conclusions.

The complete record we reviewed reflects that Dr. Louis Sherwood, a former academic Chairman and former head of the Medical and Scientific Affairs division of U.S. Human Health, was the most senior U.S. Human Health representative to meet with physicians who were identified as anti-Vioxx to educate them about Vioxx. His scientific and academic background made him, it was believed, well-suited to the job. While one can legitimately question some of the conduct attributed to Dr. Sherwood, it is clear that when complaints came to the attention of Mr. Gilmartin, he responded appropriately.

After Mr. Gilmartin received the letter from Dr. Fries* accusing Dr. Sherwood of intimidating and threatening professors and physicians who questioned the safety of Vioxx, Mr. Gilmartin directed Mr. Anstice, President, Human Health – The Americas, to investigate the allegations, which he did. Mr. Anstice asked Dr. Sherwood to write a memorandum responding to Dr. Fries'* allegations.

Dr. Sherwood's four-page, single-spaced memorandum reflects his belief, in each instance, that he was completely justified in the manner in which he contacted physicians and discussed data with them to correct their misapprehensions. Dr. Sherwood did not think that it was appropriate for academic physicians to "go out and say anything and do anything one pleases" and he stated that he intervened on an "ad hoc basis" when such individuals did not present data in a balanced manner.

Senior Merck management, including Messrs. Gilmartin and Anstice, took steps to investigate the allegations and to ensure that any behavior by Dr. Sherwood that might have been interpreted as intimidating or threatening would not be repeated. The evidence does not suggest that Dr. Sherwood's conduct was part of an orchestrated campaign by senior management to suppress scientific discourse about Vioxx. Since Dr. Sherwood retired in 2002, we saw no need to attempt to resolve the factual disputes arising from his response to the Fries letter.

22. Allegation No. 22: Merck Sales Representatives Used Misleading Promotional Aids to Sell More Vioxx and Were Trained to Dodge Questions About Cardiovascular Risks.

a. Summary of Allegation.

According to critics, internal Company documents reveal that as soon as the VIGOR Trial results were released in March 2000, Merck "trained an army of employees visiting doctors' offices to avoid discussing negative studies about Vioxx . . ."[111] and to "dodge" questions about the cardiovascular safety of Vioxx. Sales representatives were trained using a sales aid called "Dodge Ball Vioxx." It is claimed that, to win, sales representatives had to successfully dodge 12 pages of questions – called obstacles – such as, "I am concerned about the cardiovascular effects of Vioxx."[112]

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[111] Deidra Henderson*, Merck Told Sellers to Avoid Talk of Vioxx Heart Risks, Boston Globe, May 6, 2005, at C1.

[112] Anna Wilde Mathews* & Barbara Martinez*, Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, Wall St. J., Nov. 1. 2004, at A1 (quoting document).

In addition, Merck's sales representatives used a promotional piece written by the Marketing Department called a "Cardiovascular Card" to attempt to allay physicians' concerns about Vioxx's safety profile.[113] It is argued that the Cardiovascular Card was misleading in that it used old data – not the data from the VIGOR Trial, or the ADVANTAGE Trial, or Protocol 090 – to try and show that Vioxx was safe. It is further argued that the Card misleadingly stated that Vioxx was eight times safer than other NSAIDs in terms of cardiovascular mortality.[114]

In addition, during the two-year period after the VIGOR Trial but before the label change, it is alleged that Merck sought to downplay the VIGOR Trial cardiovascular results by preventing sales representatives from discussing them with physicians – even in response to physician concerns or questions.

b. Our Findings and Conclusions.

The Sales Department employed an array of sales training materials to train sales representatives regarding what the Company deemed appropriate – and inappropriate – communications with physicians, including written instructions or roadmaps, Bulletins and voicemail messages. In addition, to reinforce Company-approved responses to questions that a physician might ask, Merck also developed training games. Critics have highlighted one such training game in particular, Dodge Ball Vioxx, in support of their

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113 Bernadette Tansey*, How Marketing Drives the Pharmaceutical Industry, S. F. Chronicle, May 6, 2005, at A1.

114 Deidra Henderson*, Merck Told Sellers to Avoid Talk of Vioxx Heart Risks, Boston Globe, May 6, 2005, at C1; see generally 5/5/05 memorandum from H. Waxman* to Democratic Members of the Government Reform Committee, MRK-ALE0009615-43.

claim that Merck hid product safety information from physicians by teaching sales representatives to "dodge" physician questions, particularly about cardiovascular data.

The record is clear that representatives were not instructed to "dodge" questions or hide data. Rather, Merck policy, which was designed to reinforce FDA regulations, was that representatives could only discuss with physicians data referenced in the label and were prohibited from discussing the VIGOR Trial data until the product label was changed in April 2002.

There is evidence that Merck's competitors were informing physicians of the VIGOR Trial results and arguing that the VIGOR Trial proved that Vioxx was prothrombotic. Since, as noted above, Merck sales representatives were not to address issues not on the product label, Merck's Marketing and Medical and Scientific Affairs Departments produced a number of different materials that could be given to or shared with physicians who inquired about the cardiovascular safety of Vioxx.

First, representatives were provided with a promotional aid called a "Cardiovascular Card" that presented data from the Vioxx clinical program that were included in the product label. In response to questions about Vioxx's cardiovascular safety profile, sales representatives could show the Card, which presented cardiovascular data from the trials that were referred to in the label. The purpose of the Card appears to have been to reinforce that Vioxx was safe at the dosages (12.5 mg and 25 mg) and indication (osteoarthritis) for which it was most commonly prescribed. We note that the Cardiovascular Card was approved internally by the Vioxx Medical/Legal Review Board to ensure its accuracy before it was released to the field, and was submitted to the FDA's

Division of Drug Marketing, Advertising, and Communications. There is no evidence that either this review board, comprising an attorney and two physicians, or DDMAC believed that the Card depicted cardiovascular data from the Phase IIb/III osteoarthritis trials anything other than accurately.

Second, if a physician asked a question about the VIGOR Trial data specifically, the sales representative could request, through a physician information request (or "PIR"), that Merck send the physician a written response letter. Merck's Medical and Scientific Affairs Department would then send these physicians letters that did refer to the VIGOR Trial results.

Third, after the article about the VIGOR Trial was published in the New England Journal of Medicine, Merck's Medical and Scientific Affairs Department provided reprints of the article to physicians who requested information on the VIGOR Trial. Starting on February 28, 2001, these reprints were accompanied by a cover letter that explained that the cardiovascular data in the article were based on a reporting cut-off date of February 10, 2000 and that provided the additional adjudicated data.

Thus, while the Cardiovascular Card standing alone did not present all the available cardiovascular data concerning Vioxx, there is no reason to believe that any responsible Merck official considered the Cardiovascular Card to be misleading in the context in which it was to be used.

D. Summary of Principal Criticisms and Findings Concerning Merck's Post-withdrawal Analysis and Reporting of Cardiovascular Data Arising From The APPROVe Trial.

The press release that Merck issued on September 30, 2004 stated that Merck decided to withdraw Vioxx from the market based on data from the APPROVe Trial that demonstrated "an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo." According to the release, "[t]he results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX. . . ."[115] The article about the APPROVe Trial cardiovascular results that was subsequently published in the New England Journal of Medicine likewise stated: "the event rates [in the Vioxx and placebo groups] were similar for the first 18 months."[116] Merck has characterized the data in this way in numerous public statements throughout the post-withdrawal period.

The principal criticisms of Merck's post-withdrawal analysis and reporting of APPROVe Trial cardiovascular data arise from this 18-month claim.

First, critics allege that the claim that the risk emerged only after 18 months of continuous use is not supported by the data from the APPROVe Trial, either singly or in combination with other data from the Vioxx development program.

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[115] 9/30/04 Merck press release, "Merck Announces Voluntary Worldwide Withdrawal of Vioxx," MRK-AFF0000040, at 40.

[116] Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1092.

Second, Merck announced on May 30, 2006 that it had made an error in an article about the APPROVe Trial cardiovascular data published in the New England Journal of Medicine (the "APPROVe article") in identifying the test used to determine whether the cardiovascular hazard ratio was constant over time or whether it increased over time. Critics claim that the error casts doubt on Merck's claim that the cardiovascular event rates on Vioxx and placebo were similar for the first 18 months of the trial and diverged thereafter.

Third, following the termination of the APPROVe Trial, in which data were collected on adverse events that occurred while patients were on treatment or within 14-days after discontinuing treatment, Merck undertook to collect follow-up data on patients originally enrolled in that trial to determine whether and to what extent the increased cardiovascular relative risk seen in the APPROVe Trial resolved 15 or more days after patients stopped taking Vioxx. It is alleged that the results of this follow-up study establish that the hazard ratio on Vioxx increased with respect to placebo not at the 18-month mark as Merck has claimed, but rather at approximately 4 months. These allegations and our findings with respect to each are discussed more fully below.

23. Allegation No. 23: Merck's Claim that the Increased Risk of Cardiovascular Events on Vioxx Has Been Observed Only After 18 Months of Continuous Treatment Is Not Supported by the Data.

a. Summary of Allegation.

Critics allege that Merck's claim based on post-hoc analyses that the increased relative risk of cardiovascular events on Vioxx relative to placebo in the APPROVe Trial emerged after 18 months of continuous treatment is not supported by the data. Critics

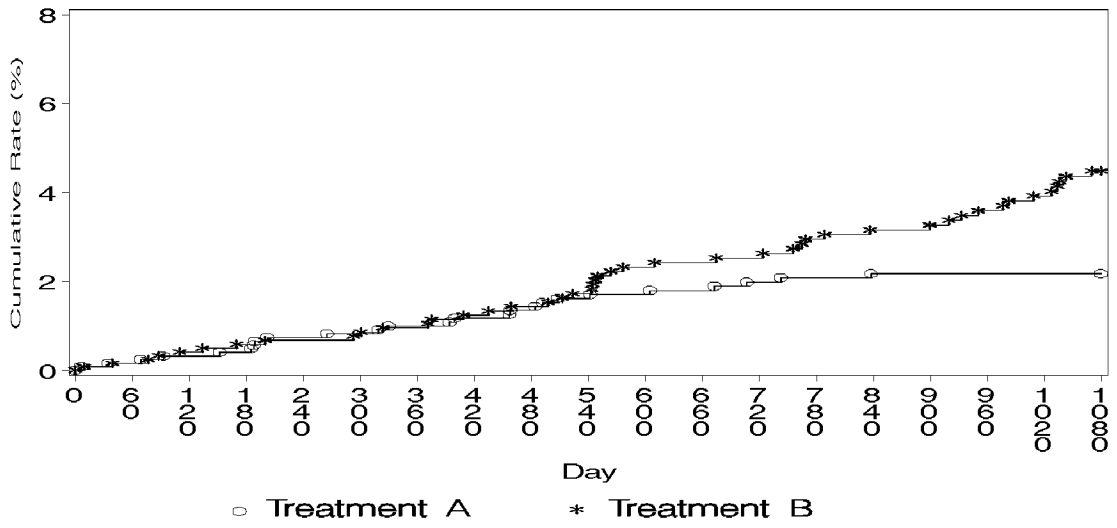
further claim that, even when the APPROVe Trial cardiovascular data are considered together with other cardiovascular data from Merck's clinical trials of Vioxx, the data are still not sufficient to rule out the possibility of an increased risk significantly earlier than 18 months into the course of treatment.

b. Our Findings and Conclusions.

Merck scientists developed the view that the APPROVe Trial cardiovascular data showed an increased relative risk beginning at 18 months based on a number of post-hoc statistical analyses that Merck scientists conducted on the base study data. These analyses included use of a Kaplan-Meier plot, also called a time-to-event plot, which creates curves reflecting the cumulative rate of events in each treatment group over time. As shown in the figure below, the vertical axis quantifies the cumulative rate of cardiovascular events with continuous use of each treatment (Vioxx and placebo) as measured in days along the horizontal axis. The plot that MRL scientists reviewed in September 2004 (reproduced below) appears to show that there was an increase over time in the risk of confirmed thrombotic events, and that the separation between Vioxx and placebo became apparent after approximately 18 months.[117]

[117] 9/13/04 Pre-Meeting Report from H. Quan to APPROVe ESMB, MRK-AEO0029517, Figure 2a at 37.

APPROVe Trial – Kaplan-Meier Plot for Confirmed Thrombotic Events
(August 2004 Data)



Using the preliminary APPROVe Trial cardiovascular data that were available in the summer of 2004, an MRL statistician conducted a statistical test designed to determine whether the hazard rates were proportional over time (i.e., whether the risk of an event on Vioxx relative to placebo remained constant over the course of the trial). As fully explained in Appendix R, a common method for testing the proportionality of the hazard rates is to use a Cox proportional hazards model fitted with a covariate for the assigned treatment (here, Vioxx or placebo) and either (i) a covariate for the interaction between treatment and the "logarithm of time" (the "Logarithm of Time Test") or (ii) a covariate for the interaction between treatment and "linear time" (the "Linear Time Test"). The relevant outcome of these proportional hazards tests is a p-value of between 0 and 1.0 that indicates whether sufficient evidence exists to reject the assumption built into the Cox proportional hazards model that the hazard rates are proportional over time.

As discussed in detail in Appendix R, many biostatisticians using a Cox proportional hazards model to test the constancy of the hazard ratio would deem results as high as p=0.10, in conjunction with graphical analysis, to be sufficient evidence to reject the assumption of proportional hazards because such tests have low power. However, Merck statisticians frequently use a p-value of 0.05 as a conventional cut-off. As explained more fully below, an MRL statistician ran both the Logarithm of Time Test and the Linear Time Test and determined that there was sufficient evidence to reject the assumption that the hazard ratio was constant over time.

Finally, another important statistical analysis of the APPROVe Trial data that Merck scientists performed before withdrawing Vioxx involved reviewing the hazard ratio between Vioxx and placebo over time broken down into 6-month increments. A table reflecting the results of this analysis is reproduced below. This analysis similarly indicated "a trend for the treatment differences for major [cardiovascular] outcomes to increase over time."[118] As illustrated below, this analysis, which was based on relatively few events in each six-month segment, indicated that there was a greater number of confirmed thrombotic events on Vioxx ("Treatment B") versus placebo ("Treatment A") in every six-month increment except for the second, and that this difference was markedly greater after the 18-month mark (540 days) than it was during the first 18 months. The results for the APTC composite cardiovascular endpoint, also reproduced below, likewise showed a marked increase in hazard ratios after the 18-month mark.

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[118] Minutes of 9/17/04 APPROVe ESMB meeting, MRK-AFF0000124, at 24.

APPROVe Trial (August 2004 Data)
Confirmed Thrombotic Events in 6-Month Intervals

Relday	Treatment A		Treatment B		Hazard Ratio
	Number of Events	Hazard (SE)	Number of Events	Hazard (SE)	
0 - 180	5	0.0040(0.0018)	7	0.0058(0.0022)	1.4459
181 - 360	7	0.0060(0.0023)	4	0.0037(0.0018)	0.6147
361 - 540	7	0.0063(0.0024)	8	0.0078(0.0028)	1.2490
541 - 720	4	0.0038(0.0019)	8	0.0083(0.0029)	2.2000
721 - 900	2	0.0020(0.0014)	7	0.0076(0.0029)	3.8938
> 900	0	0(0)	11	0.0245(0.0074)	.

APPROVe Trial (August 2004 Data)
APTC Events in 6-Month Intervals

Relday	Treatment A		Treatment B		Hazard Ratio
	Number of Events	Hazard (SE)	Number of Events	Hazard (SE)	
0 - 180	3	0.0024(0.0014)	6	0.0050(0.0020)	2.0672
181 - 360	4	0.0034(0.0017)	2	0.0018(0.0013)	0.5385
361 - 540	5	0.0045(0.0020)	3	0.0029(0.0017)	0.6553
541 - 720	2	0.0019(0.0013)	7	0.0072(0.0027)	3.8372
721 - 900	2	0.0020(0.0014)	6	0.0065(0.0026)	3.3241
> 900	0	0(0)	9	0.0199(0.0066)	.

In assessing the APPROVe Trial cardiovascular data, MRL scientists and outside consultants also reviewed the Kaplan-Meier plots that had been prepared in connection with analyses of cardiovascular data from two placebo-controlled trials that tested the efficacy of Vioxx in preventing or slowing the progression of Alzheimer's disease. These plots similarly reflected an apparent change in the hazard ratio at approximately the 18-month mark, but because the hazard rate on Vioxx was lower than that on placebo for the first 18 months and averaged out so that the hazard rates of both treatments were similar over a 36-month period, it previously had not been possible to draw any conclusion from the change that appeared after approximately 18 months.

These analyses support the claims that the APPROVe Trial cardiovascular data from the base study provided reasonably strong evidence of a non-constant hazard ratio, and that the cardiovascular event rates between the two arms of the study appeared similar during the first 18 months and then diverged. We are aware of no evidence conclusively demonstrating that the divergence in hazard rates in the APPROVe Trial began before the 18-month mark, but the data cannot be characterized as providing definitive evidence that the risk of experiencing a cardiovascular adverse event was in fact equal between the Vioxx and placebo arms for the first 18 months. As Dr. Scott Zeger*, Chair of the Department of Biostatistics at Johns Hopkins University and a member of Merck's Board of Scientific Advisors, cautioned in an email to senior Merck statisticians preparing for the post-withdrawal February 2005 FDA Advisory Committee Meeting, Merck should not "conclude that the [APPROVe] data prove there is no elevated risk until 18 months," because the "confidence intervals can not rule out [an increased relative risk of] 1.5-2.0 as early as 6 months." Dr. Zeger* agreed that "there is reasonably compelling evidence that the relative risk is not constant across all time."[119]

Merck has made many public statements concerning the first 18 months of the APPROVe Trial and generally has used characterizations – such as "[t]he two curves appeared to be similar"[120] or "the event rates were similar in the two groups"[121] or "[t]he

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[119] 1/31/05 email from S. Zeger* to J. Bolognese, MRK-AGO0069292.

[120] 3/15/05 APPROVe Trial abbreviated Clinical Study Report, Cardiovascular Safety Report, MRK-I8940100962, at 82.

increased relative risk became apparent after 18 months of treatment"[122] – that are consistent with, and do not overstate the import of, the underlying APPROVe Trial cardiovascular data. The Company has on occasion, however, made statements about its analyses of the hazard ratio that could be misconstrued to suggest that those data prove that there is no elevated risk during the first 18 months. For example, its September 30, 2004 press release announcing the withdrawal of Vioxx stated:

> In this study, there was an increased relative risk for confirmed cardiovascular events . . . beginning after 18 months of treatment in the patients taking VIOXX compared to those taking placebo. The results for the first 18 months of the APPROVe study did not show any increased risk of confirmed cardiovascular events on VIOXX. . . .[123]

Similarly, Merck's January 21, 2005 submission to the FDA concerning the APPROVe Trial cardiovascular data stated that "in the APPROVe study, an increased risk of CV events . . . was first seen beginning after 18 months of chronic treatment"[124] and "[data] from the APPROVe study confirm the findings of our other clinical trial databases that there is no evidence for an increase in the relative risk of sustaining a

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121 Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1092.

122 Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1092.

123 9/30/04 Merck press release, "Merck Announces Voluntary Worldwide Withdrawal of Vioxx," MRK-AFF0000040, at 40.

124 MRL Background Package for 2/16/05 – 2/18/05 Joint Meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, MRK-S0420050740, at 774.

thrombotic CV event for the rofecoxib group versus placebo over the first 18 months of treatment."[125] However, this same submission to the FDA also contained statements such as "Although the frequency of [cardiovascular] events were low and did not appear to be elevated compared to placebo during the first 18 months of use, a decision was made to voluntarily withdraw rofecoxib from the marketplace"[126] and "Prior to 18 months there was no apparent difference in the cumulative incidence of these [cardiovascular] events in the two groups as evidenced by the overlapping [Kaplan-Meier] plots."[127]

We find that MRL scientists were reasonable in concluding, on the basis of all available data from the base study and the results of post-hoc analyses, that there was reasonably strong evidence that the hazard ratio in the APPROVe Trial was not constant over time and that an increase in the hazard ratio appeared to begin after approximately 18 months of continuous use of Vioxx. In addition, although Merck has in some instances described the APPROVe Trial cardiovascular data in a manner that could be misinterpreted to suggest that those data preclude the possibility of an elevated risk in the first 18 months, Merck's communications concerning the 18-month issue, when considered in the aggregate, lead us to conclude that the Company only intended to assert

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[125] MRL Background Package for 2/16/05 – 2/18/05 Joint Meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, MRK-S0420050740, at 778.

[126] MRL Background Package for 2/16/05 – 2/18/05 Joint Meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, MRK-S0420050740, at 757.

[127] MRL Background Package for 2/16/05 – 2/18/05 Joint Meeting of the FDA Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, MRK-S0420050740, at 773.

that the APPROVe Trial data provided no evidence of an increased relative risk during the first 18 months.

24. Allegation No. 24: The Article in the New England Journal of Medicine About the APPROVe Trial Cardiovascular Results and Merck's Corrective Statements Were Purposefully Misleading.

a. Summary of Allegation.

In February 2005, an article concerning the APPROVe Trial cardiovascular data that was co-authored by MRL scientists and a group of outside authors was published in the New England Journal of Medicine (the "APPROVe article"). The APPROVe article stated that, in the APPROVe Trial, the cardiovascular event rates for the Vioxx and placebo groups were similar for the first 18 months of the trial and diverged thereafter and that "[t]he changing pattern of the treatment effect over time was confirmed by a failed test for proportionality of hazards (P=0.01)."[128] According to the article, the test "evaluat[ed] the interaction between the logarithm of time and the assigned treatment" (i.e., was the Logarithm of Time Test).[129]

On May 30, 2006, Merck issued a press release announcing that it had recently discovered an error in the published APPROVe article and, as a result, was "correcting its

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[128] Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1097.

[129] Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1095.

prior description of one of the statistical methods used to analyze certain data."[130] Specifically, the release stated:

> The reference to logarithm of time in the description of methods published in the NEJM and submitted to regulatory agencies was in error. The reported result (p-value = 0.01) came from a statistical model using linear time, not logarithm of time. Recent tests show that the result using logarithm of time has a p-value = 0.07.[131]

The release stated that the error did not change any of the conclusions about the data set forth in the APPROVe article.

In addition, the release stated that "The VIOXX cardiovascular data analysis plan called for numerous statistical and graphical methods to be used to assess whether the relative risk of VIOXX compared to placebo was constant over time or if it changed over time. . . " and that "the use of the variable, logarithm of time, was an element in the primary method specified." The Company attached to the release an excerpt from the Statistical Data Analysis Plan for Protocol 203 – its planned pooled analysis of cardiovascular data from three placebo-controlled trials, one of which was the APPROVe Trial – that pertained to proportionality testing.

These events give rise to several allegations pertaining to the APPROVe article and Merck's public statements regarding the error:

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130 5/30/06 Merck press release, "Merck Corrects Description of a Statistical Method Used in APPROVe Study," MRK-AFN0110064, at 64.

131 5/30/06 Merck press release, "Merck Corrects Description of a Statistical Method Used in APPROVe Study," MRK-AFN0110064, at 64.

First, it is argued that Merck purposefully reported in the APPROVe article the proportionality p-value based on the Linear Time Test (rather than the Logarithm of Time Test as indicated) because that method yielded a statistically significant result that allowed Merck to make the claim that the hazard ratio in the APPROVe Trial changed over time, whereas the Logarithm of Time Test yielded a result that was not statistically significant. According to critics, had the APPROVe article reported the non-significant p-value resulting from the Logarithm of Time Test, Merck would have been precluded from claiming that the assumption of the Cox proportional hazards model – that the hazard ratio is constant – did not hold. It follows, critics claim, that Merck would have been precluded from claiming that the cardiovascular event rates in the APPROVe Trial were similar for the first 18 months and diverged thereafter.

Second, the APPROVe article stated that "[a] test of the proportional-hazards assumption was specified in the cardiovascular analysis plan."[132] It is argued that this language was intended to give the impression that the method for testing the proportionality of hazards was pre-specified in the APPROVe Trial Data Analysis Plan when, in fact, the referenced "cardiovascular analysis plan" was for a separate study – Protocol 203 (the Company's planned pooled analysis of cardiovascular data from three placebo-controlled studies, one of which was the APPROVe Trial) – and did not govern the analysis of APPROVe Trial cardiovascular data standing alone. It is further argued that the authors of the APPROVe article deliberately mischaracterized the method for

[132] Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1095.

testing the proportional hazards assumption as pre-specified so as to lend credibility to what was really a post-hoc analysis not entitled to much weight.

Third, it is similarly argued that Merck's public statements regarding the error gave the erroneous impression that the Company's analysis of the proportionality of the hazard rates in the APPROVe Trial was pre-specified so as to lend credibility to that analysis and bolster the Company's claim that the hazard ratio in the APPROVe Trial changed over time. Critics point to language in the May 30, 2006 press release describing analyses specified in the Statistical Data Analysis Plan for Protocol 203 for testing whether the hazards ratio in the APPROVe Trial changed over time and stating that Merck conducted such analyses "[a]s specified in the analysis plan."[133] Although a subsequent section of the release states that "[t]here was no Statistical Analysis Plan . . . for the cardiovascular data from APPROVe alone,"[134] critics contend that the release conveys the impression that the Statistical Data Analysis Plan for Protocol 203 governed the APPROVe Trial analyses.

Critics also contend that an Open Letter from Dr. Peter Kim, President of MRL, that was posted on Merck's website on June 26, 2006, gives the impression that the proportionality testing conducted on the APPROVe Trial cardiovascular data was pre-specified (although the Open Letter attached an "Assessment" regarding Merck's view of

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[133] 5/30/06 Merck press release, "Merck Corrects Description of a Statistical Method Used in APPROVe Study," MRK-AFN0110064, at 64.

[134] 5/30/06 Merck press release, "Merck Corrects Description of a Statistical Method Used in APPROVe Study," MRK-AFN0110064, at 65.

the error that concedes that there was no specific plan for the analysis of the cardiovascular event hazard rate over time in the APPROVe Trial).[135]

Fourth, it is argued that, if in fact the analyses set forth in the Statistical Data Analysis Plan for Protocol 203 governed the APPROVe Trial standing alone, then Merck's May 30, 2006 press release was misleading because it stated that the error in the article could be corrected by substituting "linear time" for "logarithm of time" in the description of the analysis performed.

The very purpose of pre-specification is to avoid bias in analyzing the results of a clinical trial by stating in advance what statistical methods will be used to analyze the data and how the results will be interpreted. When a test is pre-specified in a statistical analysis plan, it is argued, those analyzing the data must conduct that test and accept its outcome.

The Statistical Data Analysis Plan for Protocol 203 stated that the "primary method for testing the proportional hazards assumption" was the Logarithm of Time Test and that a p-value greater than 0.05 resulting from that test "is not inconsistent with proportionality, i.e., constancy of treatment effect over time."[136] According to critics, because the p-value resulting from the Logarithm of Time Test was greater than p=0.05, the error can only be corrected by reporting the p-value for the specified Logarithm of Time Test and accepting the conclusion it requires – that the assumption of proportional

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[135] 6/26/06 letter from P. Kim, "An Open Letter from Merck," MRK-AFO0300152, at 54.

[136] Protocol 203 Statistical Data Analysis Plan, MRK-AAD0200169, at 94.

hazards cannot be rejected. Merck's claim in its May 30, 2006 press release that "the linear test is an appropriate method to assess changes in relative risk over time"[137] is beside the point since the Logarithm of Time Test, and not the Linear Time Test, was the specified test.

Finally, the cardiovascular analysis plan referenced in the article specified analyses of two separate composite cardiovascular endpoints – confirmed thrombotic events and APTC composite cardiovascular endpoint events. It is argued that the results for the APTC composite cardiovascular endpoint were markedly less favorable to Vioxx and less supportive of the 18-month claim than those for the confirmed thrombotic endpoint but were not reported in detail and that the article incorrectly stated that the results for the two were "similar" so as to avoid disclosing unfavorable results.

b. Our Findings and Conclusions.

There is no evidence to support the contention that Merck purposefully misidentified the covariate used in the Cox proportional hazards model as the Logarithm of Time Test rather than the Linear Time Test in the APPROVe article. We find that the misidentification occurred because the MRL statisticians involved in drafting and reviewing the article assumed that the Logarithm of Time Test had in fact been performed and that it was that test that generated the p-value of 0.01 that was reported in the APPROVe article. The error that led to the misreporting (both in the article and in the submission to the FDA about the APPROVe Trial cardiovascular results) was made

[137] 5/30/06 Merck press release, "Merck Corrects Description of a Statistical Method Used in APPROVe Study," MRK-AFN0110064, at 64-65.

months before work on the article began when the MRL statistician analyzing the data on behalf of the APPROVe Trial External Safety Monitoring Board switched the relevant statistical program from the Logarithm of Time Test to the Linear Time Test, did not document that switch, and later failed to recall that the switch had been made. In addition, given the totality of the data available at that time, we do not believe that the error in the APPROVe article materially affects any of the conclusions reached, and we find that the data and MRL scientists' post-hoc analyses supported the view that the hazard ratio in the APPROVe Trial changed over time.

As discussed below, however, we also find that Merck's public disclosures about the error lacked clarity and necessary context. The published APPROVe article stated that the analysis performed to test the assumption that the hazard ratio was constant was "specified" in the cardiovascular data analysis plan.[138] The evidence shows that the analysis performed was post-hoc and was not pre-specified. The APPROVe article and Merck's subsequent disclosures about the error – including Merck's May 30, 2006 and June 26, 2006 press releases – should, in our view, have made clear that the data analysis conducted, while consistent with good statistical practice, was not pre-specified for the APPROVe Trial alone. Alternatively, MRL statisticians could have drafted a statistical analysis plan to govern their analyses of the APPROVe Trial cardiovascular data.

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[138] Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1099.

(1) Source of the Error

Throughout the summer and early fall of 2004, Dr. Hui Quan, the MRL statistician who worked for the APPROVe Trial External Safety Monitoring Board during the pendency of the trial, conducted numerous analyses of the APPROVe Trial cardiovascular data in preparation for the September 17, 2004 meeting of the External Safety Monitoring Board. In the course of this work, Dr. Quan noted, based on the Kaplan-Meier plots he prepared for both the confirmed thrombotic and APTC composite cardiovascular endpoints, that the hazard ratio did not appear constant but instead appeared to change at around the 18-month mark.

Dr. Quan believed that, if in fact the hazard ratio was not constant over time but instead was increasing, the External Safety Monitoring Board should be informed so that it could evaluate whether any action was appropriate.[139] To test whether the hazard ratio was non-constant, Dr. Quan's usual practice (consistent with Merck's convention) was to use the Logarithm of Time Test. Although no contemporaneous record of Dr. Quan's work exists, Dr. Quan's recollection was that the Logarithm of Time Test as applied to the data then available to him yielded a p-value above 0.05. This result struck Dr. Quan as inconsistent with other analyses he had performed, most notably the Kaplan-Meier plot, which seemed clearly to indicate a change in the hazard ratio.

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[139] 6/8/06 email from H. Quan to J. Bolognese et al., MRK-ARQ0007271 (stating that Dr. Quan switched the covariate in the relevant computer program from Logarithm of Time to Linear Time "in order not to hide any thing [sic] from ESMB").

Dr. Quan then ran the Linear Time Test, which (like the Logarithm of Time Test) is a standard means of testing the constancy of the hazard ratio. According to Dr. Quan, based on the data available at the time, the Linear Time Test yielded a p-value that was smaller than that generated by the Logarithm of Time Test and therefore more consistent with Dr. Quan's prior analyses (such as the Kaplan-Meier plots).

Based on Dr. Quan's review of the p-values generated by the two tests, as well as "fit statistics" included in the outputs from the tests, he concluded that the Linear Time Test covariates fit the data better than the Logarithm of Time Test covariates. (As explained in Appendix R, Dr. Jennifer Ng, another MRL statistician, was tasked later in the fall of 2004 with conducting various statistical analyses of the APPROVe Trial cardiovascular data independently of the work that Dr. Quan was doing. Dr. Ng's Memorandum about the analyses also supported the conclusion that the Linear Time Test "fit" the APPROVe Trial data better than the Logarithm of Time Test.)

In preparing the September 13, 2004 report to the APPROVe Trial External Safety Monitoring Board, Dr. Quan used the program he had modified previously. The report stated that the proportionality p-value for the confirmed thrombotic endpoint was 0.006 – a statistically significant deviation from the proportional hazards assumption, meaning that there was sufficient evidence to reject the assumption of a constant hazard ratio over time.

Dr. Quan's September 13, 2004 report to the External Safety Monitoring Board did not state whether he had obtained the p=0.006 result using the Logarithm of Time Test or the Linear Time Test. According to Dr. Quan, the switch from the Logarithm of

Time Test to the Linear Time Test was never documented outside the program itself, which reflects which covariate (logarithm of time or linear time) was used in the Cox proportional hazards analysis.

(2) Duplication of the Error

Work began on the article about the APPROVe Trial cardiovascular data in late October 2004. The article, which was published in the New England Journal of Medicine in February 2005, was authored by seven external scientists and five MRL scientists. The statistical analyses on which the article was based were performed by Dr. Quan as an extension of the work he had done as the unblinded statistician for the APPROVe Trial External Safety Monitoring Board. The published article used final data that became available in December 2004. The APPROVe article stated that a "test of the proportional-hazards assumption . . . was accomplished by evaluating the interaction between the logarithm of time and the assigned treatment . . ."[140] and stated further that "[t]he changing pattern of the treatment effect over time was confirmed by a failed test for proportionality of hazards (P=0.01)."[141] This p-value, as noted above, was the result based on final data using the Linear Time Test, not the Logarithm of Time Test. The result for the Logarithm of Time Test, which was not reported in the article, was p=0.07.

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[140] Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1095.

[141] Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1097.

Based on the extensive record we reviewed, including numerous drafts of and correspondence about the article, we find that the error in the article with respect to the proportional hazard testing was inadvertent. A proportionality p-value was first inserted in the draft in November 2004, although there was no description of the method used to achieve this result. At that time, the p-value reported was p=0.006 based on August 2004 data analyzed by Dr. Quan. When final data became available in December 2004, the p-value of 0.01 (rounded down from p=0.014) was included instead. Both of these p-values were generated using the Linear Time Test. According to Dr. Quan and Mr. Bolognese, the two MRL statisticians who were co-authors of the article, once the program was changed to linear time at Dr. Quan's direction in the summer of 2004, it continued to generate results, including the p-value, using the Linear Time Test, although Dr. Quan did not recall that he had made the switch.

A description of the method used to test the proportional hazards assumption was first added to the draft manuscript on January 11, 2005 and subsequently changed on February 13, 2005, after reviewers at the New England Journal of Medicine asked the authors whether the test was described correctly. It is not clear whether Dr. Quan or Mr. Bolognese added the language about the statistical test, although each agreed that the language was added by one of them. At around the same time that the description of the method was revised, the authors added that the Logarithm of Time Test was "specified" in the "cardiovascular-analysis plan." Handwritten notes on galley proofs reflect that an editor thought that the February 13 description was confusing. The language that appears in the February 15 published article was then substituted.

According to Dr. Quan and Mr. Bolognese, they assumed when the article was being drafted that the Logarithm of Time Test had been used because it is a widely accepted method to test the Cox proportional hazards assumption, is the conventional starting method at Merck, and is the method typically used by Dr. Quan. Neither Dr. Quan nor Mr. Bolognese checked the program prior to publication to confirm that assumption. In addition, both Dr. Quan and Mr. Bolognese, as well as numerous witnesses including external authors, stated that the issue of which test had been used to confirm that the assumption of proportional hazards did not hold was not an issue on which people were focused during the manuscript review process because they accepted that the hazard ratio was not constant based on the totality of the statistical analyses performed.

Based on our review of the record, we find that the erroneous description of the model used to test the proportional hazards assumption (which also was duplicated in Merck's submission to the FDA of an abbreviated Clinical Study Report, dated March 15, 2005) was inadvertent and was not made with any intent to mislead.

The error was discovered by Mr. Thomas Cook, a Merck statistician working on analyzing cardiovascular data from the APPROVe Trial follow-up study discussed below. In the course of his work, Mr. Cook ran numerous statistical tests, some of which previously had been conducted on the data from the base study, including the Logarithm of Time Test. That test, however, yielded a p-value of 0.07, not 0.01, when Mr. Cook ran it for confirmed thrombotic events. This caused him to check the covariate used in testing the proportional hazards assumption for purposes of the APPROVe article, which

led to the discovery that the p-value of 0.01 reported in the APPROVe article and in the abbreviated Clinical Study Report was generated by the Linear Time Test.

(3) Import of the Error

Based on the final APPROVe cardiovascular data, the Logarithm of Time Test for confirmed thrombotic events reflects a p-value of 0.07 while the Linear Time Test, as reported in the New England Journal of Medicine, reflects a p-value of 0.01 for the same endpoint. According to critics, because the p-value generated by the Logarithm of Time Test is greater than 0.05, Merck had no basis for stating that the hazard rate changed. In fact, it is argued, Merck's own Statistical Data Analysis Plan for Protocol 203 provided that a p-value greater than 0.05 "is not inconsistent with proportionality, i.e., constancy of treatment effect over time," in other words, is not sufficient to support rejection of the proportional hazards assumption.[142]

As a general matter, tests for proportional hazards have low statistical power, especially if they are not based on a significant number of events. In the APPROVe Trial, only 72 patients experienced cardiovascular events over the course of the 3-year study: of the 1287 patients in the Vioxx arm of the study, 46 patients experienced a confirmed thrombotic event compared to 26 of the 1299 patients in the placebo group. As discussed above, under these circumstances, many biostatisticians using a Cox proportional hazards model to evaluate the constancy of the hazard ratio would deem results as high as p=0.10, in conjunction with graphical analysis, to be sufficient evidence

[142] Protocol 203 Statistical Data Analysis Plan, MRK-AAD0200169, at 94.

to reject the assumption of proportional hazards and would see no meaningful difference between a p-value of 0.01 and 0.07. If the Statistical Data Analysis Plan for Protocol 203, which specified the Logarithm of Time Test as the "primary method" and set a significance level at p=0.05, were binding on this analysis of APPROVe Trial cardiovascular data, then the authors of the APPROVe article would have been required to report that the result of the Logarithm of Time Test was p=0.07 and that this result was not inconsistent with a finding that the hazard ratio is proportional over time. As discussed below, however, we find that the Protocol 203 Statistical Data Analysis Plan was not required to be followed in analyzing cardiovascular data from the APPROVe Trial alone. As a result, there is no meaningful difference in the conclusion with respect to confirmed thrombotic events.

In addition, while the test of the proportional hazards assumption is the most formal means of evaluating whether there is a change in the hazard ratio over time, other analyses may also be considered. As explained above, the Kaplan-Meier curves of the APPROVe Trial cardiovascular data appeared to reflect a clear change in the hazard rate at around the 18-month mark, as did the analysis of events in 6-month time intervals. These are all post-hoc analyses and therefore are not entitled to the same weight that would have been accorded to pre-specified analyses, but taken together, they provide reasonably strong evidence of a changing hazard ratio.

(4) APTC Endpoint Events

In addition to analyzing confirmed thrombotic events, MRL scientists also analyzed cardiovascular events in the APPROVe Trial using the Antiplatelet Trialists'

Collaboration ("APTC") composite cardiovascular endpoint. As discussed above at pages 84 and 85, this endpoint consisted of cardiovascular death, myocardial infarction, stroke (both ischemic and hemorrhagic), and death due to unknown cause or due to bleeding. With respect both to the confirmed thrombotic and the APTC composite cardiovascular endpoints, the APPROVe article concluded, as discussed above, that the difference between the placebo and Vioxx groups was evident in the second 18 months of the study, whereas the event rates were similar for the first 18 months. The APPROVe article stated that "[t]he changing pattern of the treatment effect over time [for the confirmed thrombotic endpoint] was confirmed by a failed test for proportionality of hazards (P=0.01)" and that "[f]indings for the APTC end point were similar."[143]

The evidence reflects that MRL scientists concluded based on the Kaplan-Meier curves and 18-month segment analyses that the hazard rate for APTC events appeared to change at approximately 18 months, like the changing hazard rate for confirmed thrombotic events. The p-value for APTC composite endpoint events based on the Linear Time Test, however, was p=0.119, a result that is not statistically significant as measured against the conventional p-value of 0.05 to measure significance, or even against the more generous p-value of 0.10 used by many biostatisticians for testing the assumption of proportional hazards.

MRL scientists believed that given the small numbers of events, the fact that the p-value was 0.119 for such events using the Linear Time Test was not particularly

[143] Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1097.

meaningful, especially when viewed in the context of the totality of the cardiovascular data from the APPROVe Trial. We found no evidence that the Logarithm of Time Test was conducted on the final data for the APTC endpoint before the APPROVe article was written. It would no doubt have been better if the authors had included in the APPROVe article the proportionality p-value for APTC composite cardiovascular endpoint events as well as for confirmed thrombotic events.

(5) Pre-specification of Data Analyses Conducted

The evidence shows that the MRL scientists' analyses of the cardiovascular events in the APPROVe Trial were post-hoc – i.e., were not dictated by any pre-specified plan. The APPROVe Trial Data Analysis Plan did not address statistical analyses of cardiovascular data in great detail and instead referred to the Cardiovascular Adjudication SOP generally, as well as to the combined analysis that would be performed pursuant to the Statistical Data Analysis Plan for Protocol 203. The Statistical Data Analysis Plan for Protocol 203 set forth analyses to be performed once the APPROVe, ViP and VICTOR Trials were completed and data from the three trials were pooled. Thus, there was not any plan in place that specified in detail how the cardiovascular data from the prematurely terminated APPROVe Trial should be analyzed on a stand-alone basis.

With respect to checking the assumption that the hazard ratio was constant, the Statistical Data Analysis Plan for Protocol 203 stated:

> Analytical and graphical methods will be employed to verify the proportional hazards assumption. The primary method for testing the proportional hazards assumption will be by including the factor treatment*log(time) in the model; nonsignificance (p>0.050) of this factor is not

> inconsistent with proportionality, i.e., constancy of treatment effect over time.[144]

The two MRL statisticians independently analyzing the APPROVe Trial cardiovascular data, Dr. Quan and Dr. Ng, did not rely on the Statistical Data Analysis Plan for Protocol 203 in conducting their analyses. Dr. Quan, for example, in conducting analyses for the External Safety Monitoring Board, was guided by his experience as well as by requests from the External Safety Monitoring Board members. Dr. Ng similarly was not governed by a formal analysis plan and ran a series of tests and analyses suggested during brainstorming sessions with senior MRL statisticians.

The published APPROVe article stated that "[a] test of the proportional hazards assumption was specified in the cardiovascular-analysis plan."[145] It did not indicate that, in light of the premature termination of the APPROVe Trial, there was no data analysis plan that governed how the APPROVe Trial cardiovascular data standing alone should be analyzed. In our view, it would have been preferable to have included in the article a statement to the effect that, due to the unanticipated circumstances, there was no data analysis plan that dictated the analyses to be conducted on the APPROVe Trial cardiovascular data alone. The article could have reached the same conclusions and simply stated that Merck followed best statistical practices and conventions in analyzing the APPROVe Trial cardiovascular data and that those analyses were generally consistent

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144 Protocol 203 Statistical Data Analysis Plan, MRK-AAD0200169, at 94.

145 Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1095.

with the pre-specified analyses set forth in the Protocol 203 Statistical Data Analysis Plan.

We did not find evidence as to why the authors of the APPROVe article did not include this additional context. Although analysis of the proportionality of hazards was identified in the article as having been specified, the authors, based on recommendations from New England Journal of Medicine peer reviewers, also stated that other analyses conducted, including the analysis of when the hazard ratio appeared to change, were post-hoc:

> In a post hoc analysis, the difference between the two groups in the incidence of thrombotic events was evident in the second 18 months of the study, whereas the event rates were similar for the first 18 months. . . . The changing pattern of the treatment effect over time was confirmed by a failed test for proportionality of hazards (P=0.01).[146]

The press release that Merck issued on May 30, 2006 correcting the description of the statistical method used to test the proportional hazards assumption, and the follow-up release that Merck issued on June 26, 2006, refer several times to "specified" analyses,[147] and the May 30 release attaches an excerpt from Protocol 203 regarding the "Check of [proportional hazards] Model Assumptions."[148] As indicated above, the May 30, 2006

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146 Bresalier* RS, Sandler* RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102, at 1097.

147 5/30/06 Merck press release, "Merck Corrects Description of a Statistical Method Used in APPROVe Study," MRK-AFN0110064, at 64; 6/26/06 Merck press release, "Merck Stands Behind Original APPROVe Study Results," MRK-ASW0005632, at 33.

148 Excerpt of Protocol 203 Statistical Data Analysis Plan, "Check of Model Assumptions," MRK-AFN0110067 (attached to 5/30/06 Merck press release, "Merck Corrects Description of a Statistical Method Used in APPROVe Study," MRK-AFN0110064).

press release stated in a separate section that "[t]here was no Statistical Analysis Plan . . . for the cardiovascular data from APPROVe alone."[149] Both releases nevertheless create the erroneous impression that the testing performed on the APPROVe Trial cardiovascular data was pre-specified.

A number of MRL employees involved in drafting and reviewing these press releases (the June 26 release repeats nearly verbatim three of the paragraphs from the May 30 release) stated that the intent of the drafters was to convey that Merck had a plan in place to analyze cardiovascular data and that the post-hoc analyses of the APPROVe Trial cardiovascular data were conducted in a manner that was consistent with that plan. This additional context was included in an assessment about the APPROVe Trial cardiovascular data analysis that accompanied an Open Letter from Dr. Peter Kim dated June 26, 2006:

> In the absence of a specific plan for the analysis of CV event HR [hazard rate] over time in APPROVe alone, the analysis of the proportional hazards assumption for the APPROVe CV data proceeded in a manner consistent with good statistical practice and consistent with the DAP for Protocol 203.[150]

While the releases are not as clear as they could have been, we find no basis to believe that anyone at Merck intended them to mislead the public regarding the APPROVe Trial cardiovascular data analysis. It also must be noted that whether or not

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[149] 5/30/06 Merck press release, "Merck Corrects Description of a Statistical Method Used in the APPROVe Study," MRK-AFN0110064, at 65.

[150] 6/26/06 letter from P. Kim, "An Open Letter from Merck," MRK-AFO0300152, at 54.

analyses were pre-specified, Merck withdrew Vioxx on the basis of Merck scientists' view that the APPROVe Trial cardiovascular data reflected a higher relative risk for patients using Vioxx than for those using placebo.

25. Allegation No. 25: New Data Collected from Patients Who Were Enrolled in the APPROVe Trial Indicate that the Relative Risk of a Cardiovascular Event on Vioxx Increases Almost Immediately – Not After 18 Months as Merck Has Claimed.

a. Summary of Allegation.

Vioxx was withdrawn from the market on September 30, 2004 on the basis of cardiovascular data from the APPROVe Trial consisting of cardiovascular adverse events that occurred while patients were on treatment (Vioxx or placebo) or within 14 days of having discontinued treatment. After the APPROVe Trial was terminated, the Protocol was amended to collect and analyze follow-up data on cardiovascular events that occurred more than 14 days after patients discontinued therapy in an effort to evaluate whether the increased relative risk of cardiovascular adverse events on Vioxx seen during the course of the base study would return to normal after patients stopped using the drug. MRL scientists and members of the APPROVe Trial Administrative Committee began discussing these protocol amendments less than a week after Vioxx was withdrawn from the market and finalized them in August 2005. Merck first submitted results of this follow-up study to the FDA and described them in a press release on May 11, 2006.

Critics have argued that these follow-up data, when combined with data from the base study, demonstrate that the increased risk of cardiovascular adverse events on Vioxx as compared to placebo in the APPROVe Trial emerged after only a few months of use –

not after 18 months of continuous use as Merck has argued publicly. Critics further allege that Merck deliberately presented these data in a confusing and incomplete manner in its May 11 press release to avoid undermining the Company's claim that there was no increased relative risk during the first 18 months of the APPROVe Trial.

Finally, critics have questioned whether Merck had these data prior to the publication of the 2005 APPROVe article and have alleged that these data were intentionally withheld from that article so as not to undermine the 18-month claim.

b. Our Findings and Conclusions.

The APPROVe Trial Protocol specified, as was standard in all Merck trials, that data would be collected on serious adverse events, including cardiovascular events, that occurred while patients were on treatment or within 14 days after discontinuation of treatment. After Vioxx was withdrawn from the market in September 2004, MRL scientists, members of the APPROVe Trial Administrative Committee, and representatives of the FDA recognized that an important open question remained: whether patients who took Vioxx in the APPROVe Trial would continue to experience increased rates of thrombotic events compared to placebo more than 14 days after stopping use of the drug.

To answer this question, MRL scientists, in consultation with the APPROVe Trial Administrative Committee and the FDA, instituted two amendments to the APPROVe Trial Protocol in August 2005. The amendments provided for the collection and adjudication of all cardiovascular events experienced by any patient originally enrolled in the base study at any time within four years of having enrolled – i.e., within the

three-year duration of the base study or a fourth follow-up year – regardless of whether that patient was still enrolled in the study or on therapy at the time of the event. Data on cardiovascular events that occurred more than 14 days after discontinuation of the study drug had been only sporadically reported during the base study and therefore had not provided an adequate basis for meaningful analysis.

The Statistical Data Analysis Plan for the follow-up study specified two different analyses: (i) an analysis of cardiovascular events that occurred either during treatment or after the discontinuation of treatment among all patients randomized in the base study who had taken at least one study dose (the "Intention-to-Treat Analysis"); and (ii) an analysis of cardiovascular events occurring among these same patients fifteen days or more after the discontinuation of treatment (the "Off-Drug Analysis"). Both analyses included all relevant events that occurred during the three-year term of the base study plus a fourth follow-up year. The specified primary and secondary endpoints for both analyses, respectively, confirmed thrombotic events and APTC composite endpoint events, were the same cardiovascular endpoints analyzed following termination of the APPROVe Trial base study. Critics base their claim on the results of the Intention-to-Treat analysis, which is the focus of discussion below.

(1) Results

On May 11, 2006, Merck reported preliminary analyses of these data to the FDA and issued a press release that set forth Merck's conclusions about the results' impact on the Company's prior analyses of cardiovascular data from the base study. The results may be summarized as follows:

- For the Intention-to-Treat Analysis (including both on-drug and off-drug data), there was a statistically significant increased relative risk of both confirmed thrombotic events and APTC composite cardiovascular endpoint events on Vioxx versus placebo over the course of the four-year study period, and there was insufficient evidence to reject the assumption of proportional hazards.[151]

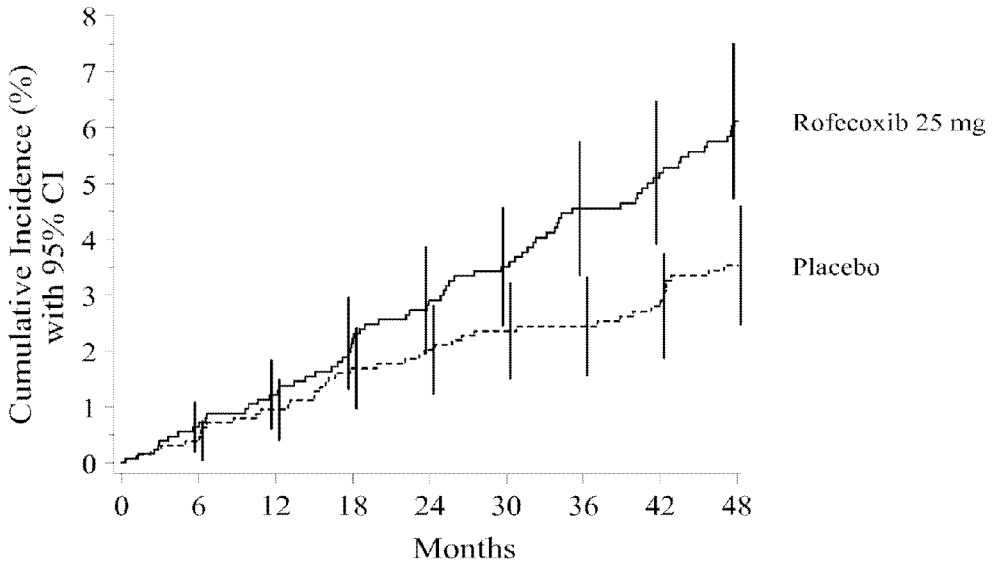
- For the Off-Drug Analysis, there were more cardiovascular events in the Vioxx arm than in the placebo arm – 28 versus 16 confirmed thrombotic events, and 21 versus 12 APTC events, on Vioxx versus placebo – but the difference was not statistically significant.

The Statistical Data Analysis Plan for the follow-up study specified the use of Kaplan-Meier time-to-event plots and a test of the proportionality of the hazard rates over time. Critics claim that the follow-up data refute Merck's 18-month claim based on the appearance of the Kaplan-Meier plots and the statistically non-significant result of the proportional hazards test. With respect to the proportional hazards test, MRL statisticians ran both the Logarithm of Time Test and the Linear Time Test for both endpoints (confirmed thrombotic events and APTC composite endpoint events) in the Intention-to-Treat Analysis. All four tests resulted in p-values greater than p=0.05, meaning that there was not sufficient evidence in the Intention-to-Treat Analysis to reject the assumption

[151] In the Intention-to-Treat Analysis in the follow-up study, the relative risk for confirmed thrombotic events on Vioxx versus placebo was 1.74 (95% confidence interval, 1.19 to 2.55), and the relative risk for APTC composite cardiovascular endpoint events on Vioxx versus placebo was 1.86 (95% confidence interval, 1.19 to 2.90). 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, at 217, 228.

that the hazard ratio was proportional throughout the trial.[152] The Kaplan-Meier time-to-event plots for the two endpoints in the Intention-to-Treat Analysis are set forth below:

APPROVe Extension – Intention-to-Treat Analysis
Kaplan-Meier Plot – Confirmed Thrombotic Events[153]

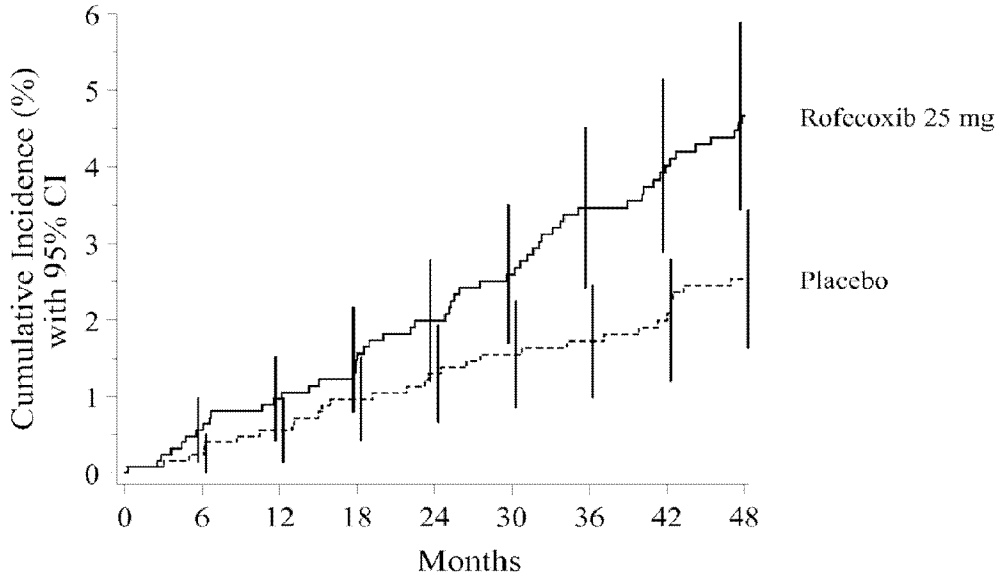


Patients at Risk									
Rofecoxib 25 mg	1287	1221	1187	1152	1131	1117	1092	1032	989
Placebo	1300	1247	1224	1189	1173	1157	1133	1071	1027

[152] For the confirmed thrombotic endpoint in the Intention-to-Treat Analysis, the p-values were p=0.345 for the Linear Time Test and p=0.306 for the Logarithm of Time Test. 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, Figure B2 at 220-21. For the APTC endpoint, the corresponding p-values were p=0.748 and p=0.687, respectively. Id. Figure B6 at 231.

[153] 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, Figure B1 at 219.

APPROVe Extension – Intention-to-Treat Analysis
Kaplan-Meier Plot – APTC Events[154]



Patients at Risk									
Rofecoxib 25 mg	1287	1220	1188	1158	1140	1125	1102	1042	1002
Placebo	1300	1249	1228	1196	1181	1165	1140	1079	1036

Finally, the Company conducted a post-hoc analysis of cardiovascular events among patients who had completed the three-year base APPROVe Trial and for whom fourth-year follow-up data had been collected. There were numerically more confirmed thrombotic events among patients assigned to the Vioxx arm (15) than among those assigned to the placebo arm (9), but this difference was not statistically significant.

(2) Import of Follow-up Data

Analyses based on extended follow-up data such as the Intention-to-Treat Analysis have potential benefits and potential drawbacks, as discussed more fully in Appendix R. Proponents of such analyses contend that collecting data only on adverse

[154] 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, Figure B5 at 230.

events that occur while patients are on therapy or within 14 days of discontinuing therapy may exclude drug-related events that take place more than 14 days after termination of treatment, thereby potentially introducing bias into the analyses – especially if patients discontinue due to other adverse events such as hypertension and remain at risk for subsequent cardiovascular adverse events.

Others, including Merck witnesses whom we interviewed, contend that a 14-day follow-up period is reasonably designed to capture events that are drug-related and that a longer period of follow up may tend to dilute a safety signal. Merck witnesses took the position that the Intention-to-Treat Analyses specified for the follow-up study were significantly less meaningful than the on-drug analyses arising from the base study and should be heavily discounted if not disregarded entirely because they (i) mixed data on on-drug and off-drug events and (ii) incorporated events that may have occurred, in the case of early drop-outs, long after the patient discontinued therapy, thereby potentially diluting an on-drug safety signal by the addition of events that occur in similar numbers in both arms of the study in the off-drug period.

While it is beyond our mandate to attempt to resolve this scientific debate, we note that the Intention-to-Treat Analyses – like all analyses conducted on the APPROVe Trial cardiovascular data – were secondary analyses designed and conducted on a limited number of events after the base study had already been unblinded. The Intention-to-Treat Analyses may form a useful component of scientists' overall understanding of the cardiovascular safety profile of Vioxx, and they raise the possibility that an increased relative risk of cardiovascular events on Vioxx versus placebo may appear before the

18-month mark. Like any post-hoc analyses, however, they do not, standing alone, provide the basis for any firm conclusions. While the Company's position with respect to these data may be overly categorical, the known data in totality neither prove nor disprove the existence of an increased cardiovascular risk on Vioxx before 18 months of continuous treatment. (The fact that a result cannot be ruled out or disproved cannot be interpreted as signaling that the opposite is true or has been proved.)

(3) May 11, 2006 Press Release Regarding Follow-up Study

On May 11, 2006, Merck issued a press release announcing the results of the preliminary analyses of the APPROVe Trial follow-up study. The first paragraph of that press release stated as follows:

> In the off-drug follow-up period for patients in the APPROVe study, there was not a statistically significant difference in the risk of confirmed thrombotic cardiovascular events in patients who had previously taken VIOXX compared to those who had previously taken placebo, according to preliminary analyses announced today by the study sponsor, Merck & Co., Inc. This prespecified analysis included patients regardless of when they discontinued study therapy. Furthermore, in the one-year off-drug follow-up period for patients who completed approximately three years of therapy in the APPROVe study, there was not a statistically significant difference in the risk of confirmed thrombotic events in patients who had previously taken VIOXX compared to those who had previously taken placebo. In these analyses, the data were insufficient to conclude that there was an increased relative risk of confirmed thrombotic cardiovascular events following discontinuation of therapy. In the prespecified primary analysis of each patient's four-year data (that combined data from the on-drug period and the off-drug period regardless of when patients discontinued study therapy) the difference in the risk of confirmed thrombotic cardiovascular events between groups initially observed in

> the on-drug period of the study remained statistically significant.[155]

Attached to the press release was a four-page summary of the results of the follow-up study that Merck had included in its May 11 report to the FDA. The summary set forth four "Conclusions" to be drawn from the follow-up data, the first two of which resulted from a post-hoc analysis that divided the Intention-to-Treat data set into pre- and post-18 month segments and compared them to the corresponding segments in the base study as follows:

- For the first 18 months, the relative risk of confirmed thrombotic cardiovascular events for rofecoxib compared to use of placebo in the ITT analysis was similar to that observed in the on-drug base study.
- Beyond 18 months, the relative risk of confirmed thrombotic cardiovascular events for rofecoxib compared to use of placebo in the ITT analysis was approximately half of that observed in the on-drug base study. This lowering of the relative risk was mostly due to the off-drug follow-up data observed during the period beyond month 36 and to the off-drug follow-up data in patients who prematurely discontinued study therapy.[156]

Neither the press release nor the four-page summary mentioned the results of the pre-specified Kaplan-Meier plots and analyses of the proportionality of hazards for the four-year data that critics have argued establish an increased relative risk of cardiovascular events on Vioxx well before the 18-month mark. In addition, neither the press release nor the four-page summary mentioned the results for the secondary APTC

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[155] 5/11/06 Merck press release, "Merck Announces Preliminary Analyses of Off-Drug Extension of APPROVe Study," MRK-S0420112019, at 19.

[156] 5/11/06 APPROVe Off-Drug Extension Preliminary Analyses of Thrombotic Cardiovascular Safety, MRK-ARQ0002293, at 96.

composite events endpoint, which were generally less favorable to Vioxx and less supportive of the 18-month claim than the reported results for the confirmed thrombotic events endpoint. Notably, the post-hoc analysis of the off-drug data showed that during the first six months after discontinuation of therapy, there was a statistically significant increase in the risk of APTC events among those patients that had previously taken Vioxx.[157]

While the press release quoted above is difficult to understand and it can be argued that other information should have been included, the fact that Merck shortly thereafter posted on its website the entire 137-page report it submitted to the FDA suggests that there was no intention to mislead.

In addition, the plots themselves, as well as the views of Drs. Furberg* and Nissen*, the Company, and the authors of the published APPROVe article about the meaning of those data, have recently been fully aired in the New England Journal of Medicine and in responsive Merck-issued press releases. As a result, while it may have been preferable to set forth the results of those pre-specified analyses in the original press release for the benefit of the scientific community, any arguable lack of full and clear disclosure as of May 11 was quickly remedied.

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[157] The relative risk for Vioxx versus placebo for this period was 3.74 (95% confidence interval, 1.04 to 13.42). 5/26/06 APPROVe Extension Statistical Package, MRK-S0420112195, Table B14 at 233. While more confirmed thrombotic events occurred among patients who had previously taken Vioxx than among those who had previously taken placebo (12 versus 5, respectively), the difference was not statistically significant (relative risk 2.44; 95% confidence interval, 0.86 to 6.94). Id. Table B7 at 233.

E. Summary of Principal Criticisms and Findings Concerning Financial Interests of Merck Senior Management.

Each of the criticisms discussed in this Report rests on a common premise: that Merck personnel engaged in alleged misconduct with respect to the development, testing and/or marketing of Vioxx because they were financially motivated to conceal the drug's risks so as to ensure its success in the marketplace. These allegations take on two forms: (i) allegations that sales of Vioxx had an undue influence in Merck's compensation structure; and (ii) allegations that Merck senior management sought to enrich themselves by trading Merck common stock on the basis of material nonpublic information.

Our conclusions with respect to these allegations are based on our finding that compensation for executive officers and non-executive employees at Merck was driven by formulas based on multiple operational and strategic factors. While sales of Vioxx, like those of other products, played a role in the Company's overall success, they did not have an unwarranted impact on compensation. In addition, as discussed below, we found no evidence to support the allegation that Merck's senior management traded on the basis of material nonpublic information pertaining to Vioxx's cardiovascular safety.

26. Allegation No. 26: Merck Senior Managers Turned a Blind Eye to the Cardiovascular Risks of Vioxx so as not to Jeopardize Their Compensation.

a. Summary of Allegation.

Critics argue that Merck senior management was financially motivated to downplay or ignore the cardiovascular risks of Vioxx, both before the drug was approved by the FDA and while it was on the market. Prior to approval, it is argued, the Company

needed a major drug to replace lost profits from other drugs that were going off patent. In addition, Merck's future depended on its keeping pace with other drug manufacturers like Searle/Pfizer, which had a selective Cox-2 inhibitor in the pipeline. For these reasons, critics allege that senior management did not heed the signals that Vioxx posed a cardiovascular danger.

After Vioxx was approved for sale in the United States, it is alleged that Merck senior management continued to downplay or ignore mounting data concerning the cardiovascular risks of Vioxx and put patients at risk so as not to jeopardize their compensation and the value of their equity holdings.

b. Our Findings and Conclusions.

As discussed in other parts of this Report, we found no evidence that Merck rushed Vioxx to market prematurely or before adequate safety testing was conducted. In addition, we found that MRL scientists seriously investigated the FitzGerald prostacyclin hypothesis, repeatedly pooled and analyzed cardiovascular data from Vioxx clinical trials, and believed in good faith that Vioxx was not prothrombotic. Thus, one could argue on the basis of these two findings that there was no need for us to investigate further any alleged ill motives for Merck's seeking FDA approval for Vioxx or for marketing the drug.

Critics have also alleged, however, that financial motivation played a role in Merck senior management's decision to keep Vioxx on the market in the face of alleged signals that it posed a serious cardiovascular risk. We therefore investigated the manner

in which Merck senior management was compensated and the effect that the profitability of the Vioxx franchise may have had on compensation.[158]

Throughout the relevant period, compensation decisions for executive officers and non-executive employees were guided by the Company's compensation philosophy. This philosophy set compensation based on Merck's performance vis-à-vis peer companies as well as individual performance. The Company sought to retain key employees by compensating them at competitive levels and to align employees' interests with those of shareholders interests through the use of long-term incentives (e.g., stock option grants). To this end, the Company utilized three forms of compensation for executives: (i) base salary; (ii) annual bonus; and (iii) equity in the form of stock option grants, and later, performance and restricted share units.

As discussed more fully in Appendix S, although the Compensation and Benefits Committee of the Board of Directors and the Chief Executive Officer had some discretion in setting executive compensation at Merck, the process was largely a formulaic one, driven by numeric calculations derived from various Company-wide and departmental performance assessments as well as personal performance and the marketplace. For example, the salary component of executive compensation was set based on the marketplace for comparable positions as well as the executive's personal performance. Similarly, the annual bonus was determined based on (i) a "Company Performance Grid" score, a multi-factor assessment of the Company's performance with

[158] We discuss below in the Report the specific allegations made concerning post-approval evidence of a safety problem, and our findings with respect to each such allegation.

reference to various financial and strategic measures, and (ii) a "Division Performance Grid" score, an even more granular assessment of each division's annual objectives and achievements. Finally, the equity award component was set in light of the market but also took into account various components of the Company Performance Grid as well as the executive's personal performance.

While sales of Vioxx, like those of all of the Company's key franchise products, impacted executive bonuses insofar as they affected scores on the Company Performance Grid, we did not find that the impact was disproportionate or determinative of compensation rates. As discussed in Appendix S, the Company Performance Grid score depended upon several operational metrics (including, but not limited to, earnings per share growth versus other leading health care companies, sales growth versus other leading health companies, and return on investment in operating assets) and several strategic metrics (such as manufacturing productivity, research and development, and Human Resources initiatives). Each of the above metrics was assigned a point value that contributed to the Company's ultimate score. Earnings per share was the most significant metric in the Grid and was assigned 30 points (from 2003 on, 35 points) out of a possible 100 plan points, while sales growth, return on investment in operating assets, manufacturing productivity, and Human Resource initiatives were each assigned 10 points.

Although Vioxx played a role in the earnings per share and sales growth metrics in the Company Performance Grid, we determined, for the reasons set forth below and discussed more fully in Appendix S, that executive compensation was not

disproportionately influenced or dictated by Vioxx. First, while the Company has acknowledged the importance of Vioxx in its product portfolio, its earnings per share and sales growth assessments relied on four or five other key franchise products, including Zocor, Prinivil, and several other products. Second, the earnings per share and sales growth metrics were only two components of a multi-factor assessment and both were assessed in relation to the activities of Merck's peer healthcare companies. Third, the earnings per share metric is not driven solely by top-line growth in the form of sales, but rather measures the Company's structural efficiency and reflects Company expenses and costs. Fourth, based on the point values assigned to the metrics in the Grid, sales growth, return on investment in operating assets, manufacturing productivity, and Human Resource initiatives were given equal weight and therefore had an equal effect on compensation. Furthermore, several of the above mentioned metrics not directly linked to sales – i.e., return on investment in operating assets, manufacturing productivity, and Human Resource initiatives – were given in the aggregate the same or comparable weight to the earnings per share metric.

In conclusion, there is no question that senior management at Merck quite appropriately had a financial interest in the Company's success. It is also clear, however, that Vioxx was but one of several key franchises upon which Company profitability depended. In light of the multi-tiered level of review over compensation decisions, the formulaic method used to calculate compensation for executive officers and non-executive employees, and the Company's diversified product portfolio, Vioxx sales were

merely a factor in the Company's overall financial success and did not have an unwarranted impact on awards for executive officers or non-executive employees.

27. Allegation No. 27: Merck Senior Executives Traded on Material, Nonpublic Information Concerning Vioxx.

a. Summary of Allegation.

Various complaints filed against Merck have made broad allegations that Merck insiders traded the Company's securities on the open market based on material non-public information about Vioxx and its cardiovascular risk profile in violation of the federal securities laws.[159]

b. Our Findings and Conclusions.

As explained more fully in Appendix S, federal law prohibits corporate insiders from trading on the basis of material nonpublic information.[160] Most of the Company's officers and directors are subject to additional regulations that require them to report most of their transactions involving Merck stock and prohibit them from selling the Company's stock within six months of a purchase, or vice versa ("short-swing transactions").[161] Our investigation examined the Company's policies with respect to the

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[159] See, e.g., Consolidated and Third Amended Class Action Complaint, Pringle v. Merck & Co., No. 03-3125, E.D. La., at ¶278 ("During the Class Period, a number of Defendants and other Merck insiders sold substantial amounts of Merck common stock from their personal holdings while in possession of adverse non-public information about the risks of VIOXX."). In addition, the Company's Board of Directors has received letters making similar allegations. See, e.g., 12/10/04 demand letter from J. Abraham* to C. Colbert.

[160] See 15 U.S.C. § 78j; 17 C.F.R. § 240.10b-5 (prohibiting the use of a fraudulent device in connection with securities transactions); Dirks v. SEC, 463 U.S. 646, 654 (1983) ("[A]n insider will be liable under Rule 10b-5 for inside trading only where he fails to disclose material nonpublic information before trading on it and thus makes "secret profits.") (citations omitted).

[161] 15 U.S.C. § 78p.

securities regulations as well as the trading activity of individual corporate officers and directors.

The evidence shows that the Company adopted a restrictive trading window policy, which limited the times when its senior officers and directors could trade in Merck securities to four pre-established periods each year. We find this policy to be reasonably well designed to promote compliance with the governing law. The Company opened its trading windows several days after its quarterly and annual earnings releases,[162] when a great deal of previously nonpublic material information would have been widely disseminated. Thus, the policy minimized the possibility that senior managers could profitably trade on the basis of nonpublic material information.

In addition to implementing this trading window policy, the Company regularly issued trading restriction memoranda, which advised the recipients that they were in possession of nonpublic information that could potentially be viewed as material and requested that they not trade Merck securities. Senior corporate officers and directors frequently received such memoranda, which prohibited them from trading even during window periods. The evidence shows that information relating to Vioxx was from time to time the subject of such memoranda or verbal instructions not to trade.

As part of our investigation, we reviewed the trading records of the Company's most senior officers and directors between May 1999 and December 2004. It appears that, with one inadvertent exception, all directors and senior managers complied with the

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[162] 3/5/99 memorandum from M. McDonald to Section 16 Officers, MK-STK0000500.

Company's internal insider trading policies.[163] Furthermore, consistent with the Company's guidance, it appears that senior management held rather than sold the Company's equity securities granted to them.

We find no basis to support the allegation that senior managers traded on the basis of material nonpublic information concerning Vioxx's cardiovascular safety. As stated throughout this Report, there is no evidence that anyone in senior management at Merck believed that Vioxx presented an increased cardiovascular risk to patients before the APPROVe Trial cardiovascular data were unblinded in September 2004. The data were unblinded between two trading windows and promptly disclosed. According to Merck policy, corporate officers and directors could not trade in Merck stock for almost a full month after disclosure of the APPROVe Trial cardiovascular data and the decision to withdraw Vioxx.[164] Our review of senior managers' trading records indicate that no officers or directors traded prior to the public release of the APPROVe Trial results.

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163 As explained in Appendix S, we did identify one transaction that appears to have violated the Company's policies. This transaction was a small open-market acquisition of fewer than 90 shares by one of the Company's directors. According to Ms. Celia Colbert, Secretary of the Company, this trade occurred at the beginning of the director's tenure and was executed, without his knowledge, by one of his financial advisors. There is no evidence that the director traded on the basis of material nonpublic information.

164 As explained in Appendix Q, the External Safety Monitoring Board recommended stopping the APPROVe Trial on September 17, 2004. This announcement followed a trading window period that ended on August 9, 2004. MK-STK0000470. Merck announced the results of the APPROVe Trial and its decision to voluntarily withdraw Vioxx from the market on September 30, 2004. 9/30/04 Merck press release, "Merck Announces Voluntary Worldwide Withdrawal of VIOXX," MRK-AFJ0008607, at 07. The next trading window did not open until October 26, 2004. 10/21/04 memorandum from N. Van Allen to Directors and Officers Subject to Section 16(b), MK-STK0000469.

CONCLUSION

We have attempted to examine all of the principal allegations of wrongdoing that have been asserted with respect to Merck's development, marketing and data reporting associated with Vioxx to determine whether senior management of the Company acted with integrity. As indicated at the outset, we recognize that our conclusions may not satisfy all of Merck's critics. We believe, however, that the detailed factual examination that is set forth in this Report and the accompanying Appendices fully supports the conclusions we have reached concerning the integrity of Merck's senior management and will enable others to evaluate these conclusions.

As the debate on Merck's conduct continues, we suggest several important points that should be considered. Chief among them is the fact that, at the time Vioxx was developed and marketed, selective Cox-2 inhibitors were viewed as a major improvement in the science of pain management that could prevent painful gastrointestinal problems and even deaths associated with traditional NSAID therapy.

It is noteworthy that, during the pre-approval scientific debate over Dr. FitzGerald's* prostacyclin hypothesis, neither Merck's outside advisors nor Dr. FitzGerald* himself thought that the existence of his hypothesis should delay the commercial distribution of Vioxx. Merck's Board of Scientific Advisors considered the "hypothetical adverse effects" of Vioxx in May 1998 but concluded:

> The gain in safety achieved by the elimination of serious and fatal gastrointestinal toxicity will free patients from one of the most serious adverse effects in current drug therapy. Thus, there is a strong mandate for introduction of Vioxx into medical practice as soon as possible.

Despite the current claim that the FitzGerald prostacyclin hypothesis established that Vioxx was prothrombotic and posed a cardiovascular danger, we have seen no evidence that any scientist suggested at the time that Vioxx or any other selective Cox-2 inhibitor should be kept off the market on the basis of that hypothesis.

In assessing the reactions of Merck's scientists to post-marketing evidence or theories that some claim showed, or at least suggested, that Vioxx was prothrombotic, it is important to look at the way in which those scientists responded to such information. There is no evidence that MRL scientists ignored or turned a blind eye to any credible evidence or hypothesis that suggested that Vioxx was prothrombotic. As the discussion throughout this Report and in the Appendices demonstrates, even when MRL scientists had doubts about the scientific validity of a significant hypothesis or finding, they gave it careful consideration, often seeking the advice of their outside scientific advisors, and performed detailed tests and analyses. While there may be room for legitimate scientific debate as to whether MRL scientists reached the right conclusion on each occasion, we believe that their conclusions were reached in good faith and were reasonable under the circumstances.

While it is often common to speak of a corporation as a monolith, Merck, like all corporations, is a collection of individuals. During the course of our investigation we have had the opportunity to meet and question most of the top scientists and members of

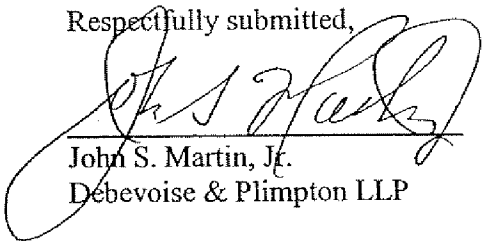
senior management who worked on Vioxx during the time at issue. Drs. Scolnick and Kim, each of whom headed MRL, are extremely impressive scientists who appear on the basis of all available evidence to be fully committed to the scientific process and to firmly believe in the value of that process to yield the truth. The MRL scientists that we interviewed generally described Dr. Scolnick as "data driven." Dr. Kim, who had been the Associate Head of the Department of Biology of the Massachusetts Institute of Technology, joined Merck because he believed that its resources provided him with a greater ability to develop new drugs that would be of great benefit to patients. In addition, it is worth noting that at the time Vioxx was withdrawn from the market, numerous Merck employees (including Dr. Scolnick and Mr. Kenneth Frazier, Senior Vice President and General Counsel of the Company) and their immediate families (including Mr. Gilmartin's wife and Dr. Kim's mother) as well as members of Merck's Board of Directors were using Vioxx.

The other Merck scientists whom we interviewed impressed us as highly skilled and dedicated professionals. While we lack the scientific expertise to judge the scientific validity of the judgments they made, we are satisfied that, prior to receiving the cardiovascular results of the APPROVe Trial, none of them believed that Vioxx was prothrombotic. Our conclusion in this regard is bolstered by the fact that in the vast documentary record we reviewed, the documents reflect consistent and thoughtful scientific discourse concerning the interpretation of the VIGOR Trial results, but no significant disagreement with the Company's position that it did not believe Vioxx was

prothrombotic or that the differences in the cardiovascular statistics in the VIGOR Trial were best explained by the cardioprotective effects of naproxen.

Finally, it must be remembered that when Merck scientists were presented with the cardiovascular data from the APPROVe Trial – the first long-term double-blinded placebo-controlled clinical trial in which there was a significantly increased relative risk of cardiovascular events on Vioxx – the Company immediately withdrew the drug from the market, even though some of their outside advisors urged them to keep it on the market with a stronger cardiovascular warning. This conduct is not consistent with the view that Merck's corporate culture put profits over patient safety.

Respectfully submitted,



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