

APPENDIX C

MERCK'S NEW DRUG APPLICATION
FOR APPROVAL TO MARKET VIOXX.

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APPENDIX C

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On November 23, 1998, Merck submitted to the FDA a New Drug Application seeking approval to market Vioxx in the United States.¹ As noted in Appendix A, one of Merck's principal regulatory goals was to obtain an FDA-approved label for Vioxx that either eliminated or modified the standard NSAID-class gastrointestinal warning based on data regarding Vioxx's favorable gastrointestinal safety profile as compared to traditional non-selective NSAIDs. The proposed label for Vioxx submitted with the New Drug Application did not contain the NSAID-class gastrointestinal warning. Searle/Pfizer's New Drug Application for Celebrex, which also sought to eliminate or modify the NSAID-class gastrointestinal warning, had been submitted five months earlier and was still pending.

Merck requested six-month priority review status for the Vioxx New Drug Application, which the FDA had granted for Celebrex, and which, on January 11, 1999, the FDA granted for Vioxx.² On December 31, 1998, the FDA approved Celebrex for

¹ On March 23, 1999, two months before the FDA approved Vioxx, Merck also submitted to the FDA a "Safety Update Report," composed of "safety information for [Vioxx, accumulated] subsequent to the original [November 23, 1998 New Drug Application]." 3/23/99 letter from R. Silverman to R. DeLap*, MRK-ACD0077169, at 69. We refer to the contents of the November 23, 1998 original submission and the March 23, 1999 Safety Update Report collectively as the "New Drug Application."

² 1/11/99 letter from A. Zaccola* to R. Silverman, MRK-AAF0001137, at 37 ("Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 22, 1999, in accordance with 21 C.F.R. 314.101(a). If the application is filed, the user fee goal date will be May 23, 1999."); see also 1/11/99 Merck press release, "FDA Grants Priority Review for Vioxx™,

sale in the United States. On April 20, 1999, the FDA's Arthritis Advisory Committee voted unanimously to recommend approval of Vioxx,³ and on May 20, 1999, the FDA approved Vioxx for sale in the United States. The FDA-approved labels for both Vioxx and Celebrex included the NSAID-class gastrointestinal warning.

This Appendix discusses: (i) Merck's discussions with the FDA in the spring of 1998 regarding the data necessary to remove the NSAID-class gastrointestinal warning; (ii) the contents of the New Drug Application for Vioxx, particularly the data on its gastrointestinal, cardiovascular and renal safety; (iii) the FDA's review of the New Drug Application for Vioxx; (iv) the FDA Arthritis Advisory Committee's review of the New Drug Application for Vioxx; (v) Vioxx labeling negotiations between the FDA and MRL; and (vi) the Vioxx label that the FDA approved in May 1999.

A. Spring 1998 Communications with the FDA.

On March 24, 1998, when Vioxx and Celebrex were in advanced stages of development, the FDA convened a meeting of its Arthritis Advisory Committee consisting of experts, consumer advocacy group representatives, industry representatives,

Merck's Investigational Medicine for Osteoarthritis and Pain," MRK-AFI0162152.

Under the FDA's policy, the FDA assigned priority review to an NDA if it appeared at the time of the filing that the drug would be "a significant improvement" compared to marketed products . . . in the treatment, diagnosis, or prevention of a disease." Center for Drug Evaluation MAPP 6020.3 at 1, <http://www.fda.gov/cder/mapp/6020-3.pdf>.

³ The Committee voted by an 8 (yes) to 0 (no) vote to recommend approval of Vioxx for the treatment of the signs and symptoms of osteoarthritis and by a 6 (yes)/2 (undecided) vote to recommend approval of Vioxx as an analgesic. Summary minutes of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ECNDA0298, 299-300; Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 870-71.

and patients to discuss standards for removing the gastrointestinal warning language from the labels of selective Cox-2 inhibitors.⁴ The FDA has several advisory committees, which advise the FDA generally “on the safety and effectiveness, including the labeling and advertising, and regulatory control” of human prescription drugs.⁵

As discussed in Appendix A, Merck at that time was in the process of collecting gastrointestinal safety data from (i) six-month endoscopy studies,⁶ which used an endoscope to examine the gastrointestinal tract for gastroduodenal ulcers and lesions and which, MRL scientists believed, would predict the effect of Vioxx on the clinically significant gastrointestinal outcomes, such as perforations, ulcers and bleeds (“PUBs”), and (ii) Protocol 069, an analysis of pooled (or combined) PUBs data from the Phase IIb/III osteoarthritis trials of Vioxx.

At the March 1998 meeting, the Arthritis Advisory Committee acknowledged that endoscopy studies provided “very useful” information about a drug’s impact on the gastrointestinal tract, but concluded that safety data from a large clinical trial assessing the effect of Vioxx on clinically significant gastrointestinal outcomes, such as PUBs (as opposed to the less serious endoscopically detectable gastroduodenal ulcers), would be

⁴ Minutes of the 3/24/98 FDA Arthritis Advisory Committee meeting, MRK-AAF0000678, at 78.

⁵ 21 C.F.R. § 14.160(a) (West 2006).

⁶ Minutes of 5/12/98 Vioxx Project Team meeting, MRK-GUE0051593, at 602 (frozen file of endoscopy studies in May/June 1998).

required before the NSAID-class gastrointestinal warning could be removed from the labels of selective Cox-2 inhibitors, such as Vioxx and Celebrex.⁷

On April 30, 1998, approximately one month after the meeting of the Arthritis Advisory Committee, MRL representatives met with representatives of the FDA's Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products⁸ to discuss the clinical development of Vioxx for the treatment of rheumatoid arthritis.⁹ At this meeting, the FDA indicated that data from Merck's endoscopy studies and Protocol 069 were unlikely to support wholesale removal of the NSAID-class gastrointestinal warning but might be sufficient to support modification of the warning.¹⁰ According to Dr. Robert Silverman, Merck's principal regulatory liaison responsible for Vioxx-related communications with the FDA, the FDA viewed pooled analyses, such as Protocol 069,

⁷ Minutes of 3/24/98 FDA Arthritis Advisory Committee meeting, MRK-AAF0000678, at 78; Undated slide presentation, "MK-0966 GI Clinical Outcomes Study," MRK-NJ0364020, at 25 (slide summarizing FDA Arthritis Advisory Committee's opinion following the meeting as "GI Outcomes Data would be necessary to remove the GI Warning"); 4/15/98 memorandum from E. DiCesare to Distribution, MRK-ABP0003190, at 200.

⁸ The Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, now referred to as the Division of Anesthesia, Analgesia, and Rheumatology Products, is the part of the FDA's Center for Drug Evaluation and Research that reviews anti-inflammatory and analgesic drugs. Analgesia and Anti-inflammatory Drug Information, http://www.fda.gov/cder/drug/Analgesia_antiinflam/default.htm. The role of the FDA's Center for Drug Evaluation and Research (CDER) is to promote and protect "the health of Americans by assuring that all prescription and over-the-counter drugs are safe and effective." The Center evaluates all new drugs before they are sold, and serves as a consumer watchdog for the more than 10,000 drugs on the market to ensure they continue to meet the highest standards. Improving Public Health: Promoting Safe and Effective Drug Use, <http://www.fda.gov/opacom/factsheets/justthefacts/3cder.html>.

⁹ 9/2/98 letter from R. Silverman to R. DeLap*, MRK-I8940040477, at 77.

¹⁰ Undated slide presentation, "MK-0966 GI Clinical Outcomes Study," MRK-NJ0364020, at 26; Undated slide presentation, "FDA Conference RA Clinical Program on April 30, 1998," MRK-ABC0013670, at 74; Minutes of 4/30/98 End of Phase II FDA meeting, MRK-AAF0000756, at 58-59.

with skepticism because, in the FDA's view, there were no generally accepted standards for how such analyses should be conducted.¹¹ Nonetheless, MRL scientists believed that Merck's gastrointestinal safety data were compelling and should support a better label.

B. The New Drug Application for Vioxx.

On November 23, 1998, Merck submitted to the FDA a New Drug Application seeking approval to market Vioxx in the United States. Regulatory requirements for a New Drug Application and Merck's New Drug Application for Vioxx are discussed below.

1. General Overview of the New Drug Application Process.

Before marketing a new drug in the United States, a drug company (or "sponsor") must seek authorization from the FDA by filing with the Agency a New Drug Application. A New Drug Application must include both pre-clinical and clinical data on the drug and must demonstrate that the drug is safe and effective under the proposed conditions of use.¹² The New Drug Application must also include the sponsor's proposed labeling for the drug and an integrated summary of all available information concerning the safety and efficacy of the drug.¹³ The FDA may approve the drug for a particular

¹¹ The FDA noted, for instance, that Protocol 069 compared pooled data on Vioxx against pooled data on a variety of NSAID comparators combined, resulting in blended NSAID values that clinicians would not be able to replicate. Draft of 5/20/99 approved Vioxx product label, MRK-ABH0015584, at 91 (attached to 5/15/99 facsimile from R. DeLap to R. Silverman, MRK-ABH0015583).

¹² See generally 21 C.F.R. § 314.50 (West 2006).

¹³ 21 C.F.R. § 314.50(c)(2)(i), (d)(5)(v), (d)(5)(vi)(a) (West 2006).

indication if the FDA finds that the drug is safe and effective for its intended use and that the benefits of the drug exceed its known risks.¹⁴

In reviewing a New Drug Application, the FDA typically convenes an advisory committee of experts in relevant fields to provide input on data and make recommendations regarding approval and labeling. The FDA is not bound by these recommendations.

2. Overview of the Vioxx New Drug Application.

The New Drug Application for Vioxx contained data from 60 clinical studies, including studies in patients with osteoarthritis, acute pain, and rheumatoid arthritis, and comprised more than 150,000 pages.¹⁵ In the aggregate, the studies included close to 10,000 patients,¹⁶ over 5,400¹⁷ of whom had been treated with Vioxx.¹⁸ The New Drug

¹⁴ FDA – CDER – Drug Applications, <http://www.fda.gov/cder/regulatory/applications/NDA.htm>.

¹⁵ MRL Background Package for 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ACD0064939, at 65117 (listing studies submitted as part of the New Drug Application). Prior to filing the New Drug Application, MRL representatives met with the FDA to discuss the format and organization of the New Drug Application, including the safety table format, to ensure the New Drug Application fulfilled the requirements of the FDA's reviewers. See, e.g., Minutes of 12/19/97 sponsor meeting, MRK-AAF0000655-70.

¹⁶ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 657.

¹⁷ 11/23/98 NDA (Synopsis of Application: Worldwide Clinical Summary), MRK-OS420000310, at 390; 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 448.

¹⁸ The New Drug Application for Vioxx was one of the largest new drug applications Merck had ever filed and included more data on patient exposure to the new drug than most new drug applications submitted to the FDA up to that point. 4/1/05 deposition of A. Nies at 436 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); see also Transcript of 2/16/05 FDA Arthritis Advisory Committee meeting at 235, <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4090T1.pdf> (testimony of M.L. Villalba* (FDA): "I want to point out that this number is a substantial number for an NDA. This is greater than most NDAs. Although most of the COX-2 selective agents had this kind of size of NDA, but before we used to approve products based on much smaller data. These numbers are above minimum requirements by the International Conference on Harmonization Guidances.").

Application also included data concerning the gastrointestinal, cardiovascular and renal safety of the drug.

In the New Drug Application, Merck sought FDA approval to market Vioxx for: (i) the acute and chronic treatment of the signs and symptoms of osteoarthritis; (ii) the relief of acute pain; and (iii) the treatment of primary dysmenorrhea (i.e., menstrual cramps). Although the New Drug Application included data from several studies in patients with rheumatoid arthritis, the original New Drug Application did not seek approval to market Vioxx for that indication.¹⁹

The New Drug Application consisted of multiple sections,²⁰ including a section entitled “Clinical Documentation,” which reported on the clinical pharmacology, clinical efficacy, and clinical safety of Vioxx.²¹ The clinical safety subsection (also known as the

The Vioxx New Drug Application exceeded greatly the minimal requirements by the International Conference on Harmonization Guidances, which required that a New Drug Application contain data on 300 patients for 6 months and 100 patients for 1 year. Counting all doses of Vioxx, the Vioxx New Drug Application included data on 1,396 patients for at least 6 months and 822 patients for at least one year. 5/19/99 Medical Officer Review by M.L. Villalba, MRK-ADI0005375, at 448.

¹⁹ Merck sought approval to market Vioxx for treatment of the signs and symptoms of rheumatoid arthritis in February 2001. 1/4/02 letter to from R. Silverman to J. Bull, MRK-0242000001, at 01 (referring to the supplemental New Drug Application for rheumatoid arthritis). The few studies in patients with rheumatoid arthritis included (i) 10-day methotrexate interaction Phase I clinical pharmacology studies (Protocols 011 and 030), (ii) a 6-week Phase IIa study in patients treated with 125 and 175 mg (Protocol 017), (iii) a 16-week extension using 125 mg, and a 30-week extension using 75 mg, and (iv) a 52-week Phase IIb dose-ranging study (Protocol 068). 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1605; 3/23/99 Safety Update Report, MRK-ACD0077167, at 469.

²⁰ 11/23/98 NDA Index, MRK-OS420000033, 34-37.

²¹ 11/23/98 NDA Index, MRK-OS420000033, at 36; 11/23/98 NDA Clinical Documentation Table of Contents, MRK-OS420039875, at 876-92.

“Integrated Summary of Safety”),²² in turn, consisted of multiple parts, including (i) General Safety Overview, (ii) Clinical Safety in Osteoarthritis Studies, (iii) Clinical Safety in Analgesia Studies, (iv) Gastrointestinal Safety, (v) Safety Experience from Other Indications – Rheumatoid Arthritis, and (vi) Discussion of the Vioxx Safety Profile.²³

On April 20, 1999, the FDA convened a meeting of its Arthritis Advisory Committee to assist the FDA in its review of the New Drug Application for Vioxx and to make recommendations with regard to certain labeling issues.²⁴ Gastrointestinal, cardiovascular and renal safety data included in the New Drug Application, as well as the FDA’s and the Arthritis Advisory Committee’s views about those data, are summarized below.

C. Gastrointestinal Safety.

1. The New Drug Application.

In its New Drug Application for Vioxx, Merck took the position that the submitted data demonstrated that Vioxx had a “[gastrointestinal] safety profile similar to placebo and superior to NSAIDs.”²⁵ In making this assertion, Merck relied, among other

²² 4/1/05 deposition of A. Nies at 438 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.) (stating that the “clinical safety” part of the New Drug Application is “what is called an integrated summary of safety”).

²³ 11/23/98 NDA Clinical Documentation Table of Contents, MRK-OS420039875, at 885-91.

²⁴ See generally transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646-960.

²⁵ MRL Background Package for 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ACD0064939, at 5113.

things, on the results of its two six-month endoscopy studies (Protocols 044 and 045) and a combined analysis of PUBs in the Phase IIb/III osteoarthritis studies (Protocol 069).

According to the New Drug Application:

- In the two endoscopy studies, “[t]reatment with VIOXX 25 mg daily or 50 mg daily resulted in significantly lower percentages of patients with gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily.”²⁶
- “In a predefined, combined analysis of the two [endoscopy studies] at 12 weeks of treatment, the percentages of patients with endoscopically detected gastroduodenal ulcers were similar between VIOXX 25 mg daily, VIOXX 50 mg daily, and placebo.”²⁷
- In a prespecified, combined analysis of eight Phase IIb/III osteoarthritis studies, the risk of developing an upper gastrointestinal PUB was 55% lower in patients treated with Vioxx (12.5 mg, 25 mg, or 50 mg daily) than in patients treated with a traditional non-selective NSAID (ibuprofen 2,400 mg daily, diclofenac 150 mg daily, or nabumetone 1,500 mg daily) (relative risk 0.45; confidence interval, 0.25 to 0.81; p=0.006).²⁸

Based on these results, Merck’s proposed label for Vioxx did not include the NSAID-class gastrointestinal warning.²⁹ Instead, the proposed label stated in the Precautions section:

Although studies of VIOXX 25 mg or 50 mg demonstrated similarity to placebo in the incidence of endoscopically detected ulcers at 12 weeks, and a combined analysis of

²⁶ 11/23/98 NDA (Proposed text of labeling), MRK-OS420000230, at 62.

²⁷ 11/23/98 NDA (Proposed text of labeling), MRK-OS420000230, at 64.

²⁸ 11/23/98 NDA (Proposed text of labeling), MRK-OS420000230, at 70-72.

²⁹ 11/23/98 NDA (Proposed text of labeling), MRK-OS420000230, at 76.

eight trials . . . showed a cumulative incidence of upper gastrointestinal PUBs significantly less than that in patients treated with nonspecific [Cox] inhibitors for up to 12 months of treatment, ulcers and upper gastrointestinal PUBs did occur in osteoarthritis patients treated with VIOXX or placebo. Therefore, physicians should be aware that individual patients may develop PUBs irrespective of treatment, but the risk is lower in patients treated with VIOXX than in patients treated with nonspecific [Cox] inhibitors.³⁰

(Citations omitted.)

In December 1998, one month after the Vioxx New Drug Application was submitted, the FDA determined that the data submitted in Searle/Pfizer's New Drug Application for Celebrex had not demonstrated conclusively that Celebrex was safer than non-selective NSAIDs from a gastrointestinal perspective. Therefore, the FDA required that the Celebrex label include the NSAID-class gastrointestinal warning. MRL scientists believed, however, that MRL's gastrointestinal safety studies of Vioxx had generated more compelling evidence in support of Merck's claim that Vioxx's gastrointestinal safety profile was superior to that of traditional non-selective NSAIDs.³¹ Neither company had conducted a large gastrointestinal outcomes trial in support of its New Drug Application.

³⁰ 11/23/98 NDA (Proposed text of labeling), MRK-OS420000230, at 77.

³¹ See E. Scolnick, "Scientific Review," at 4, http://www.merck.com/newsroom/vioxx_withdrawal/pdf/VIOXX_scientific_review.pdf (stating that Searle/Pfizer's endoscopy data were "far less convincing than" the gastrointestinal safety data MRL had collected on Vioxx).

2. The FDA's Review.

Based on its review of the Vioxx New Drug Application, the FDA was not convinced that MRL's studies had demonstrated that Vioxx's gastrointestinal safety profile was comparable to that of placebo or superior to that of traditional non-selective NSAIDs for several reasons. First, although the FDA agreed that there were large differences in endoscopic gastroduodenal ulcer rates between Vioxx and ibuprofen, suggesting a substantial difference in safety profile,³² the FDA maintained, as it had suggested in the spring of 1998, that "[t]he correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, [had] not been fully established."³³

Second, FDA statisticians took the position that it was inappropriate from a statistical point of view to pool the two endoscopy studies (as was prespecified in MRL's data analysis plan for assessing comparability of Vioxx to placebo) because (i) ulcer rates in placebo arms of the two studies were "distinctly different,"³⁴ and (ii) in one of the studies, ulcer rates on Vioxx were lower than on placebo.³⁵ MRL's prespecified data

³² Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 811 (testimony of L. Goldkind* referring to "obvious robust and large differences between ibuprofen and both dosages of Vioxx" throughout the study).

³³ 5/20/99 approved Vioxx product label, MRK-ACD0078494, at 504.

³⁴ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 813 (testimony of L. Goldkind*: "And really the question is, can a valid, combined, statistical analysis be performed on two studies with such divergent data?").

³⁵ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 819-20 (testimony of Q. Li*: "[F]acing such strong study by treatment interaction it is not appropriate to combine the study results because the two study results do not conform to each other. Therefore, the

analysis plan for comparing Vioxx to placebo had called for a combined analysis of the two studies to increase their power to show comparability between Vioxx and placebo. In the absence of pooling, neither study alone had sufficient power to detect a small difference between Vioxx and placebo (or, by the same token, to establish that Vioxx and placebo were comparable in their gastrointestinal effects).³⁶

Third, the FDA concluded that the pooled analysis of PUBs in the Phase IIb/III osteoarthritis studies was “not demonstrative of clinically significant differences” between Vioxx and comparator non-selective NSAIDs, based on the FDA’s view that: (i) results of this analysis were “less clear [than the results of the endoscopy studies] due to the small number of such events;”³⁷ (ii) the results of comparisons between different doses of Vioxx and individual NSAIDs were too “dissimilar” to pool;³⁸ (iii) the individual studies were too dissimilar (in size, design, and duration) to pool;³⁹ and (iv) it

claim based on the combined analysis that the ulcer rate of [Vioxx] is similar to placebo is not appropriate.”).

³⁶ The concept of power is discussed in Exhibit 3 to the Report, entitled “Statistical Significance”.

³⁷ Summary minutes of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ECNDA0298, at 301.

³⁸ 5/15/99 draft of 5/20/99 approved Vioxx product label, MRK-AAF0002055, at 062 (attached to 5/15/99 facsimile from R. DeLap* to R. Silverman, MRK-AAF0002054) (FDA comment: “069 PUB comparisons are problematic for several reasons, e.g. multiple comparators with dissimilar results shouldn’t be combined to give ‘NSAID’ values . . .; and absence of replication of findings vs. individual comparators”).

³⁹ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 805 (testimony of L. Goldkind*: “Several issues bear further scrutiny. One is potential for bias for merging data from studies of varying designs, dosages, endpoints and duration.”).

was “unclear if [the population enrolled in the Phase IIb/III osteoarthritis studies was] representative of the general population.”⁴⁰

3. FDA Arthritis Advisory Committee Meeting.

At the April 20, 1999 meeting of the FDA’s Arthritis Advisory Committee convened to review the Vioxx New Drug Application, Dr. Qian Li*, a statistician at the FDA, stated that “it [was] not appropriate to combine the . . . results [of the two endoscopy studies for comparison to placebo] because the two study results [did] not conform to each other.”⁴¹ Later during the meeting, Dr. Scott Zeger*, Senior Associate Dean for Academic Affairs and Professor of Biostatistics, School of Hygiene and Public Health, Johns Hopkins University, and an MRL consultant, argued that the two endoscopy studies “can be combined [and] should be combined” because, despite the difference in ulcer rates on placebo, the two necessary conditions for “poolability”⁴² – similarity in trial design and absence of evidence that the effect of Vioxx was qualitatively different in the two studies – were met.⁴³

⁴⁰ 5/20/99 approved Vioxx product label, MRK-ACD0078494, at 505; see also transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 819-820 (testimony of Q. Li*: “[T]he interpretation of the study results cannot be generalized simply because there are differences that exist - - different risks were associated with different doses of rofecoxib and different NSAIDs.”).

⁴¹ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 819.

⁴² Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 875 (testimony of B. Goldmann referring to the issue as one of “poolability”).

⁴³ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 876-79 (testimony of S. Zeger*: “And I think it’s our obligation as public health scientists to do so, because it’s only through combining evidence like this where it’s available, that we can ask the hard questions such as, whether Vioxx™ is comparable to placebo.”).

At the meeting, the FDA also argued that it was not appropriate to combine the Phase IIb/III osteoarthritis studies in a pooled analysis of PUBs, whereas MRL argued that such pooling was appropriate.⁴⁴ The members of the Arthritis Advisory Committee were divided on the pooling issues and suggested that the FDA and MRL continue their discussion on the subject.⁴⁵

With respect to how the label should address the issue of gastrointestinal safety, the FDA stated that its position toward selective Cox-2 inhibitors had been to “find[] some middle ground” – *i.e.*, to include the NSAID-class gastrointestinal label “but qualifying that to say, well we have some evidence that can be presented in the label that this might be different but we’re still working on it.”⁴⁶ The eight-member Arthritis Advisory Committee agreed with the FDA’s proposed approach, voting unanimously in favor of including in the Vioxx label the NSAID-class gastrointestinal warning but also describing in the label at least some results of the gastrointestinal safety studies performed by MRL.⁴⁷

⁴⁴ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 893 (testimony of MRL consultant J. Wittes*).

⁴⁵ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 899 (testimony of S. Abramson* (Chairman of the Arthritis Advisory Committee): “[T]he committee itself appears to be somewhat split with respect to combining the studies, and I think this is an issue that needs to have continued discussion between the sponsor and the agency. I’m not sure that we in this forum now are going to add much more to this discussion.”).

⁴⁶ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 908 (testimony of R. DeLap*: “I think we’re trying to settle a very important issue here and our stance has always been to be careful until you’re sure you know the answer.”).

⁴⁷ Summary minutes of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ECNDA0298, at 301.

D. Cardiovascular Safety.

1. The New Drug Application.

Merck's New Drug Application for Vioxx was submitted to the FDA in November 1998, a little more than a year after MRL first learned of Dr. FitzGerald's* prostacyclin hypothesis. During that year, MRL had completed numerous studies, which had generated a significant amount of cardiovascular adverse experience data for comparison between Vioxx, comparator NSAIDs and placebo. By November 1998, MRL had analyzed the incidence of (i) "serious" cardiovascular adverse events (as defined by the FDA's regulations) in the Phase II/III osteoarthritis studies,⁴⁸ and (ii) all thrombotic events regardless of their "seriousness" in the Phase II/III osteoarthritis studies (summarized in Tables 1 – 3 below).⁴⁹ Based on these analyses, MRL had concluded that the incidence rates of "serious" cardiovascular adverse experiences "were not statistically different" between Vioxx, NSAID comparators and placebo,⁵⁰ and that the incidence rates of thrombotic adverse experiences were "similar" between Vioxx,

⁴⁸ "Serious" adverse events are defined by regulation as "any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect." 21 C.F.R. § 312.32 (West 2006).

⁴⁹ This second analysis assessed the incidence of an "extensive list . . . of adverse experience terms that represented peripheral, myocardial, and central nervous system thromboembolic experiences." 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1254.

Some Merck documents refer to certain cardiovascular events as "thrombotic." 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, and we do not distinguish between them for purposes of these Appendices.

⁵⁰ 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1254.

NSAID comparators, and placebo.⁵¹ MRL reported the results of both of these analyses, as well as the underlying adverse experience data, in the New Drug Application.⁵²

⁵¹ 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1254. According to Dr. Nies, not every New Drug Application has a separate section on thrombotic events. 4/1/05 deposition of A. Nies at 438 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

In addition, in March 1999, in response to a request from the FDA, Merck provided the FDA with “life table analyses” and “complete survival analysis curves” for cardiovascular events at six weeks, 12 weeks, six months, one year and 86 weeks. 3/1/99 email from S. Cook* to MRL Regulatory Liaison – Domestic (R. Silverman), MRK-99420003584, at 84-85 (requesting data); 3/12/99 letter from R. Silverman to R. DeLap*, MRK-ACD0069211-49 (responding to request). In this submission, MRL concluded: “For all the cardiovascular and cerebrovascular events, the incidence rates were generally similar among placebo, rofecoxib, and NSAID comparators.” 3/12/99 letter from R. Silverman to R. DeLap*, MRK-ACD0069211, at 23.

The New Drug Application also reported serious cardiovascular adverse experiences from the analgesia and rheumatoid arthritis studies, noting that the number of events in those studies were too small to yield meaningful comparisons to placebo or active comparators. 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1513 (“Due to the relatively small sample sizes within each category of treatments, statistical analyses were not routinely performed to compare the frequencies of adverse experiences [in the analgesia studies].”), 2605 (“[N]o comparison to either the placebo or ibuprofen groups is made [for the rheumatoid arthritis studies].”).

⁵² As discussed in Appendix A, the osteoarthritis studies excluded patients with a recent history of myocardial infarction or unstable angina and with a transient ischemic attack or cerebrovascular accident within two years prior to entry, although a significant percentage of the patients enrolled in the studies had a preexisting cardiovascular condition, largely hypertension. 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1254 (most patients in the osteoarthritis studies had preexisting cardiovascular conditions, and approximately 40% had a history of hypertension). Only one of the nine Phase II/III osteoarthritis studies allowed the use of low-dose aspirin.

Table 1
Number (%) of Patients with Thrombotic Cardiovascular Adverse Experiences
6-Week Osteoarthritis Studies (Protocols 010, 029, 033, 040, and 058)⁵³

	Placebo (N=412)	Vioxx					Ibuprofen 2,400 mg (N=470)	Nabumetone 1,500 mg (N=115)
		5 mg (N=149)	12.5 mg (N=725)	25 mg (N=735)	50 mg (N=97)	125 mg (N=74)		
		n (%)	n (%)	n (%)	n (%)	n (%)		
Patients with one or more adverse experiences	1 (0.2)	0 (0.0)	5 (0.7)	6 (0.8)	1 (1.0)	1 (1.4)	2 (0.4)	0 (0.0)

Table 2
Number (%) of Patients with Thrombotic Cardiovascular Adverse Experiences
6-Month Osteoarthritis Studies (Protocols 034, 035, 044, 045)⁵⁴

	Placebo [†] (N=371)	Vioxx						Ibuprofen 2,400 mg (N=377)	Diclofenac 150 mg (N=498)
		12.5 mg (N=490)		25 mg (N=879)		50 mg (N=379)			
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Patients with one or more adverse experiences	3 (0.8)	6 (1.2)	9 (1.0)	4 (1.1)	2 (0.5)	9 (1.8)			

[†] Placebo group had one-third less exposure than the Vioxx groups.

Table 3
Number (%) of Patients with Thrombotic Cardiovascular Adverse Experiences
6-Month-to-86-Week Osteoarthritis Studies (Protocols 029-10, 034, 058-10)⁵⁵

	Vioxx						Diclofenac 150 mg (N=439)	Nabumetone 1,500 mg (N=92)
	12.5 mg (N=550)		25 mg (N=547)		50 mg (N=123)			
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Patients with one or more adverse experiences	7 (1.3)	6 (1.1)	3 (2.4)	5 (1.1)	1 (1.1)			

⁵³ 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1255.

⁵⁴ 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1256.

⁵⁵ 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1257.

2. Discussion of the FitzGerald Prostacyclin Hypothesis in the New Drug Application.

By November 1998, MRL scientists including Dr. Scolnick had concluded that there was no evidence that Vioxx suppressed production of prostacyclin in the vasculature (as opposed to other parts of the body), as Dr. FitzGerald* had assumed, and had requested that Merck Frosst conduct experiments to further explore this issue.⁵⁶ In addition, they had determined that there was no evidence in the Phase II/III osteoarthritis studies that patients on Vioxx were at an increased risk of thrombotic events as compared to patients on NSAID comparators or placebo.

The Clinical Study Report for Protocol 023 submitted with the New Drug Application stated that the clinical implications of altering the balance between prostacyclin and thromboxane were unknown:

[T]he results of [Protocol 023] suggest that some of the systemic [prostacyclin] production may derive from COX-2 The clinical implications of partially inhibiting the production of [prostacyclin] without inhibiting thromboxane generation systemically are unknown but any untoward effects should be revealed by the long term safety and efficacy trials with [Vioxx].⁵⁷

⁵⁶ Such studies conducted at Merck Frosst prior to approval of Vioxx are discussed in Appendix A.

⁵⁷ Protocol 023 Clinical Study Report, MRK-AGO0002456, at 562; see also 12/16/98 letter from R. Silverman to R. DeLap*, MRK-AAF0001101, at 01 (attaching a “desk copy” of Protocol 023 Clinical Study Report). Dr. Morrison, who was the primary author of the quoted section of the Clinical Study Report, stated that the document referred to “untoward effects,” instead of concern about increased risk of cardiovascular events, because prostacyclin was suspected to play an important role in several parts of the body (not just the vasculature) and the phrase “untoward effects” was meant to reflect this broader importance of prostacyclin. Dr. Gertz stated that the phrase “untoward effects” was common clinical terminology.

The New Drug Application included a copy of the abstract about Protocol 023 presented at the April 15 – 18, 1998 American Heart Association Vascular Biology Meeting,⁵⁸ which set forth the findings that Vioxx reduced urinary excretion of the prostacyclin metabolite and had no effect on the thromboxane metabolite and concluded that Vioxx affected “prostacyclin biosynthesis or metabolism as evidenced by a reduction in PGI-M excretion.”⁵⁹

The “Benefits Versus Risks Relationship” section of the New Drug Application stated:

Platelets express only COX-1 and are incapable of expressing COX-2 since they lack a nucleus. Inhibition of the synthesis of the platelet COX-1 product, Thromboxane A2[,] by NSAIDs impairs the ability of platelets to aggregate. The inhibition of platelet function by aspirin has beneficial effects on cardiovascular morbidity and mortality. [Vioxx] doses, up to and including 40 times the maximal dose, do not inhibit platelet function or bleeding time and thus may not provide the cardiovascular benefits of aspirin. However, the rates of cardiovascular events, such as stroke and myocardial infarction, were low and were similar among placebo and [Vioxx] patients. Thus, no evidence from the [Vioxx] clinical program suggests that specific COX-2 inhibition predisposes to acute thrombotic events.⁶⁰

(Emphasis added; citations omitted.)

⁵⁸ 11/23/98 NDA Attachment 325, MRK-OS420123664, at 66 (copies of all “published clinical literature as of 1 July 1998,” including the abstract from the April 1998 conference). The abstract is discussed in Appendix A.

⁵⁹ 11/23/93 NDA Attachment 325, MRK-OS420123664, at 66.

⁶⁰ 11/23/98 NDA Clinical Documentation – Benefits Versus Risks Relationship section, MRK-OS420041705, at 718; see also 11/23/98 NDA (Synopsis of Application: Worldwide Clinical Summary), MRK-OS420000310, at 467.

The section of the New Drug Application discussing MRL's analysis of thrombotic events in the Phase II/III osteoarthritis studies (mentioned above in Section D.1 of this Appendix) stated that the analysis of thrombotic events was undertaken to explore a theoretical question:

Specific Cox-2 inhibitors do not interfere with platelet function. Therefore, theoretically there might be a risk for thromboembolic cardiovascular adverse experiences with long-term treatment with a COX-2 specific inhibitor compared to long-term NSAID therapy (where Cox-1 inhibition inhibits platelet aggregation).⁶¹

Dr. Brian Daniels, Associate Director, Immunology/Pulmonary Department, Clinical Sciences, MRL, who prepared the first draft of this section of the New Drug Application,⁶² stated that the paragraph referred to the NSAID cardioprotection hypothesis that was raised in Dr. Musliner's November 21, 1996 memorandum (discussed in Appendix A), not the FitzGerald prostacyclin hypothesis.⁶³

⁶¹ 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1254 (stating that the analysis was undertaken to explore "this question"); see also 3/23/98 Safety Update Report, MRK-ACD0077167, at 334 (including an updated analysis of thrombotic events in osteoarthritis studies and using the same language).

⁶² 10/20/04 deposition of B. Daniels at 524 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.) ("Q: Doctor, did you prepare this document[?]; A: Yes. Like I said, I was responsible for this document.").

⁶³ Dr. Reicin, currently Vice President, Clinical Immunology and Analgesia, Clinical Sciences, MRL, who had no role in preparing this section of the New Drug Application but co-authored later documents with a similar statement (Merck's March 2000 submission to the FDA (discussed in Appendix I), and the article about the VIGOR Trial published in the New England Journal of Medicine (discussed in Appendix F)), reads the statement as an umbrella statement that encompasses both the NSAID cardioprotection hypothesis and the FitzGerald prostacyclin hypothesis.

3. Discussion of the FitzGerald Prostacyclin Hypothesis in Merck's
Background Package for the Arthritis Advisory Committee Meeting.

In April 1999, MRL submitted to the FDA a 204-page Background Package for the Arthritis Advisory Committee meeting summarizing the contents of the New Drug Application.⁶⁴ As discussed in Appendix A, by March 1999 – one month before the FDA Arthritis Advisory Committee meeting regarding the Vioxx New Drug Application – MRL scientists had concluded that Vioxx suppressed synthesis of prostacyclin (as opposed to its metabolism or renal clearance). They believed, however, that it was unclear whether such suppression occurred in the vasculature, and if so, whether it would have any clinical implications. By this time, a Merck Frosst study of rabbit aortas “suggest[ed] that normal vascular [prostacyclin] synthesis [was] dependent on the activity of COX-1 and not COX-2” in both normal rabbits and rabbits with atherosclerosis.⁶⁵

MRL's Background Package submitted for the Arthritis Advisory Committee meeting, in the “Summary of Benefits and Risks” section, 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,

⁶⁴ MRL Background Package for 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ACD0064939-5143; see also Summary minutes of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ECNDA0298, at 299 (“The Advisory Committee members had been provided a background document from both the sponsor and the Agency approximately 20 days before the meeting.”).

⁶⁵ 3/16/99 memorandum from E. Wong to D. Riendeau (cc: B. Gertz, A. Nies et al.), MRK-ABC0006410, at 14.

to suggest that rofecoxib carries any increased risk for cardiovascular events.⁶⁶

The section of the Background Package discussing the incidence of thrombotic events, like the analog section of the New Drug Application, referred to the fact that selective Cox-2 inhibitors “did not interfere with platelet function” and that “[t]herefore, theoretically, there might be a risk for thromboembolic cardiovascular adverse experiences with long-term treatment with a [selective Cox-2 inhibitor] compared with long-term NSAID therapy (where COX-1 inhibition reduces platelet aggregation).”⁶⁷

4. FDA Arthritis Advisory Committee Meeting.

At the April 20, 1999 FDA Arthritis Advisory Committee meeting, Dr. Beth Seidenberg, head of the Pulmonary/Immunology Group, Clinical Sciences, MRL, discussed safety data on Vioxx, including thrombotic event rates observed in the Phase II/III osteoarthritis studies and concluded: “The rates for [Vioxx,] as you can see, are if anything, lower than with the NSAID group.”⁶⁸ The FitzGerald prostacyclin hypothesis was not discussed at the meeting.

⁶⁶ MRL Background Package for 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ACD0064939, at 5109.

⁶⁷ MRL Background Package for 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ACD0064939, at 5056. MRL’s Background Package submitted to the FDA for a subsequent meeting of the Arthritis Advisory Committee stated that “MRL reviewed the incidence of thrombotic cardiovascular serious adverse experiences throughout the rofecoxib [osteoarthritis] development program” “[t]o investigate [the two] possibilities”: (i) “that a highly selective COX-2 inhibitor . . . might be prothrombotic;” and (ii) that “nonselective inhibitors of COX-1 and COX-2 with potent and sustained antiplatelet activity might be cardioprotective.” MRL Background Package for 2/8/01 FDA Arthritis Advisory Committee meeting, MRK-ABK0456845, at 6859.

⁶⁸ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 752.

5. The FDA's Review.

In May 1999, Dr. Maria Lourdes Villalba*, the FDA's primary medical officer assigned to the Vioxx New Drug Application, prepared a document summarizing her review of the New Drug Application. Dr. Villalba* noted that "[t]here [was] a theoretical concern that patients chronically treated with a Cox-2 selective inhibitor [might] be at higher risk for thromboembolic cardiovascular adverse experiences than patients treated with Cox-1/Cox-2 inhibitors (conventional NSAIDs), due to the lack of effect of Cox-1 inhibition on platelet function."⁶⁹

Based on her review, Dr. Villalba* noted that, in the Phase II/III osteoarthritis studies, the "incidence of thromboembolic events with [Vioxx] appear[ed] to be similar to comparator NSAIDs" but that "[t]he data seem[ed] to suggest that in 6-week studies, thromboembolic events [were] more frequent in patients receiving [Vioxx] than placebo."⁷⁰ Dr. Villalba* stated, however, that "[i]t [was] difficult to reach meaningful conclusions [because] the number of events [was] relatively small and the length of the exposure and doses of rofecoxib used were different among studies."⁷¹ Dr. Villalba* also

⁶⁹ 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 478. In discussing the original New Drug Application for Vioxx at the February 16, 2005 meeting of the FDA Arthritis Advisory Committee, Dr. Villalba* stated: "[T]his was 1998. There were theoretical concerns regarding that inhibition of prostacyclin could induce pro-thrombotic events. But based on these [New Drug Application] data, there was not much to say about it. Also, Celebrex had recently been approved, in December '98, and Celebrex had not shown anything either." Transcript of 2/16/05 FDA Arthritis Advisory Committee meeting at 237, <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4090T1.pdf>.

⁷⁰ 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 479.

⁷¹ 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 479.

stated that “it [was] impossible to answer with complete certainty whether the risk of . . . thromboembolic events [was] increased in patients on rofecoxib.”⁷² She concluded that “[a] larger database [would] be needed to answer [the cardiovascular] and other safety comparison questions”⁷³ and that “only post-marketing surveillance [could] allow appreciating the complete safety profile” of Vioxx.⁷⁴ Dr. Villalba* also noted that “[t]he data [did] not seem to indicate a dose response relationship” for cardiovascular thrombotic events with Vioxx.⁷⁵

E. Renal Safety.

1. The New Drug Application.

The New Drug Application included a section discussing “Renal/Vascular” effects of Vioxx, which stated that the incidence of clinical renal events, such as edema and hypertension, was low and that “the magnitude of this effect was generally minor and similar to NSAIDs.”⁷⁶ The New Drug Application also noted that, “although [Vioxx was] associated with clinical effects on blood pressure, weight, and edema-type adverse experiences, the observed effects [were] generally mild and without consequences such as discontinuation of study therapy or alteration of concomitant medications.”⁷⁷

⁷² 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 479.

⁷³ 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 479.

⁷⁴ 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 448.

⁷⁵ 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 478.

⁷⁶ 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1425-26.

⁷⁷ 11/23/98 NDA Clinical Documentation - Clinical Safety section, MRK-OS420040927, at 1426.

2. The FDA's Review.

In her review of the Vioxx New Drug Application, Dr. Villalba* noted that, “[a]lthough no patient developed hypertension at the dose of rofecoxib 50 mg [daily] in the [osteoarthritis] 6-week study, in 6-month [osteoarthritis] trials, [the 50 mg] dose was associated with higher incidence of hypertension and edema compared to rofecoxib 25 mg [daily] and ibuprofen 800 mg [three times a day].”⁷⁸

Dr. Villalba* also noted:

The data reviewed . . . confirms that rofecoxib doses of 12.5 and 25 mg [daily] give the optimal risk/benefit ratio. It also indicates a clear dose-response relationship in terms of efficacy and adverse events. In the six-week dose ranging study . . . the [50 mg dose] was more efficacious than the [25 mg dose] with minimal increases in toxicity (mostly fluid retention and edema). However, in six-month studies, the 50 mg dose was associated with a numerically higher incidence of hypertension, fluid retention, edema, renal-related laboratory abnormalities and GI adverse events compared to the 12.5 and 25 mg . . . doses.⁷⁹

In the section of the Medical Officer Review entitled “Overall Conclusions of the Rofecoxib Program,” Dr. Villalba* concluded that Vioxx was “generally safe and effective for the short term management of acute pain and dysmenorrhea (50 mg [daily]

⁷⁸ 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 486.

⁷⁹ 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 390; see also Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 825-26 (testimony of J.C. Pelayo*: “The incidence of vascular renal adverse events [such as hypertension and edema] associated with Vioxx™ is dose-dependent. The vascular renal profile of Vioxx™ is clearly distinguishable from placebo and is qualitatively similar to all the NSAIDs. . . . However, vascular renal adverse events occurred at a higher rate with Vioxx™ primarily at 50 mg than with other NSAIDs at their recommended dosage. Whether that would translate into clinically significant difference in vascular renal morbidity cannot be determined from the available osteoarthritis clinical database.”).

for up to 5 days) and for the treatment of the signs and symptoms of osteoarthritis (12.5 or 25 mg [daily]).”⁸⁰

3. FDA Arthritis Advisory Committee Meeting.

At the April 20, 1999 meeting of the FDA Arthritis Advisory Committee, the Committee appeared to agree with the FDA’s conclusion that: (i) “[t]he overall renal effects of [Vioxx] at the proposed dose for [osteoarthritis] (12.5 to 25 mg) . . . appear[ed] to be similar to those of currently used approved NSAIDs”; and (ii) “chronic doses of 50 mg [daily] or higher might be associated with increased renal adverse effects.”⁸¹

At the Arthritis Advisory Committee meeting, Dr. Villalba* noted that the higher doses of Vioxx appeared to be more effective in treating pain and expressed concern about the so-called “dose creep” “phenomenon . . . common with other [NSAIDs]” with “patients . . . tempted to increase the dose from 12.5 to 25, from 25 to 50.”⁸²

Dr. Bonnie Goldmann, Vice President, Domestic Regulatory Affairs, MRL, stated that it was not clear from the completed studies that the 50 mg dose was more effective than the 25 mg dose in the treatment of osteoarthritis pain but noted that MRL was cognizant of the “dosage creep” phenomenon and recommended 12.5 mg as the primary dose for

⁸⁰ 5/19/99 Medical Officer Review by M.L. Villalba*, MRK-ADI0005375, at 5487.

⁸¹ Summary minutes of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ECNDA0298, 301-02 (stating that seven members agreed with the FDA’s position, including 4 “with reservations,” and one member disagreed with the FDA’s position).

⁸² Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 765 (testimony of M. L. Villalba*).

osteoarthritis “exactly for that reason.”⁸³ MRL’s proposed label for Vioxx stated that the recommended starting dose for the treatment of osteoarthritis was 12.5 mg once daily and that “[s]ome patients may receive additional benefit by increasing the dose to 25 mg once daily” and that “[t]he maximum recommended daily dose is 25 mg.”⁸⁴ Under the proposed label, the 50 mg dose was recommended only for short-term treatment of acute pain.⁸⁵

At the meeting, the Chairman of the FDA’s Arthritis Advisory Committee, Dr. Steven Abramson* (Hospital for Joint Diseases, New York University Medical Center), asked the Committee members whether “because the 50 mg [dose] appear[ed] to have greater [renal] toxicity . . . a statement should be made more explicitly in the label that doses in the 50 mg range chronically may be associated with a higher incidence of fluid retention or edema, compared to other [NSAIDs].”⁸⁶ While some committee members thought that the data suggested that the 50 mg dose might have greater renal side effects than traditional non-selective NSAIDs, the consensus appeared to be that the data did not warrant such a statement in the label.

⁸³ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 834-35 (testimony of B. Goldmann).

⁸⁴ MRL Background Package for 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ACD0064939, at 65142 (proposed label).

⁸⁵ MRL Background Package for 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-ACD0064939, at 65142 (proposed label).

⁸⁶ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 837-38.

For instance, Dr. Kevin McConnell* from the University of Virginia, a member of the Committee, stated that the data did not establish that the 50 mg dose of Vioxx was “worse [in terms of its renal side effects] than the other 19 or 20 [NSAIDs] that are out there [on] the market” and that to “hamstring [Vioxx] for adverse renal effects . . . would be quite improper.”⁸⁷ Dr. Daniel Lovell* from the University of Cincinnati, another member of the Committee, stated that the labeling should (i) reflect the data that were available; and (ii) state that the 50 mg dose had not been studied for the acute pain indication for more than five days.⁸⁸

F. May 1999 Label Negotiations.

As discussed in Appendices A and I, as part of the drug approval process, the FDA and sponsor company must agree upon a label for a new drug before the drug may be marketed in the United States. Between the April 20, 1999 FDA Arthritis Advisory Committee meeting and the May 20, 1999 approval of Vioxx, representatives of Merck and the FDA negotiated over which data from the New Drug Application should be reflected in the label and what assertions could be made in the label based on those data. These negotiations focused principally on the gastrointestinal aspects of the label.

As stated above, Merck’s original proposed label, submitted in November 1998 as part of the New Drug Application, omitted the NSAID-class gastrointestinal warning and included descriptions of (i) results from the two endoscopy studies; (ii) a pooled analysis

⁸⁷ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 934-35, 937.

⁸⁸ Transcript of 4/20/99 FDA Arthritis Advisory Committee meeting, MRK-AAF0001646, at 1872.

of the two endoscopy studies comparing Vioxx to placebo; and (iii) a combined analysis of PUBs in the Phase IIb/III osteoarthritis studies. For reasons discussed above, the FDA, however, wanted to include the NSAID-class gastrointestinal warning and omit much of the gastrointestinal safety information presented by Merck.

Merck agreed early in the label negotiations to include the NSAID-class gastrointestinal warning, but pressed hard to include results of the gastrointestinal safety studies (particularly the combined analysis of the two endoscopy studies comparing the rate of gastroduodenal ulcers between Vioxx 25 mg and 50 mg and placebo) that would enable Merck to make better gastrointestinal safety claims than Searle/Pfizer. Although the FDA agreed to include data from the individual endoscopy studies, it continued to refuse to include the results of the pooled analysis of the two studies comparing Vioxx to placebo or the pooled analysis of PUBs in the Phase IIb/III osteoarthritis studies.

Dr. Scolnick, among others at MRL, thought that all data on the gastrointestinal safety of Vioxx should be reflected in the label. After receiving the FDA's May 13, 1999 counterproposal label, which omitted most of the proposed gastrointestinal safety data, Dr. Scolnick emailed Dr. David Blois, Senior Vice President, Global Regulatory Affairs, and Dr. Bonnie Goldmann, Vice President, Domestic Regulatory Affairs:

[T]he ONLY way to handle is to GO THERE AND INVOLVE LUMPKIN [Deputy Director of the FDA's Center for Drug Evaluation] and word by word agree to final circular [i.e., label] next mon/tue. . . . THIS GROUP IS DYSFUNCTIONAL AND WILL NOT RESPOND TO

YOU NOT IN PERSON TELECONS.⁸⁹

G. The Approved Label.

On May 20, 1999, the FDA approved Vioxx for marketing in the United States.⁹⁰

The final approved label included the indications for use that Merck had sought but did not go as far as Dr. Scolnick and others at MRL had hoped in describing the gastrointestinal safety data.

1. Indication.

The approved label stated that Vioxx was indicated for relief of the signs and symptoms of osteoarthritis, management of acute pain in adults, and treatment of primary dysmenorrhea.⁹¹

2. Dosage.

The approved label stated that, for the treatment of osteoarthritis:

- The recommended starting dose was 12.5 mg once daily;
- “Some [osteoarthritis] patients may receive additional benefit by increasing the dose to 25 mg once daily”;
- The maximum recommended daily dose for the treatment of osteoarthritis was 25 mg.⁹²

⁸⁹ 5/14/99 email from E. Scolnick to D. Blois and B. Goldmann, MRK-ABH0015578, at 78. There is no evidence that anyone from MRL attempted to involve Dr. Lumpkin* in the label negotiations.

⁹⁰ Undated letter from R. DeLap* to R. Silverman, MRK-ACD0078494-517 (enclosing “final printed labeling” and received May 20, 1999).

⁹¹ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 504.

⁹² 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 516.

The label also stated that, for management of acute pain and treatment of primary dysmenorrhea:

- The recommended initial dose was 50 mg once daily;
- Subsequent doses should be 50 mg once daily as needed;
- “Use of Vioxx for more than 5 days in management of pain has not been studied.”⁹³

3. Gastrointestinal Safety Information.

With respect to gastrointestinal safety, the label included the standard NSAID-class gastrointestinal warning, together with language suggesting that the gastrointestinal effects of Vioxx might be different. Thus, the Warning section of the label stated that NSAIDs cause “[PUBs] in approximately 1% of patients treated for 3 – 6 months, and in about 2 – 4% of patients treated for one year,” but noted that it was “unclear” at the time “how [those] rates apply to VIOXX.”⁹⁴ The Warning section also stated that “[a]mong 3,357 patients who received VIOXX in controlled clinical trials of 6 weeks to one year duration . . . at a daily dose of 12.5 mg to 50 mg” – the Phase IIb/III osteoarthritis studies – “a total of 4 patients experienced a serious upper GI event,” but added that it was “unclear if [the population enrolled in these Phase IIb/III osteoarthritis studies] was representative of the general population.”⁹⁵ The label did not include the

⁹³ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 516.

⁹⁴ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 505.

⁹⁵ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 505.

statement originally requested by MRL that Vioxx patients in the Phase IIb/III osteoarthritis studies had significantly lower rates of PUBs than patients on comparator non-selective NSAIDs.⁹⁶

The Clinical Studies section of the label included data from the individual endoscopy studies but did not include certain other data (such as the comparison of gastroduodenal ulcers between Vioxx and placebo) that Dr. Scolnick and others at MRL had sought to include during the labeling negotiations. This section stated that treatment with Vioxx 25 mg daily or 50 mg daily was associated with a significantly lower rate of endoscopic gastroduodenal ulcers than treatment with ibuprofen 2,400 mg daily,⁹⁷ but did not include the results of the pooled analysis of the two endoscopy studies comparing Vioxx to placebo. Instead, the label stated that “the [endoscopy] studies cannot rule out at least some increase in the rate of endoscopic gastroduodenal ulcers when comparing VIOXX to placebo” and that “[t]he correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established.”⁹⁸

⁹⁶ See generally 5/20/99 approved Vioxx product label, MRK-ACD0078497-517.

⁹⁷ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 501.

⁹⁸ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 504.

4. Cardiovascular Safety Information.

With regard to cardiovascular issues, the approved label stated:

- Vioxx at 12.5, 25, and 50 mg had no effect on platelet aggregation;⁹⁹
- Vioxx 50 mg once daily had no effect on the antiplatelet activity of low-dose aspirin; and
- “VIOXX [was] not a substitute for aspirin for cardiovascular prophylaxis.”¹⁰⁰

The Adverse Reactions section of the label discussed adverse experiences “regardless of causality” in Phase II/III osteoarthritis studies.¹⁰¹ This section stated that there were no cardiovascular adverse experiences, other than hypertension, that were reported in more than 2% of the patients receiving Vioxx 12.5 mg and 25 mg.¹⁰² It also listed specific adverse experiences (including cardiovascular adverse experiences) that had occurred in the osteoarthritis studies in more than 0.1% but less than 1.9% of patients treated with Vioxx regardless of causality.¹⁰³

⁹⁹ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 501, 504 (“There was no inhibition of ex vivo arachidonic acid- or collagen-induced platelet aggregation . . .”).

¹⁰⁰ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 509. The label also noted that “[c]oncomitant administration of low-dose aspirin with VIOXX may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX alone.” Id.

¹⁰¹ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 512.

¹⁰² 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 513 (untitled table).

¹⁰³ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 514-15.

5. Renal Safety Information.

The Warnings section of the label also stated that the drug was not recommended for patients with advanced renal disease because there was no safety information regarding the use of Vioxx in such patients.¹⁰⁴ The Precautions section included the NSAID-class renal precaution that “[l]ong-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.”¹⁰⁵ The label went on to say that “[r]enal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion.”¹⁰⁶ With regard to Vioxx, the label stated that “[c]linical trials with VIOXX at daily doses of 12.5 and 25 mg have shown renal effects (e.g., hypertension, edema) similar to those observed with comparator NSAIDs,” and that “[they] occur with an increased frequency with chronic use of VIOXX at doses above the 12.5 to 25 mg range.”¹⁰⁷

The label also included a precaution on “Fluid Retention and Edema”: “Fluid retention and edema have been observed in some patients taking VIOXX. . . . VIOXX should be used with caution, and should be introduced at the lowest recommended dose,

¹⁰⁴ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 506.

¹⁰⁵ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 507.

¹⁰⁶ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 507.

¹⁰⁷ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 507. The FDA-approved label for Celebrex stated that “[c]linical trials with Celebrex have shown renal effects similar to those observed with comparator NSAIDs” and did not say anything about the incidence rates at higher doses. 12/31/98 Celebrex approved product label, MRK-ADN0010624, at 34.

in patients with fluid retention, hypertension, or heart failure.”¹⁰⁸ Finally, the Adverse Reactions section included a table showing the relative rates of edema and hypertension from the osteoarthritis studies. The table stated that 3.5% of patients treated with Vioxx 12.5 or 25 mg experienced hypertension, compared to 3.0% with ibuprofen, 1.6% with diclofenac, and 1.3% with placebo. The table also stated that 3.7% of patients treated with Vioxx 12.5 or 25 mg had lower extremity edema, compared to 3.8% on ibuprofen, 3.4% on diclofenac, and 1.1% on placebo.¹⁰⁹ The label also stated that the incidence of hypertension and lower extremity edema among osteoarthritis patients taking Vioxx 50 mg daily was 8.2% and 6.3%, respectively.¹¹⁰

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¹⁰⁸ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 507-08.

¹⁰⁹ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 513 (untitled table).

¹¹⁰ 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 514.