

APPENDIX N

FDA ANALYSIS OF VIOXX CARDIOVASCULAR  
DATA AND LABEL ISSUES.

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## APPENDIX N

### FDA ANALYSIS OF VIOXX CARDIOVASCULAR DATA AND LABEL ISSUES.

#### A. Overview.

As described in Appendix I, Merck submitted to the FDA on June 29, 2000 a supplemental New Drug Application proposing revisions to the Vioxx label reflecting data from the VIGOR Trial. By letter dated October 15, 2001, the FDA provided its first counterproposal label to Merck, and negotiations over the wording of the label began in earnest. Before the parties agreed on a revised label, Merck submitted a total of 12 label proposals, and the FDA submitted four counterproposals.<sup>1</sup> The presentation of cardiovascular safety data from the VIGOR Trial was a key element of the parties' label negotiations, but by no means its sole component. This Appendix discusses the parties' proposed labels and negotiations over the label language from Merck's initial submission in June 2000 through the FDA's approval of the revised label in April 2002.

#### B. Background of Label Negotiations.

##### 1. Negotiation Procedures.

The revisions to the Vioxx label describing the VIGOR Trial that Merck proposed in June 2000 required advance FDA approval because they involved substantive changes to several sections of the label. The FDA's Center for Drug Evaluation and Research is responsible for approving new drugs and monitoring the safety of drugs already on the

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<sup>1</sup> 4/10/02 letter from N. Braunstein to L. Simon\*, MRK-AFV0041337, at 337; MRL 3/2/01 draft label, MRK-ACD0003164.

market.<sup>2</sup> Within the Center for Drug Evaluation and Research, the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products was charged with reviewing the proposed changes to the Vioxx label. Proposed labeling changes submitted through a supplemental New Drug Application are subject to the same general procedures as the initial application for approval to market a drug, except that the applicant's submission to the Agency is limited to the information "needed to support the change" to the label.<sup>3</sup>

The regulations require the Agency to reach a decision on a supplemental New Drug Application within 180 days, unless (i) the FDA and the applicant mutually agree to extend the deadline, or (ii) the applicant submits a "major amendment" to the application.<sup>4</sup> The filing of a "major amendment," such as "significant new data from a previously unreported study or detailed new analyses of previously submitted data,"<sup>5</sup> automatically extends the regulatory timeline for a period up to 180 days to allow the FDA to review the new information.<sup>6</sup>

At the conclusion of the review period, the Agency may approve an application, deny it or issue an "approvable" letter.<sup>7</sup> An "approvable" letter indicates that the Agency plans to approve the application, subject to the applicant's submission of additional

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<sup>2</sup> See "The CDER Handbook," <http://www.fda.gov/cder/handbook.index.htm>.

<sup>3</sup> 21 C.F.R. §§ 314.70, 314.71(b).

<sup>4</sup> 21 C.F.R. § 314.100 (a), (c); 21 C.F.R. § 314.71(c).

<sup>5</sup> 21 C.F.R. § 314.60(a).

<sup>6</sup> 21 C.F.R. § 314.60(a).

<sup>7</sup> 21 C.F.R. § 314.100(a).

information or completion of other conditions set forth in the letter.<sup>8</sup> The timeline for final action on the application is extended for at least 45 days after the submission of the requested information.<sup>9</sup>

As a practical matter, the FDA's review frequently extends well beyond the initial 180-day period foreseen in the regulations. To expedite the process, Congress enacted the Prescription Drug User Fee Act, which requires companies seeking FDA approval of new drugs or biological products to pay a user fee along with their application.<sup>10</sup> In exchange for the fee, the FDA agrees to meet certain expedited performance goals designed to ensure a timely review.<sup>11</sup> The Prescription Drug User Fee Act performance goal to review and act on Merck's June 2000 supplemental New Drug Application was 10 to 12 months.<sup>12</sup>

The FDA retains ultimate authority over drug labeling through its power to deny approval of a label change and to take enforcement action against misbranded drugs (including withdrawal of approval). Within this framework, the regulations provide for a cooperative process in which the FDA and the company seek to achieve a consensus through discussion and negotiation. At a minimum, the FDA must provide opportunities

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<sup>8</sup> 21 C.F.R. § 314.110(a).

<sup>9</sup> 21 C.F.R. § 314.110(a)(1); 21 C.F.R. § 314.60(a).

<sup>10</sup> Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571 (codified at Food, Drug, and Cosmetic Act §§ 735-736, 21 U.S.C. §§ 379g-379h (amended 2002)); U.S. FDA – Prescription Drug User Fees – Overview, <http://www.fda.gov/oc/pdufa/overview.html>.

<sup>11</sup> U.S. FDA – Prescription Drug User Fees – Overview, <http://www.fda.gov/oc/pdufa/overview.html>.

<sup>12</sup> 8/3/00 letter from L. Vaccari\* to D. Erb, MRK-00420021830; see also FDA - CDER - News - PDUFA Reauthorization Performance Goals and Procedures, <http://www.fda.gov/cder/news/pdufagoals.htm>.

for the company seeking a label change to meet with Agency officials 90 days after submission of the application and again at the conclusion of review.<sup>13</sup> At other times, the applicant may request meetings with the director of the division responsible for reviewing the application “to discuss scientific, medical, and other issues that arise during the review process.”<sup>14</sup> Disputes not resolved at the division level may be elevated to higher levels within the Agency.<sup>15</sup> If the parties are unable to resolve the dispute, the applicant must accept the FDA’s proposal or face a denial of the application.

In some instances, a pharmaceutical company may make changes to the label of a given drug prior to FDA approval—namely, when the changes (i) add or strengthen patient risk information in the Contraindications, Warnings, Precautions, or Adverse Reactions section of the label; (ii) add or strengthen a statement about drug abuse, dependence, or over-dosage; or (iii) add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product.<sup>16</sup> Minor changes concerning the description of the drug or information about how the drug is supplied may be made without advance FDA approval as long as the company notifies the FDA of the change in its next annual report to the FDA.<sup>17</sup> All other changes must be submitted to the FDA for advance approval through a supplemental New Drug Application.<sup>18</sup>

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<sup>13</sup> 21 C.F.R. § 314.102(c), (d).

<sup>14</sup> 21 C.F.R. § 314.102(e).

<sup>15</sup> 21 C.F.R. § 314.103(c)(2); 21 C.F.R. § 10.75..

<sup>16</sup> 21 C.F.R § 314.70(c)(6)(iii)(a)-(c).

<sup>17</sup> 21 C.F.R § 314.70(d)(2).

<sup>18</sup> 21 C.F.R § 314.70(b)(2)(v)(A), (b)(3).

2. Responsibility for Label Negotiations and Drafting.

Various departments and interdisciplinary committees within Merck played roles in the process of negotiating and drafting the Vioxx post-VIGOR label. First, Merck's Regulatory Affairs Department coordinated the submission of the initial supplemental New Drug Application and subsequent communications with the FDA regarding proposed revisions to the Vioxx label. As Vice President of Domestic Regulatory Affairs, Dr. Bonnie Goldmann supervised both written and oral communications with the Agency. Drs. Robert Silverman and Ned Braunstein of the Regulatory Affairs Department also played prominent roles in communicating with the FDA during the VIGOR label negotiations.<sup>19</sup>

Second, the Worldwide Product Circular Review Committee had primary responsibility for revising the text of the proposed label. Throughout the VIGOR label negotiations, the Committee was chaired by Dr. Diane Benezra-Kurshan and had seven voting members.<sup>20</sup>

A subcommittee of the Worldwide Product Circular Review Committee prepared the draft label language, which was then approved by the full Committee.<sup>21</sup> Among other things, members of the Worldwide Product Circular Review Committee reviewed the

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<sup>19</sup> 11/19/04 deposition of R. Silverman at 106 (In re Vioxx Litig., No. 619, N.J. Super Ct.).

<sup>20</sup> Ms. Joanne Lahner of Merck's Legal Department, Dr. Alise Reicin of Clinical Sciences, Dr. Silverman and later Dr. Braunstein of Regulatory Affairs, Dr. Thomas Simon of the Clinical Gastroenterology group, Dr. Thomas Bold of the Worldwide Product Safety and Epidemiology Department, Dr. Judith Cohn of the Editing and Labeling group and Mr. Riad El-Dada of United States Human Health were Committee members. See, e.g., 10/23/01 WPCRC approval form, MRK-ABY0030526; 12/5/01 WPCRC approval form, MRK-ABS0342589.

<sup>21</sup> 7/29/05 deposition of T. Bold at 309-310 (In re: Vioxx Litig., No. 619, N.J. Super. Ct.).

labels of other selective Cox-2 inhibitors, such as Celebrex and Bextra, to ensure parity or to identify potential distinctions.<sup>22</sup> Dr. Benezra-Kurshan coordinated the drafting process and scheduled meetings of the Worldwide Product Circular Review Committee to discuss the label and prepare counterproposal drafts. She also recorded and kept track of proposed edits to the label.

Third, the draft language proposed by the Worldwide Product Circular Review Committee was approved by vice presidents from MRL and Marketing,<sup>23</sup> by the Clinical Development Oversight Committee,<sup>24</sup> and ultimately by the Human Health Product Approval Committee, before it was submitted to the FDA.<sup>25</sup>

### 3. Regulations Governing Labeling.

Like all label language for pharmaceutical products, Merck's proposed amendments to the Vioxx label were subject to FDA standards for prescription drug

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<sup>22</sup> See, e.g., undated email from D. Chitty to D. Anstice et al., MRK-AFZ0002669.

<sup>23</sup> 5/17/00 email from G. Margiatto to MRL (D. Blois, B. Goldmann, A. Nies, R. Perlmutter, S. Reines, E. Slater, and U. Taglieber) and Marketing (W. Dixon, E. McKinney) vice presidents requesting approval of Vioxx USPC and USPPi, MRK-AAX0002194; see also 10/29/01 memorandum and approval form from D. Chitty to MRL (D. Blois, B. Goldmann, A. Nies, S. Reines, U. Taglieber) and Marketing (W. Dixon, S. Kornowski) vice presidents requesting approval of WPCRC changes to FDA 10/15/01 draft counterproposal, MRK-ADI0007542.

<sup>24</sup> Minutes of 5/23/00 CDOC meeting, MRK-ABD0001061, at 65-66.

<sup>25</sup> 6/1/00 HHPAC Meeting Background Package, MRK-ABL0000985, at 986 (attached to 5/30/00 memorandum from R. Bissett to "HHPAC Members," MRK-ABL0000983). The Human Health Product Approval Committee was a high-level cross-disciplinary committee chaired by the President of MRL, Dr. Edward Scolnick. Although it was generally responsible for approving drug development plans and clinical studies and endorsing high-level scientific decisions impacting products and resource allocations, the Committee was also involved in high-level review and approval of the VIGOR label. See, e.g., 4/20/00 HHPAC materials, MRK-ABI0002307; 6/1/00 HHPAC materials, MRK-ABL0000983.

labeling.<sup>26</sup> While a complete explanation of FDA regulations is beyond the scope of this Appendix, generally, these regulations provide that labeling must include “[a]dequate information” for prescription, including “the essential scientific information needed for the safe and effective use of the drug.”<sup>27</sup> The labeling must be “informative and accurate and neither promotional in tone nor false or misleading in any particular.”<sup>28</sup>

More specifically, the FDA’s regulations list both required and permissible subheadings for the labeling.<sup>29</sup> For example, each label must include sections describing the chemical properties of the drug (“Description”), its mechanism of action in the body (“Clinical Pharmacology”), recommended dosage (“Dosage and Administration”), and the diseases or conditions for which it may be prescribed (“Indications and Usage”).<sup>30</sup> Data from a clinical trial such as the VIGOR Trial may be included in an optional “Clinical Studies” section under the following two conditions.<sup>31</sup> First, if the study relates to an approved use of the drug, the study itself must be “an adequate and well-controlled clinical investigation” as defined by the Agency’s regulations.<sup>32</sup> Second, if the study

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<sup>26</sup> The Food, Drug, and Cosmetic Act defines labeling as any written, printed or graphic matter on or accompanying the container of an article. Food, Drug, and Cosmetic Act § 201(m), 21 U.S.C. § 321(m).

<sup>27</sup> 21 C.F.R. § 201.100(d)(1); 21 C.F.R. § 201.56(a).

<sup>28</sup> 21 C.F.R. § 201.56(b).

<sup>29</sup> 21 C.F.R. § 201.57.

<sup>30</sup> 21 C.F.R. § 201.57(a), (b), (c), (j).

<sup>31</sup> 21 C.F.R. § 201.57(m).

<sup>32</sup> 21 C.F.R. § 201.57(m)(1) (citing 21 C.F.R. § 314.126(b)).

implicates a risk of the drug, discussion of the risk must also be included in the appropriate section of the labeling.<sup>33</sup>

The regulations provide for discussion of risk in four different sections of the label (in descending order of severity): (i) Contraindications, (ii) Warnings, (iii) Precautions, and (iv) Adverse Reactions.<sup>34</sup>

- The “Contraindications” section lists “situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit.”<sup>35</sup> This section relates to “[k]nown hazards and not theoretical possibilities” of a hazard.<sup>36</sup>
- The “Warnings” section must indicate “serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur.”<sup>37</sup> The labeling must be revised to include a warning “as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.”<sup>38</sup> Potentially fatal adverse reactions must be included in the Warnings or Contraindications section.<sup>39</sup>
- The “Precautions” section contains “information regarding any special care to be exercised by the practitioner for safe and effective use of the drug” and includes a number of subsections, such as information to be given to patients and

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<sup>33</sup> 21 C.F.R. § 201.57(m)(2).

<sup>34</sup> 21 C.F.R. § 201.57(d)-(g).

<sup>35</sup> 21 C.F.R. § 201.57(d).

<sup>36</sup> 21 C.F.R. § 201.57(d).

<sup>37</sup> 21 C.F.R. § 201.57(e).

<sup>38</sup> 21 C.F.R. § 201.57(e).

<sup>39</sup> 21 C.F.R. § 201.57(g)(3).

the effects of the drug on children, pregnant women and the elderly.<sup>40</sup>

- Finally, the “Adverse Reactions” section of the label describes nonfatal “undesirable effect[s]” that may occur with use of the drug.<sup>41</sup>

C. Merck’s June 2000 Initial Proposed Label.

After the VIGOR Trial results were unblinded, the Worldwide Product Circular Review Committee convened several times to review and draft changes to the existing label based on data from the VIGOR Trial, with strategic input from the Arthritis and Analgesic Worldwide Business Strategy Team and the Human Health Management Committee.<sup>42</sup> As explained above, the proposed label was then reviewed and approved by the Clinical Development Oversight Committee and the Human Health Product Approval Committee.<sup>43</sup> The proposed label was submitted to the FDA along with the supplemental New Drug Application on June 29, 2000.<sup>44</sup>

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<sup>40</sup> 21 C.F.R. § 201.57(f).

<sup>41</sup> 21 C.F.R. § 201.57(g).

<sup>42</sup> 5/17/00 email from G. Margiatto to D. Blois *et al.*, MRK-AAX0002194, at 95 (requesting approval of label draft and noting that “[b]ased on guidance from the WBST, draft VIGOR text (GI and CV) was written as ‘mechanism-based,’ yet specific to Vioxx”); *see also* 5/19/00 email from B. Daniels to W. Dixon *et al.*, MRK-AAX0001431 (requesting WBST follow-up to ensure the materials for 6/1/00 HHPAC materials accurately reflect WBST recommendation regarding VIGOR label); 6/1/00 HHPAC Meeting Background Package, MRK-ABL0000985, at 986.

<sup>43</sup> Minutes of 5/23/00 CDOC meeting, MRK-ABD0001061, 65-66; *see also* 6/1/00 HHPAC Meeting Background Package, MRK-ABL0000985, at 986 (indicating that CDOC reviewed label on 5/23/00 and that MRL and Marketing Vice Presidents approved the label); 5/17/00 email from G. Margiatto to D. Blois *et al.*, MRK-AAX0002194-95 (requesting approval of Vioxx USPC and USPPi; attaching an approval form indicating deadline of 5/22/00 for approvals).

<sup>44</sup> 6/29/00 letter from D. Erb to FDA (CDER), MRK-00420008018, at 18 (attaching 6/29/00 supplemental New Drug Application).

Background materials provided for the Human Health Product Approval Committee's June 1, 2000 meeting identified several key features of the proposed post-VIGOR label.<sup>45</sup> First, the proposed label was written with a "mechanism-based" approach, presenting data in the context of Cox-1/Cox-2 biology.<sup>46</sup> Second, the proposed label replaced the NSAID-class gastrointestinal Warning with a statement in the Precautions section regarding the gastrointestinal safety profile of Vioxx.<sup>47</sup> Third, the proposed label made a number of other changes, including the statement that "VIOXX can be used with low-dose aspirin and . . . is not a substitute for aspirin in cardiovascular prophylaxis."<sup>48</sup>

According to the HHPAC background materials, the "mechanism-based" approach to describing Vioxx in the post-VIGOR label was intended to further several objectives:

- facilitate the explanation of both the gastrointestinal safety profile of Vioxx and the cardiovascular findings of the VIGOR Trial to prescribing physicians;
- allow the Sales and Marketing Departments to develop more effective promotional messages (by closely linking the science with the results);
- facilitate the drafting of the future label for Arcoxia, a more selective Cox-2 inhibitor; and

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<sup>45</sup> 6/1/00 HHPAC Meeting Background Package, MRK-ABL0000985, at 89-90.

<sup>46</sup> 6/1/00 HHPAC Meeting Background Package, MRK-ABL0000985, at 89.

<sup>47</sup> 6/1/00 HHPAC Meeting Background Package, MRK-ABL0000985, at 89.

<sup>48</sup> 6/1/00 HHPAC Meeting Background Package, MRK-ABL0000985, at 90-95.

- minimize the potential of Celebrex to benefit from the VIGOR Trial gastrointestinal safety data by avoiding Cox-2 selective inhibitor class labeling.<sup>49</sup>

The pre-VIGOR label had contained a short and indefinite description of Vioxx's mechanism of action:<sup>50</sup>

**Mechanism of Action**

VIOXX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

The June 29, 2000 label proposal expanded this description as follows<sup>51</sup>:

*Mechanism of Action*

~~VIOXX is a nonsteroidal anti-inflammatory drug (NSAID)<sup>1</sup> that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the~~

~~cyclooxygenase-1 (COX-1) isoenzyme. At therapeutic doses, VIOXX is an orally active cyclooxygenase-2 (COX-2) selective inhibitor.<sup>2</sup> Nonselective NSAIDs inhibit both COX-1 and COX-2 at therapeutic doses. COX-1 is responsible for prostaglandin-mediated normal physiologic functions such as gastric cytoprotection and platelet aggregation. COX-2 is primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever.<sup>3</sup> Selective inhibition of COX-2 by VIOXX decreases these clinical signs and symptoms without influencing gastrointestinal integrity or platelet function.<sup>4</sup>~~

In addition, the proposed label explained the data in the Clinical Studies section of the label in terms of Vioxx's mechanism of action.<sup>52</sup> Specifically, the draft label referred to Cox-1 and Cox-2 biology in both the introduction to the gastrointestinal safety section

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<sup>49</sup> 6/1/00 HHPAC Meeting Background Package, MRK-ABL0000985, at 89.

<sup>50</sup> 5/20/99 approved Vioxx product label, MRK-ACD0078497, at 497.

<sup>51</sup> 6/29/00 draft label, MRK-00410008089, at 8089-90.

<sup>52</sup> 6/1/00 HHPAC Meeting Background Package, MRK-ABL0000985, at 89.

and in the discussion of the cardiovascular data from the VIGOR Trial.<sup>53</sup> These modifications to the label stressing Vioxx's mechanism of action are reproduced below:

*Special Studies*

*Gastrointestinal*

COX-1 is the predominant cyclooxygenase isoform constitutively expressed in the gastrointestinal (GI) tract.<sup>5</sup> Therefore, selective inhibition of COX-2 was postulated to be associated with a decreased risk of serious GI toxicity relative to nonselective NSAIDs. The following special studies were conducted to evaluate whether VIOXX is associated with less GI toxicity than nonselective NSAIDs.<sup>6</sup>

*Use with Aspirin*

As a selective inhibitor of COX-2,<sup>41</sup> VIOXX does not inhibit platelet function<sup>42</sup> (see CLINICAL STUDIES, *Special Studies, Platelets*) and showed no clinical anti-platelet activity in the VIGOR study relative to naproxen,<sup>43</sup> a known potent inhibitor of platelet function<sup>44</sup> that decreases platelet aggregation and prolongs bleeding time.<sup>45</sup>

In this study, in order not to confound the analysis of PUBs,<sup>46</sup> patients were not permitted to use concomitant aspirin or other anti-platelet drugs<sup>47</sup> (see CLINICAL STUDIES, *Special Studies, Gastrointestinal, VIOXX GI Clinical Outcomes Research (VIGOR) Study* for study details). The incidence of confirmed acute myocardial infarction was 0.4% in patients treated with VIOXX 50 mg daily and 0.1% in patients treated with naproxen 500 mg twice daily (difference = 0.3; 95% C.I. = 0.07, 0.57).<sup>48</sup> This is consistent with the known anti-platelet effects of naproxen.<sup>49</sup> In retrospect, aspirin was indicated for secondary cardiovascular prophylaxis in 4% of patients;<sup>50</sup> 38% of these cardiovascular events occurred in this cohort of patients.<sup>51</sup> In the remaining 96% of patients, the incidence of confirmed acute myocardial infarction was 0.2% in patients treated with VIOXX 50 mg daily and 0.1% in patients treated with naproxen 500 mg twice daily (difference = 0.1; 95% C.I. = -0.08, 0.32).<sup>52</sup> In other controlled clinical trials, spontaneous reports of these cardiovascular events were similar between VIOXX and nonselective NSAID comparators (ibuprofen, diclofenac and nabumetone).<sup>53</sup> VIOXX is not a substitute for aspirin for cardiovascular prophylaxis<sup>54</sup> (see PRECAUTIONS, *General* and PRECAUTIONS, *Drug Interactions, Aspirin*).

With regard to gastrointestinal safety, the June 2000 proposed label stated that the VIGOR Trial provided "conclusive evidence of the improved GI safety" of Vioxx as compared to the non-selective NSAID naproxen.<sup>54</sup> On the basis of that gastrointestinal safety data, the proposed label eliminated the NSAID-class gastrointestinal safety

<sup>53</sup> 6/1/00 HHPAC Meeting Background Package, MRK-ABL0000985, at 89.

<sup>54</sup> 6/29/00 letter from D. Erb to "Central Document Room," FDA, MRK-00420008018, at 18.

warning that appeared in the original Vioxx label.<sup>55</sup> In its place, the June 2000 draft label discussed gastrointestinal safety in the Precautions section and included the statement that in the VIGOR Trial “the risk of development of a PUB was 54% lower” in the Vioxx group compared to the naproxen group.<sup>56</sup>

In further support of these gastrointestinal safety claims, Merck included in the Clinical Studies section of the proposed label a discussion of Protocol 069, a combined analysis of the incidence of PUBs in the eight Merck-sponsored Phase IIb/III osteoarthritis trials.<sup>57</sup> The proposal stated that Protocol 069 found that “[t]he risk of development of a PUB was 55% lower in [osteoarthritis] patients treated with VIOXX than in patients treated with a nonselective NSAID (relative risk = 0.45, 95% CI = 0.25 - 0.81; p = 0.006).”<sup>58</sup> Merck’s goal in including Protocol 069 in the proposed label was to support the extrapolation to osteoarthritis patients of the gastrointestinal-sparing effects demonstrated in rheumatoid arthritis patients in the VIGOR Trial.<sup>59</sup>

The only mention of VIGOR Trial cardiovascular data in the June 2000 proposed label was in the Clinical Studies section, under a subheading entitled “Use with Aspirin.”<sup>60</sup> As shown above, this section stated that the between-treatment difference in the incidence of cardiovascular events in the VIGOR Trial was “consistent with the

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<sup>55</sup> MRL 6/29/00 draft label, MRK-00420008089, at 8101.

<sup>56</sup> MRL 6/29/00 draft label, MRK-00420008089, at 8102.

<sup>57</sup> MRL 6/29/00 draft label, MRK-00420008089, at 8099.

<sup>58</sup> MRL 6/29/00 draft label, MRK-00420008089, at 8099.

<sup>59</sup> See 2/27/01 letter from R. Silverman to FDA, MRK-AAF0003713, at 14.

<sup>60</sup> MRL 6/29/00 draft label, MRK-00420008089, at 8099-8100.

known anti-platelet effects of naproxen,” and noted that 38% of the myocardial infarctions occurred in the 4% of study participants retrospectively identified as indicated for aspirin use for cardiovascular protection.<sup>61</sup>

In addition, the Precautions section included the following new language: “Patients who require low dose aspirin therapy for cardiovascular prophylaxis should continue on aspirin during therapy with VIOXX.”<sup>62</sup> The proposed label also added the statement that “Vioxx can be used concomitantly with low dose aspirin,”<sup>63</sup> and included references to three six-week trials (Protocols 058, 085 and 090) in which “[n]o clinically important differences were noted for users of VIOXX plus aspirin versus VIOXX alone in the overall incidence of clinical adverse experiences.”<sup>64</sup>

According to the June 1, 2000 HHPAC background materials, Merck believed that these proposed label changes could support the following promotional messages:

<b>Proposed Change</b>	<b>Promotional Message</b>
Gastrointestinal warning moved to Precautions section. <sup>65</sup>	“VIOXX distinguishes itself from all non-selective NSAIDs by not requiring a warning on this issue.” <sup>66</sup>

<sup>61</sup> MRL 6/29/00 draft label, MRK-00420008089, at 8100.

<sup>62</sup> MRL 6/29/00 draft label, MRK-00420008089, at 8102.

<sup>63</sup> MRL 6/29/00 draft label, MRK-00420008089, at 8106.

<sup>64</sup> MRL 6/29/00 draft label, MRK-00420008089, at 8100, 8106.

<sup>65</sup> 6/1/00 HHPAC Background Document, MRK-ABL0000985, at 993.

<sup>66</sup> 6/1/00 HHPAC Background Document, MRK-ABL0000985, at 993.

Proposed Change	Promotional Message
Vioxx referred to as a “selective” Cox-2 inhibitor to further distinguish it from non-selective NSAIDs. <sup>67</sup>	“Selective inhibition of COX-2 by VIOXX produces potent pain relief with a significant reduction in serious GI side effects and no ‘aspirin-like’ effect on platelet function.” <sup>68</sup>
Vioxx is “not a substitute for aspirin for cardiovascular prophylaxis” and the lower rate of myocardial infarctions in naproxen versus Vioxx in the VIGOR Trial was “consistent with the anti-platelet effects of naproxen.” <sup>69</sup>	The lower rate of myocardial infarctions with naproxen versus Vioxx, as seen in the VIGOR Trial, was consistent with naproxen’s “potent Cox-1 inhibition and ability to block platelet aggregation and prolong bleeding time.” Vioxx could be used with low-dose aspirin. <sup>70</sup>
A paragraph on the general safety of Vioxx, indicating that the general safety profile of Vioxx 50 mg in the VIGOR Trial was similar to that reported in osteoarthritis clinical trials.	“The safety profile of VIOXX in the VIGOR study, at two times the daily dose for chronic use of rofecoxib, was similar to the existing label information for the OA clinical trials.” <sup>71</sup>

D. VIGOR Safety Update Report.

As discussed in Appendix I, on October 13, 2000, before the FDA had transmitted any labeling counterproposal, Merck submitted to the FDA a Safety Update Report reflecting the final adjudicated data from the VIGOR Trial and an updated label reflecting the additional cardiovascular data from the report.<sup>72</sup> As described in

<sup>67</sup> 6/1/00 HHPAC Background Document, MRK-ABL0000985, at 991.

<sup>68</sup> 6/1/00 HHPAC Background Document, MRK-ABL0000985, at 991.

<sup>69</sup> 6/1/00 HHPAC Background Document, MRK-ABL0000985, at 994.

<sup>70</sup> 6/1/00 HHPAC Background Document, MRK-ABL0000985, at 994-95.

<sup>71</sup> 6/1/00 HHPAC Background Document, MRK-ABL0000985, at 995.

<sup>72</sup> 10/13/00 letter from R. Silverman to FDA (CDER), MRK-00420027870, 72 (attaching the VIGOR Trial Safety Update Report).

Appendix I, of the 11 additional patients for whom cardiovascular serious adverse events had been reported after the VIGOR Trial's February 10, 2000 cardiovascular reporting cut-off date,<sup>73</sup> 5 of these events were confirmed by an adjudication committee to be thrombotic cardiovascular serious adverse experiences.<sup>74</sup> With the inclusion of these events, the incidence of myocardial infarction increased from 0.4% to 0.5% in the Vioxx arm of the trial. None of the five confirmed events occurred in patients in the 4% subgroup retrospectively identified as indicated for low-dose aspirin.<sup>75</sup>

E. February-March 2001 Submissions.

As discussed in Appendix I, FDA representatives and FDA external advisors at the February 8, 2001 Advisory Committee meeting expressed concerns about the cardiovascular safety of Vioxx in light of the VIGOR Trial cardiovascular data. In addition, while the FDA agreed that the VIGOR Trial gastrointestinal data justified some change to the discussion of gastrointestinal safety in the label, the Agency did not indicate that it considered the data sufficient to support wholesale removal of the NSAID-class gastrointestinal safety warning.<sup>76</sup> After the Advisory Committee meeting,

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<sup>73</sup> 10/13/00 letter from R. Silverman to FDA (CDER), MRK-00420027870, at 70 (attaching the VIGOR Trial Safety Update Report); 10/13/00 VIGOR Safety Update Report, MRK-00420027875, at 881.

<sup>74</sup> 10/13/00 letter from R. Silverman to FDA (CDER) attaching the VIGOR Safety Update Report, MRK-00420027870, at 70; 10/13/00 VIGOR Safety Update Report, MRK-00420027875, at 881.

<sup>75</sup> 10/13/00 VIGOR Safety Update Report, MRK-00420027875, at 895. As discussed below, as a result of these additional events in the non-aspirin-indicated subgroup, MRL omitted from subsequent label proposals the discussion of the rate of cardiovascular events in the aspirin-indicated subgroup and argued against inclusion of such a discussion in the FDA's counterproposals.

<sup>76</sup> A few weeks after the Advisory Committee meeting, Merck submitted an additional supplemental New Drug Application to the FDA to support an indication for the use of Vioxx in treating rheumatoid arthritis. 2/28/01 letter from R. Silverman to "Central Document Room," FDA, MRK-AAF0003727.

the Human Health Product Approval Committee decided that obtaining an appropriate label was more important than accelerating the approval process.<sup>77</sup>

Merck submitted a new draft label to the FDA on March 2, 2001 to address the concerns raised at the Advisory Committee meeting.<sup>78</sup> The following Section details those revisions.

1. March 2001 Revised Label.

The two most significant changes in the revised label proposal that Merck submitted in March 2001 were: (i) the restoration of the NSAID-class gastrointestinal warning; and (ii) the addition of a discussion of the VIGOR Trial cardiovascular data in the Precautions section.<sup>79</sup>

a. Gastrointestinal warning language.

Although the March 2001 proposed label restored the NSAID-class gastrointestinal warning that was in the original Vioxx label, it added the following qualification: “Although upper GI PUBs can occur in patients treated with VIOXX, the incidence was significantly less than that seen in patients taking comparator nonselective NSAIDs in randomized clinical trials.”<sup>80</sup> The warning also described the favorable gastrointestinal safety findings from both the VIGOR Trial and Protocol 069.<sup>81</sup>

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<sup>77</sup> Minutes of 3/15/01 HHPAC meeting, MRK-ABL0001208, at 208.

<sup>78</sup> See 3/22/01 memorandum from R. Silverman to A&A WBST, MRK-NJ0333400, at 400.

<sup>79</sup> See Vioxx – HHPAC Stage IV Review Meeting – Background Materials, MRK-ABL0001217, at 261 (attached to 3/20/01 memorandum from R. Bissett to Human Health Product Approval Committee, MRK-ABL0001213).

<sup>80</sup> MRL 3/2/01 draft label, MRK-ACD0003164, at 172.

<sup>81</sup> MRL 3/2/01 draft label, MRK-ACD0003164, at 172.

b. Cardiovascular precaution.

Merck's March 2001 proposed label added to the Precautions section a discussion of cardiovascular adverse events from the VIGOR Trial.<sup>82</sup> The language of this section was similar to that included in the Clinical Studies section of the previous proposal, except that the Precaution's reference to the naproxen cardioprotection hypothesis was based on statements in the FDA-approved label for naproxen, rather than on the more generalized language from the initial proposal regarding the "known anti-platelet effects of Naproxen."<sup>83</sup> In addition, the revised label omitted references to the rate of cardiovascular events in the aspirin-indicated and non-aspirin-indicated subgroups.<sup>84</sup> The text of the cardiovascular precaution is reproduced below:<sup>85</sup>

In the VIGOR study, patients were not permitted to use concomitant aspirin or other anti-platelet drugs (see CLINICAL STUDIES, *Special Studies, Gastrointestinal Safety Studies, VIOXX GI Clinical Outcomes Research (VIGOR) Study* for study details). The incidence of acute myocardial infarction was 0.5% in patients treated with VIOXX 50 mg daily and 0.1% in patients treated with naproxen 500 mg twice daily (difference = 0.4; 95% C.I. = 0.1, 0.7). As noted in its product circular, naproxen may decrease platelet aggregation and prolong bleeding time. In other controlled clinical trials in which patients were not permitted to use concomitant aspirin or other anti-platelet drugs, the incidence of myocardial infarction was similar between VIOXX, nonselective NSAID comparators (ibuprofen, diclofenac and nabumetone), and placebo.

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<sup>82</sup> MRL 3/2/01 draft label, MRK-ACD0003164, at 175 ("As noted in its product circular, naproxen may decrease platelet aggregation and prolong bleeding time.").

<sup>83</sup> MRL 6/30/00 draft label, MRK-00420008089, at 100. At this time, the Celebrex label stated that, in clinical trials, naproxen, ibuprofen, and diclofenac "significantly reduced platelet aggregation and prolonged bleeding time." 2001 approved Celebrex product label, MRK-AAF0007539, 548.

<sup>84</sup> MRL 3/2/01 draft label, MRK-ACD0003164, at 175.

<sup>85</sup> MRL 3/2/01 draft label, MRK-ACD0003164, at 175.

2. March 20, 2001 Meeting of the  
Human Health Product Approval Committee.

In March 2001, the Human Health Product Approval Committee conducted a “Stage IV Program Review” to assess “critical issues” affecting Vioxx, including topics raised by the February 2001 Arthritis Advisory Committee meeting. At this meeting, the Human Health Product Approval Committee identified two key objectives for the Vioxx label: (i) to obtain the “most favorable wording possible in the GI warnings section of the [label] to be able to aggressively promote in the U.S. and [worldwide];” and (ii) to demonstrate and include a statement in the label that the gastrointestinal safety of Vioxx was maintained in patients who used Vioxx concomitantly with low-dose aspirin.<sup>86</sup>

To achieve the first objective, the Human Health Product Approval Committee recommended negotiating with the FDA to allow inclusion of Protocol 069, MRL’s pooled analysis of the incidence of PUBs in the eight Phase IIb/III osteoarthritis studies.<sup>87</sup> To demonstrate that Vioxx maintained gastrointestinal safety when used concomitantly with low-dose aspirin, the Human Health Product Approval Committee recommended including a description of the results (not yet available) of Protocol 136, an ongoing endoscopy study comparing the incidence of gastrointestinal lesions in patients on Vioxx plus low-dose aspirin versus ibuprofen alone versus aspirin alone, as well as initiating another endoscopy study (later known as Protocol 158) to compare the gastrointestinal

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<sup>86</sup> Vioxx – HHPAC Stage IV Review Meeting – Background Materials, MRK-ABL0001217, at 224.

<sup>87</sup> Vioxx – HHPAC Stage IV Review Meeting – Background Materials, MRK-ABL0001217, at 224.

safety of Vioxx plus low-dose aspirin versus ibuprofen plus low-dose aspirin.<sup>88</sup> At the Advisory Committee Meeting, FDA reviewers Drs. Villalba\* and Targum\* had stated that the studies that MRL previously had cited to show that Vioxx could be taken safely with aspirin – Protocols 058, 085, and 090 – were not large enough or long enough “to detect differences in serious gastrointestinal events.”<sup>89</sup>

3. Submission of Data from the ADVANTAGE Trial.

As stated in Appendix I, in November 2000, the FDA had requested that Merck submit complete data from the ADVANTAGE Trial – a 12-week trial that, like the VIGOR Trial, compared the gastrointestinal safety of Vioxx versus that of naproxen.<sup>90</sup> (The dose of Vioxx in the ADVANTAGE Trial was 25 mg – half that used in the VIGOR Trial – and the study population was osteoarthritis patients.) The FDA viewed the ADVANTAGE Trial as an important counterpart to the VIGOR Trial because it contained a large database of safety information at the 25 mg dosage level, used naproxen as a comparator drug, and, unlike the VIGOR Trial, permitted aspirin use.<sup>91</sup> On February 14, 2001, Ms. Sandra Folkendt\* of the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products sent a facsimile to Dr. Silverman requesting

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<sup>88</sup> Vioxx – HHPAC Stage IV Review Meeting – Background Materials, MRK-ABL0001217, at 224. These endoscopy studies – Protocols 136 and 158 – are discussed in Appendix M.

<sup>89</sup> Report of Dr. Villalba\*, MRK-ABK0456991, at 0457013; see also Report of Dr. Targum\*, MRK-ABK0457094, at 7108, 7130 (noting that the benefits of taking Vioxx and low-dose aspirin, as opposed to taking naproxen alone, were unclear and would “require further study”).

<sup>90</sup> ADVANTAGE Clinical Study Report, MRK-AFV0154893, at 903.

<sup>91</sup> See 2/28/01 letter from L. Goldkind\* to R. Silverman, MRK-AAF0003724.

the complete report of the ADVANTAGE Trial.<sup>92</sup> Dr. Lawrence Goldkind\*, Deputy Division Director of the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products, requested these data again in a letter to Dr. Silverman dated February 28, 2001.<sup>93</sup> In a March 8, 2001 telephone conversation, Dr. Goldkind\* explained to Dr. Silverman that “the Agency believes that they cannot complete label negotiations on the VIGOR [supplemental New Drug Application] without having a chance to examine the ADVANTAGE results.”<sup>94</sup> On March 30, 2001, Merck submitted data from the ADVANTAGE Trial to the Agency.<sup>95</sup>

In the ADVANTAGE Trial, there were five confirmed myocardial infarctions in the Vioxx arm of the trial and one in the naproxen arm<sup>96</sup> – the same myocardial infarction ratio as in the VIGOR Trial. Two of the patients who suffered confirmed myocardial infarctions in the Vioxx arm of the trial were taking low-dose aspirin at the time.<sup>97</sup> Unlike the VIGOR Trial, however, patients in the Vioxx arm of the ADVANTAGE Trial experienced fewer strokes than those in the naproxen arm, and the total number of serious thrombotic events in the naproxen arm (12) exceeded that in the Vioxx arm (9).<sup>98</sup>

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<sup>92</sup> 2/14/01 facsimile from S. Folkendt\* to R. Silverman, MRK-AAF0003685, at 685.

<sup>93</sup> 2/28/01 letter from L. Goldkind\* to R. Silverman, MRK-AAF0003724.

<sup>94</sup> Dr. Silverman’s Regulatory Liaison FDA conversation record, MRK-AAF0003963, at 64.

<sup>95</sup> 3/30/01 letter from R. Silverman to J. Bull\*, MRK-AAF0003831.

<sup>96</sup> ADVANTAGE Clinical Study Report, MRK-AFV0154893, at 992.

<sup>97</sup> ADVANTAGE Clinical Study Report, MRK-AFV0154893, at 996-97.

<sup>98</sup> ADVANTAGE Clinical Study Report, MRK-AFV0154893, at 992.

Table 1

Serious Thrombotic Events in the ADVANTAGE Trial

	Naproxen Arm	Vioxx Arm
Number of Events	12	9
Myocardial Infarctions	1	5

Merck's March 30 submission to the FDA included the entire clinical study report for the trial, except for certain data sets and copies of case report forms for patients who died or discontinued due to an adverse event.<sup>99</sup> In a March 15, 2001 letter to the FDA, Dr. Silverman had written that these items required extra time to reproduce because of their size.<sup>100</sup>

F. April 2001 Approvable Letter.

In a March 22, 2001 memorandum to the Arthritis and Analgesia Worldwide Business Strategy Team, Dr. Silverman wrote that he believed that the FDA would approve the label by the end of April 2001.<sup>101</sup> He indicated that he would work to obtain the Agency's counterproposal label prior to a meeting that had been scheduled for April 11.<sup>102</sup> Dr. Silverman noted, however, that there was "a significant possibility of a two month delay" if the Agency elected to take additional time to review the ADVANTAGE Trial data and "a small possibility of a longer delay" if the Agency issued

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<sup>99</sup> 3/30/01 letter from R. Silverman to J. Bull\*, MRK-AAF0003831, at 31.

<sup>100</sup> 3/15/01 letter from R. Silverman to J. Bull\*, MRK-AAF0003775, at 75.

<sup>101</sup> 3/22/01 memorandum from R. Silverman to "A&A WBST," MRK-NJ0333400, at 401.

<sup>102</sup> 3/22/01 memorandum from R. Silverman to "A&A WBST," MRK-NJ0333400, at 400.

an “approvable” decision seeking additional information.<sup>103</sup> Dr. Silverman further observed that while the Regulatory Affairs Department was “directed at avoiding delays in securing optimal labeling,” the Human Health Product Approval Committee recently had “reiterated their advice that we take extra time . . . if necessary, to continue label negotiations that will result in optimal product labeling.”<sup>104</sup>

On April 6, 2001, the FDA issued an approvable letter with respect to Merck’s supplemental New Drug Application.<sup>105</sup> As noted above, the issuance of an “approvable” letter means that the Agency intends to approve the submission, subject to certain conditions set forth in the letter. The approvable letter, which was signed by Dr. Jonca Bull\*, Acting Director of the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products, asked Merck to submit the remaining study data from the ADVANTAGE Trial so that the Agency could “adequately interpret the cardiovascular and overall safety results in the VIGOR study.”<sup>106</sup> The Agency also requested a comprehensive safety update including data from “non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form or dose level.”<sup>107</sup>

That evening, Dr. Scolnick sent an email to Drs. Greene, Blois, and Goldmann describing the FDA’s “request for safety updates” as a “filibuster.”<sup>108</sup> Dr. Scolnick

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<sup>103</sup> 3/22/01 memorandum from R. Silverman to “A&A WBST,” MRK-NJ0333400, at 401.

<sup>104</sup> 3/22/01 memorandum from R. Silverman to “A&A WBST,” MRK-NJ0333400, at 400.

<sup>105</sup> 4/6/01 letter from J. Bull\* to R. Silverman, MRK-01420099056, at 56.

<sup>106</sup> 4/6/01 letter from J. Bull\* to R. Silverman, MRK-01420099056, at 56.

<sup>107</sup> 4/6/01 letter from J. Bull\* to R. Silverman, MRK-01420099056, at 56-57.

<sup>108</sup> 4/6/01 email from E. Scolnick to D. Greene *et al.*, MRK-ACR0009148, 148-49.

expressed concern that the FDA might be preparing to approve the Celebrex label while delaying decision on the Vioxx label and stated that, if necessary, he would take up the issue with Dr. Janet Woodcock\*, Director of the FDA's Center for Drug Evaluation and Research, which oversees the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products. Dr. Scolnick asked Drs. Greene, Blois and Goldman:

What are your plans for responding to this action as well as the letter? When will you find out what they have done for our competitor? If by any chance [sic] they get a better label now and we are asked for this much more data, I will be in Janet's [sic] office the next day . . . I look forward to hearing back from you about what you are going to do. I have never seen being nice to the FDA—except on rare occasions [sic] – pay off.<sup>109</sup>

Dr. Greene replied to Dr. Scolnick that his recollection was that the instructions from the Human Health Product Approval Committee were to “press for the best ultimate label rather than pressing to be first in the relabeling process.”<sup>110</sup> Dr. Greene agreed that the approvable letter was a “filibuster” but cautioned that Merck did not know the reasons for the FDA's actions. It was possible, he suggested, that the delay was caused by the Celebrex application and that the Division wanted to keep both products on the same timeline. Alternatively, the Division could be “singling us out for delay and for further scrutiny (related to the Advantage cardiovascular data), to our disadvantage.”<sup>111</sup> If this were the case, Merck “should clearly escalate over the head of the Division.”<sup>112</sup>

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<sup>109</sup> 4/6/01 email from E. Scolnick to D. Greene et al., MRK-ACR0009148, at 148-49.

<sup>110</sup> 4/7/01 email from D. Greene to E. Scolnick et al., MRK-ACR0009148.

<sup>111</sup> 4/7/01 email from D. Greene to E. Scolnick et al., MRK-ACR0009148.

<sup>112</sup> 4/7/01 email from D. Greene to E. Scolnick et al., MRK-ACR0009148.

Dr. Greene inquired whether there was any way to determine the status of the Celebrex application.<sup>113</sup>

In subsequent emails, Dr. Scolnick responded that Dr. Woodcock\* was the only “recourse” and expressed his frustration that “[o]ne cannot deal with them [the Division] in a rational way.”<sup>114</sup> Dr. Scolnick also expressed his concern that the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products would approve the Celebrex label and put Merck in “an unenviable position with them [Searle/Pfizer] having a weak change, us having nothing and the world thinking it is because of Cv events.”<sup>115</sup>

Dr. Scolnick further expressed the view that it was “not wise” to have given the ADVANTAGE Trial data to the FDA, because the “numbers are too small” and the FDA might “data dredge”<sup>116</sup> with the result that “we will end up with bad labeling.”<sup>117</sup>

Dr. Scolnick suggested submitting the safety data from the Alzheimer’s disease trials (Protocols 078 and 091) “since it is much more supportive.”<sup>118</sup>

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<sup>113</sup> 4/7/01 email from D. Greene to E. Scolnick et al., MRK-ACR0009148.

<sup>114</sup> 4/7/01 email from E. Scolnick to D. Greene, MRK-ACR0009148.

<sup>115</sup> 4/9/01 email from E. Scolnick to D. Greene, MRK-ACR0009151.

<sup>116</sup> Data dredging is analyzing “data without regard to accepted scientific and statistical principles in order to find some aspect that will be of interest.” Day, S. Dictionary for Clinical Trials. West Sussex, England: John Wiley & Sons; 1999: 40.

<sup>117</sup> 4/9/01 email from E. Scolnick to D. Greene, MRK-ACR0009151.

<sup>118</sup> 4/9/01 email from E. Scolnick to D. Greene, MRK-ACR0009151. Dr. Scolnick had previously expressed his dissatisfaction with the ADVANTAGE Trial, which was conducted by the Clinical Development Program, a part of the Marketing Department, and to which he referred as a “small marketing [study].” 4/07/01 email from E. Scolnick to D. Greene, MRK-ACR0009150.

1. Discussion with the FDA About Protocol 069.

On April 11, 2001, Merck representatives, including Drs. Goldmann and Silverman, met with representatives from the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products to discuss the Agency's concerns over references in the label to Protocol 069.<sup>119</sup> Merck had requested the meeting after the February 2001 Advisory Committee meeting.<sup>120</sup> In Merck's view, the gastrointestinal safety outcomes of the VIGOR Trial and Protocol 069 "corroborate[d] and complement[ed] each other" so that the Vioxx label "should include the results of both VIGOR and Protocol 069 and should acknowledge the generalizability of the findings from the two studies."<sup>121</sup> At the April 11 meeting, both sides agreed that Protocol 069 provided "meaningful information with potential value to prescribers," but the FDA representatives expressed the view that the presentation of the data in the proposed label implied that Vioxx demonstrated improved gastrointestinal safety over all NSAIDs, whereas the "difference between the rofecoxib group and the pooled NSAID comparator group . . . was primarily driven by the studies where ibuprofen was the NSAID comparator."<sup>122</sup> Merck responded that the proposed label included the qualifying language that the results in Protocol 069 "were

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<sup>119</sup> Minutes of 4/11/01 MRL/FDA meeting, MRK-01420099060.

<sup>120</sup> 2/27/01 letter from R. Silverman to "Central Document Room," FDA, MRK-AAF0003713, at 713. Merck had submitted data from Protocol 069 with the Vioxx New Drug Application in November 1998, but the FDA did not agree to include in the label comparative data concerning the incidence of gastrointestinal events on Vioxx versus the comparator drugs in the study. The New Drug Application is discussed in Appendix C.

<sup>121</sup> 2/27/01 letter from R. Silverman to "Central Document Room," FDA, MRK-AAF00003713, at 714.

<sup>122</sup> Minutes of 4/11/01 MRL/FDA meeting, MRK-01420099060, at 9060.

primarily influenced by the experience with ibuprofen,”<sup>123</sup> but the Agency stated that it did not want to “set a precedent by allowing labeling based on a subset of the information from a study when [it was] not comfortable with the entire study.”<sup>124</sup> Merck offered to provide a revised label proposal on Protocol 069 addressing the Agency’s concerns.<sup>125</sup>

Merck also proposed setting a timetable for future negotiations, but the Agency was unwilling to discuss a schedule for further negotiations until after Merck had submitted the information sought in the approvable letter, including the remaining ADVANTAGE Trial data.<sup>126</sup> Merck submitted the remaining data from the ADVANTAGE Trial to the FDA on April 16, and April 30, 2001.<sup>127</sup>

2. Merck’s May 21, 2001 Proposed Label.

On May 21, 2001, Merck submitted a revised label which changed the Clinical Studies and Warnings sections to “reflect a briefer, less prominent, and less detailed description” of Protocol 069.<sup>128</sup> About two months later, on July 12, 2001, Merck submitted the safety update report requested in the “approvable” letter.<sup>129</sup> The update included safety information from the ADVANTAGE Trial, two Alzheimer’s disease

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<sup>123</sup> Minutes of 4/11/01 MRL/FDA meeting, MRK-01420099060, at 9061.

<sup>124</sup> Minutes of 4/11/01 MRL/FDA meeting, MRK-01420099060, at 9061.

<sup>125</sup> Minutes of 4/11/01 MRL/FDA meeting, MRK-01420099060, at 9061.

<sup>126</sup> Minutes of 4/11/01 MRL/FDA meeting, MRK-01420099060, at 9061.

<sup>127</sup> 4/16/01 letter from R. Silverman to J. Bull\*, MRK-AAF0003890; 4/30/01 letter from R. Silverman to J. Bull\*, MRK-AAF0003926.

<sup>128</sup> 5/21/01 letter from R. Silverman to J. Bull\*, MRK-ACD0091200 (attaching MRL 05/21/01 draft label).

<sup>129</sup> 7/12/01 letter from R. Silverman to J. Bull\*, MRK-AAF0004103.

trials (Protocols 078 and 091), and the rheumatoid arthritis studies that had been submitted to the Agency in February 2001 in connection with Merck's application for a rheumatoid arthritis indication.<sup>130</sup>

G. The FDA's Initial Proposed Label: October 15, 2001.

By the beginning of October 2001, sixteen months after submitting its initial supplemental New Drug Application proposed label to the FDA, Merck still had not received any counterproposal from the FDA. On October 5, 2001, Dr. Goldmann called Dr. Woodcock\* at the FDA to discuss the status of the Agency's review.<sup>131</sup> Dr. Greene, who may have been on the call as well, summarized the conversation in an email to Drs. Scolnick and Kim.<sup>132</sup> Dr. Greene predicted that Merck would "not be comfortable with" the FDA's proposed label.<sup>133</sup> According to Dr. Greene, in the FDA's view "the data at hand" showed differences in both gastrointestinal and cardiovascular safety between Vioxx and naproxen.<sup>134</sup> Dr. Greene stated that the FDA felt that it could not determine "that there is a CV issue, or that there is not a CV issue" based on the existing data.<sup>135</sup> Dr. Greene further noted, however, that the Agency acknowledged that the "deal

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<sup>130</sup> 7/12/01 letter from R. Silverman to J. Bull\*, MRK-AAF0004103.

<sup>131</sup> 10/5/01 email from D. Greene to E. Scolnick and P. Kim, MRK-ABH0019975.

<sup>132</sup> 10/5/01 email from D. Greene to E. Scolnick and P. Kim, MRK-ABH0019975.

<sup>133</sup> 10/5/01 email from D. Greene to E. Scolnick and P. Kim, MRK-ABH0019975.

<sup>134</sup> 10/5/01 email from D. Greene to E. Scolnick and P. Kim, MRK-ABH0019975.

<sup>135</sup> 10/5/01 email from D. Greene to E. Scolnick and P. Kim, MRK-ABH0019975.

with the data at hand” standard “should apply to the evidentiary standard for both CV and GI safety.”<sup>136</sup>

Ten days later, on October 15, 2001, Merck received the FDA’s counterproposal label, which substantially rewrote Merck’s proposed discussion of gastrointestinal and cardiovascular data from the VIGOR Trial and included a cardiovascular warning.<sup>137</sup> The FDA also deleted Merck’s proposed references to concomitant use of Vioxx with aspirin, and added cautionary language on post-marketing events of renal failure, congestive heart failure and edema. The following Section describes the FDA’s counterproposal in greater detail.

1. Gastrointestinal Data.

With respect to gastrointestinal data, the FDA deleted Merck’s proposed modifications to the NSAID-class gastrointestinal warning,<sup>138</sup> but added modifying language stating that, in the VIGOR Trial, “the cumulative incidence of PUBs with VIOXX 50 mg – the approved dose for the treatment of acute pain and twice the maximum dose recommended for chronic use in osteoarthritis – was 1.8% over a median exposure of 9 months.”<sup>139</sup> The FDA also requested that Merck add a table to the Warnings section showing “cumulative incidences of complicated and uncomplicated ulcers” in the VIGOR Trial according to the age and gastrointestinal history of the trial

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<sup>136</sup> 10/5/01 email from D. Greene to E. Scolnick and P. Kim, MRK-ABH0019975.

<sup>137</sup> 10/15/01 email from B. Gould\* to R. Silverman, MRK-AAX0008560 (attaching draft label).

<sup>138</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 571 (attached to 10/15/01 email from B. Gould\* to R. Silverman, MRK-AAX0008560).

<sup>139</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 571.

participants.<sup>140</sup> In the Clinical Studies section, the FDA entirely redrafted Merck's description of the VIGOR Trial and its results<sup>141</sup> and deleted references to Protocol 069.<sup>142</sup>

## 2. Cardiovascular Data.

The FDA transferred the discussion of cardiovascular adverse events in the VIGOR Trial from the Precautions section of the label, where Merck had proposed placing it, to the Warnings section.<sup>143</sup> In the text of the Warning, the FDA also added that "VIOXX should be used with caution" in high-risk patients, such as those with a history of heart attacks and angina, and in patients with pre-existent hypertension and congestive heart failure.<sup>144</sup>

The FDA's proposed draft Warnings section deleted Merck's statement that, in trials other than the VIGOR Trial, the "incidence of myocardial infarction was similar between VIOXX, nonselective NSAID comparators (ibuprofen, diclofenac and nabumetone), and placebo."<sup>145</sup> The FDA replaced this text with data on myocardial infarctions from the ADVANTAGE Trial that the FDA stated were "consistent [with]" the VIGOR Trial results.<sup>146</sup> The FDA also deleted Merck's reference to the naproxen

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<sup>140</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 571.

<sup>141</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 564-66.

<sup>142</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 569-70.

<sup>143</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 572.

<sup>144</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 571-72.

<sup>145</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 574.

<sup>146</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 572.

cardioprotection hypothesis as an explanation for the between-treatment difference in cardiovascular results in the VIGOR Trial.<sup>147</sup> A comparison between the FDA’s proposed Warning and Merck’s proposed Precaution is shown below:

<b>Merck’s May 21, 2002 Proposal<sup>148</sup></b>	<b>FDA October 15, 2001 Proposal<sup>149</sup></b>
<p><b>PRECAUTIONS</b>  ***  <b>Cardiovascular Effects</b>  ***  In the VIGOR study, patients were not permitted to use concomitant aspirin or other anti-platelet drugs.... The incidence of acute myocardial infarction was 0.5% in patients treated with VIOXX 50 mg daily and 0.1% in patients treated with naproxen 500 mg twice daily (difference = 0.4; 95% C.I. = 0.1, 0.7). As noted in its product circular, naproxen may decrease platelet aggregation and prolong bleeding time. In other controlled clinical trials in which patients were not permitted to use concomitant aspirin or other antiplatelet drugs, the incidence of myocardial infarction was similar between VIOXX, nonselective NSAID comparators (ibuprofen, diclofenac and nabumetone), and placebo.</p>	<p><b>WARNINGS</b>  ***  <b>Cardiovascular Disease</b>  ***  VIOXX should be used with caution in patients at risk of developing cardiovascular thrombotic events such as those with a history of myocardial infarction and angina and in patients with pre-existent hypertension and congestive heart failure.   The risk of developing myocardial infarction in the VIGOR study was five fold higher in patients treated with VIOXX 50 mg (0.5%) as compared to patients treated with Naproxen (0.1%). . . . The finding was consistent in a smaller and shorter study using Vioxx 25mg that allowed the use of low dose [aspirin]. Prospective, well powered, long term studies required to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators other than Naproxen have not been performed.</p>

The FDA’s proposed label restructured the discussion of the VIGOR Trial in the Clinical Studies section to emphasize cardiovascular as well as gastrointestinal safety data.<sup>150</sup> While Merck’s draft had included a single table summarizing gastrointestinal results of the VIGOR Trial, the FDA proposed a table with a summary of safety events

<sup>147</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 574.

<sup>148</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 573.

<sup>149</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 571-72

<sup>150</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 567.

by body system (cardiovascular, digestive and musculoskeletal), as well as separate tables comparing the Vioxx and naproxen treatment groups with respect to gastrointestinal safety events, cardiovascular safety events generally, and cardiovascular safety events in the aspirin-indicated subgroup.<sup>151</sup>

In addition, the FDA's proposed text stated that the VIGOR Trial "demonstrated a significant increase in the risk of development of serious cardiovascular thrombotic events in patients taking VIOXX compared to naproxen."<sup>152</sup> The draft also added a paragraph stating that the ADVANTAGE Trial, which involved a 25 mg dose of Vioxx and allowed concomitant use of low-dose aspirin, "showed a similar pattern of overall, [gastrointestinal] and CV safety observed in VIGOR."<sup>153</sup>

Finally, although Merck had deleted all references to the aspirin-indicated subgroup in the March 2001 draft, the FDA proposed adding the statement that "[t]he excess of cardiovascular thrombotic events on VIOXX compared to naproxen was more marked in the subgroup of patients retrospectively identified as being at high risk for cardiovascular disease."<sup>154</sup>

### 3. Use of Vioxx with Aspirin.

The FDA's October 15 draft replaced Merck's statement that "VIOXX can be used concomitantly with low dose aspirin" with the sentence, "No long term studies on

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<sup>151</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 566-67.

<sup>152</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 567.

<sup>153</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 568.

<sup>154</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 567.

concomitant administration of VIOXX and aspirin have been conducted.”<sup>155</sup> In addition, the FDA deleted Merck’s proposed references to the six-week studies in which low-dose aspirin had been allowed (Protocols 058, 085 and 090) and about which Merck had written: “no clinically important differences were noted for users of Vioxx plus aspirin versus VIOXX alone in the overall incidence of clinical adverse experiences.”<sup>156</sup>

4. Renal Events.

The FDA’s October 15 draft noted that the Vioxx group in the VIGOR Trial had a “higher incidence of discontinuations due to hypertension- and edema-related events as well as congestive heart failure events as compared to [the] naproxen” group<sup>157</sup> and added to the Precautions section references to post-marketing reports of congestive heart failure and “severe pulmonary edema.”<sup>158</sup> The Agency’s draft also included references to post-marketing reports of renal failure in the Warnings and Precautions sections of the label.<sup>159</sup> These references did not appear in the NSAID-class labeling, as shown in the comparison below:

<b>NSAID-Class Labeling</b>	<b>October 15, 2001 FDA Draft</b>
WARNINGS <i>Advanced Renal Disease</i> In cases with advanced kidney disease, treatment with TRADENAME is not	WARNINGS <i>Advanced Renal Disease</i> No safety information is available regarding the use of VIOXX in patients with advanced kidney

<sup>155</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 575.

<sup>156</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 570.

<sup>157</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 567.

<sup>158</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 567, 573.

<sup>159</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 563, 572, 573.

NSAID-Class Labeling	October 15, 2001 FDA Draft
<p>recommended. If NSAID therapy, however, must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, <i>Renal Effects</i>).<sup>160</sup></p>	<p>disease in clinical trials. Therefore, treatment with VIOXX is not recommended in these patients. <u>In post-marketing experience, serious renal failure, including the need for dialysis and fatalities have been reported in patients with normal, as well as impaired renal function. These events may occur after short term therapy.</u> If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, <i>Renal Effects</i>).<sup>161</sup></p>
<p>PRECAUTIONS <i>Renal Effects</i> Caution should be used when initiating treatment with TRADENAME in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with TRADENAME. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS-<i>Advanced Renal Disease</i>).</p> <p>As with other NSAIDs, long-term administration of TRADENAME has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in which renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependant reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.<sup>162</sup></p>	<p>PRECAUTIONS <i>Renal Effects</i> Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of [an NSAID] may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of [NSAID] therapy is usually followed by recovery to the pretreatment state. <u>However, severe renal failure including fatalities and need for dialysis have been reported in post-marketing in association with VIOXX.</u> (see WARNINGS, <i>Advanced Renal Disease</i>). *** Caution should be used when initiating treatment with VIOXX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIOXX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS, <i>Advanced Renal Disease</i>).<sup>163</sup></p>

<sup>160</sup> Proposed NSAID Package Insert Labeling Template (Revised 12/19/96), www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1\_03\_D-FDA-TAB-B.pdf.

<sup>161</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 572.

<sup>162</sup> Proposed NSAID Package Insert Labeling Template (Revised 12/19/96), www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1\_03\_D-FDA-TAB-B.pdf.

NSAID-Class Labeling	October 15, 2001 FDA Draft
<p><b>PRECAUTIONS</b> <i>Fluid Retention, Edema, and Hypertension</i> Fluid retention and edema have been observed in some patients taking NSAIDs. Therefore as with other NSAIDs, TRADENAME should be used with caution in patients with fluid retention, hypertension, or heart failure.<sup>164</sup></p>	<p><b>PRECAUTIONS</b> <i>Fluid Retention, Edema, and Hypertension</i> Fluid retention, edema, and hypertension have been observed in patients taking VIOXX. <u>Clinical trials with VIOXX at daily doses of 12.5 and 25 mg in patients with osteoarthritis have shown effects on hypertension and edema similar to those observed with comparator NSAIDs; these occurred with an increased frequency with chronic use of VIOXX at doses above the 12.5 to 25 mg range. (See ADVERSE REACTIONS. New onset of congestive heart failure, worsening of pre-existing congestive heart failure and severe pulmonary edema have been reported in post-marketing in association with the use of VIOXX at recommended doses. VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.</u><sup>165</sup></p>

H. Merck’s Response and November 6, 2001 Counterproposal.

1. Initial Reactions.

On the afternoon of October 15, 2001, Dr. Scolnick wrote to Mr. Anstice about the FDA’s counter-proposal: “Be assured we will not accept this label.”<sup>166</sup> Mr. Anstice responded, “We knew it would be UGLY and it is. We’ll fight back and see where we get.”<sup>167</sup> Dr. Scolnick replied, “It is ugly cubed. thye [sic] are bastards.”<sup>168</sup> Dr. Scolnick

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<sup>163</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 573.

<sup>164</sup> Proposed NSAID Package Insert Labeling Template (Revised 12/19/96), [www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1\\_03\\_D-FDA-TAB-B.pdf](http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_03_D-FDA-TAB-B.pdf).

<sup>165</sup> FDA 10/15/01 draft label showing revisions to previous text, MRK-AAX0008561, at 573.

<sup>166</sup> 10/15/01 email from E. Scolnick to D. Anstice, MRK-ABW0004799.

<sup>167</sup> 10/15/01 email from D. Anstice to E. Scolnick, MRK-ABW0004799.

<sup>168</sup> 10/16/01 email from E. Scolnick to D. Anstice, MRK-ABW0004799.

has testified that this reaction was prompted by the FDA's treatment of the gastrointestinal data from the VIGOR Trial and the addition of a cardiovascular warning.<sup>169</sup> Mr. Anstice, however, has testified that his own reaction was prompted by the FDA's treatment of the gastrointestinal data.<sup>170</sup>

According to Merck's mid-2001 financial projections, a cardiovascular warning would have led to significantly lower sales for Vioxx. The July 2001 U.S. Long Range Operating Plan for Merck's analgesic and anti-inflammatory drug franchise predicted that a cardiovascular warning in the Vioxx label could reduce projected sales by as much as 50% between 2002 and 2006.<sup>171</sup> Merck's worldwide Long Range Operating Plan for Vioxx and Arcoxia from the same month predicted a 10% drop in worldwide Vioxx sales by 2006 if the U.S. Vioxx label carried a cardiovascular warning.<sup>172</sup> Securities analysts also predicted that Merck's stock price would be negatively affected if the FDA required "tougher" cautionary language regarding cardiovascular risk in the Vioxx label than in the Celebrex label.<sup>173</sup> Ms. Judy Lewent, Chief Financial Officer of Merck, has stated that

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<sup>169</sup> 6/1/05 deposition of E. Scolnick at 798-801 (In re Vioxx Litig., No. 619, N.J. Super. Ct.) ("My remarks were related to the warning and the lack of what I believed was the appropriate description of the GI safety data.").

<sup>170</sup> 3/16/05 deposition of D. Anstice at 82-83 (In re Vioxx Litig., No. 619, N.J. Super. Ct.); 4/12/05 deposition of D. Anstice at 86-87 (In re Vioxx Litig., No. 619, N.J. Super. Ct.); 5/20/05 deposition of D. Anstice at 1431-32 (In re Vioxx Litig., No. 619, N.J. Super. Ct).

<sup>171</sup> 7/01 slide presentation, "U.S. Long Range Operating Plan; Franchise: Analgesic & Anti-Inflammatory; Products: Vioxx®, Etoricoxib," MRK-ABI0008659, at 74.

<sup>172</sup> 7/01 slide presentation, "Long Range Operating Plan: 2001 – 2006," MRK-ADM0003846, at 56 (noting also that in the event of "CV Class label to warning section in the US," the estimated drop in worldwide sales was 8%).

<sup>173</sup> 12/10/01 email from L. Newcomb to L. Friedman, MRK-NJ0438693 (forwarding 12/10/01 J.P. Morgan Securities Inc. Equity Research).

the Company had to adjust its earnings projections downward in mid-2001 because of negative press coverage concerning the cardiovascular safety of Vioxx.

Members of the Worldwide Product Circular Review Committee began preparing Merck's response to the FDA's October 15, 2001 label proposal, with the goal of replying to the FDA by the following Monday, October 22, 2001.<sup>174</sup> (Merck's response was submitted on November 6.<sup>175</sup>) An internal slide presentation prepared by Dr. Braunstein summarized Merck's reactions to the FDA's counterproposal.<sup>176</sup> The presentation stated that the FDA's proposed presentation of the VIGOR Trial data "[o]bscure[d]" the VIGOR Trial's focus on gastrointestinal results.<sup>177</sup> Dr. Braunstein also noted that the FDA's October 15 label proposal:

- included myocardial infarction data alone from ADVANTAGE (although patients on Vioxx in that trial had experienced fewer strokes and serious thrombotic events overall than those on naproxen),<sup>178</sup>
- omitted cardiovascular data from other studies; and

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<sup>174</sup> 10/15/01 email from R. Silverman to D. Blois, A. Nies *et al.*, MRK-AAX0008560.

<sup>175</sup> 11/6/01 letter from R. Silverman to J. Bull\*, MRK-01420163697 (attaching MRL 11/6/01 draft).

<sup>176</sup> Slide presentation of N. Braunstein, "FDA's VIGOR Label," MRK-ACD0068340; 11/19/04 deposition of R. Silverman at 175 (*In re Vioxx Litig.*, No 619, N.J. Super. Ct.) (testifying that the presentation was prepared by Dr. Braunstein). Mr. Anstice has testified that "there was broad frustration" at Merck because of the label's representation of the gastrointestinal safety data. 04/12/05 deposition of D. Anstice at 82-89 (*In re Vioxx Litig.*, No 619, N.J. Super. Ct.).

<sup>177</sup> Slide presentation of N. Braunstein, "FDA's VIGOR Label," MRK-ACD0068340, at 40-41.

<sup>178</sup> See ADVANTAGE Clinical Study Report, MRK-AFV0154893, at 992.

- included “additional unique highlighting of ‘NSAID class’ safety issues” such as renal disease, hypertension, edema, and congestive heart failure.<sup>179</sup>

The Worldwide Product Circular Review Committee recommended that Merck “flatly reject” the October 15 draft’s comparison of overall safety events in the Vioxx and naproxen treatment groups as “inappropriate” and “unprecedented.”<sup>180</sup>

2. Merck’s November 6, 2001 Response.

On November 6, 2001, Dr. Silverman submitted Merck’s response and revised draft label to Dr. Bull\* at the FDA’s Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products.<sup>181</sup> The cover letter to the November 6, 2001 submission stated that “MRL strongly disagrees with FDA with respect to many labeling recommendations that seem inconsistent with previous conversations and meetings, inconsistent with the Advisory Committee meeting, and . . . unprecedented from a labeling and regulatory perspective.”<sup>182</sup> In particular, MRL found the FDA proposal’s departure from NSAID-class language on fluid retention, hypertension, and renal effects to be particularly inappropriate and inconsistent with the conclusions reached at the Advisory Committee meeting.<sup>183</sup>

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<sup>179</sup> Slide presentation of N. Braunstein, “FDA’s VIGOR Label,” MRK-ACD0068340, at 44.

<sup>180</sup> R. Silverman notes, MRK-ACD0118959, at 59.

<sup>181</sup> 11/06/01 letter from R. Silverman to J. Bull\* attaching MRL 11/06/01 draft label, MRK-01420163697, at 701.

<sup>182</sup> 11/06/01 letter from R. Silverman to J. Bull\* attaching MRL 11/06/01 draft label, MRK-01420163697, at 97.

<sup>183</sup> 11/06/01 letter from R. Silverman to J. Bull\* attaching MRL 11/06/01 draft label, MRK-01420163697, at 98.

Merck further described the FDA's proposal to present summaries of serious adverse experiences and discontinuations due to adverse experiences by body system for the VIGOR Trial as "unprecedented and scientifically questionable."<sup>184</sup> This was because the VIGOR Trial "was not designed as a general safety study but rather as a specific GI outcomes study in which a dose of Vioxx twice the maximum recommended dose for chronic administration was compared to a common clinical dose of naproxen."<sup>185</sup> In sum, MRL scientists believed that the labeling for Vioxx "should adhere to NSAID class labeling for the effects common to the class and should depart from class labeling only to the extent that there [was] specific information of clinical interest . . . For VIOXX, this would represent the GI data . . . and the thrombotic cardiovascular data which, although not definitive, present[ed] information of clinical interest."<sup>186</sup>

Merck's November 6 draft label differed from the FDA's October 15 proposal in several notable respects. First, the Company's revised draft transferred the discussion of cardiovascular adverse event data from the Warnings section of the label, where the FDA had placed it in its counterproposal, back to the Precautions section.<sup>187</sup> On November 8, 2001, Dr. Scolnick had sent an email to Drs. Greene and Goldmann telling

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<sup>184</sup> 11/06/01 letter from R. Silverman to J. Bull\* attaching MRL 11/06/01 draft label, MRK-01420163697, at 98.

<sup>185</sup> 11/06/01 letter from R. Silverman to J. Bull\* attaching MRL 11/06/01 draft label, MRK-01420163697, at 98.

<sup>186</sup> 11/06/01 letter from R. Silverman to J. Bull\* attaching MRL 11/06/01 draft label, MRK-01420163697, at 98.

<sup>187</sup> MRL 11/06/01 draft label showing revisions from FDA 10/15/01 draft label, MRK-ABT0002976, at 03000, 03003.

them that they would have to take a firm stand with FDA on the cardiac warning in the FDA's proposed label.<sup>188</sup> Dr. Scolnick wrote that he had taken a strong stand with the FDA against proposed warnings on two prior occasions, with Vasotec and Prilosec, and was successful both times:<sup>189</sup>

—Original Message—

**From:** Scolnick, Edward M.  
**Sent:** Thursday, November 08, 2001 8:31 AM  
**To:** Greene, Douglas Alan; Goldmann, Bonnie J  
**Cc:** Kim, Peter S  
**Subject:** History lesson  
**Importance:** High

Doug and Bonnie twice in my life I have had to say to the FDA " That label is unacceptable, we will not under any circumstances accept it." Once when they wanted a black box warning for angioedema in vasotec in 1985 and once in 1989 when Steve Fred wanted a warning about potential colon cancer in the prilosec label. You WILL have to do that on the cardiac warning for Vioxx. I assure you that you will . And i assure you i will NOT sign off on any lable 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/ Ed Scolnick

According to Dr. Scolnick, he and members of the Worldwide Product Circular Review Committee felt that that the VIGOR Trial cardiovascular data did not belong in the Warnings section because they believed that Warnings were for clear, unambiguous risks and that the significance of the VIGOR Trial cardiovascular data was unclear.<sup>190</sup> A warning, in their view, would have implied that Vioxx caused the increased cardiovascular events in the Vioxx arm of the VIGOR Trial, when in fact the reason for the between-treatment difference had not been established (although in their view the difference was most likely caused by the cardioprotective effect of naproxen). In

<sup>188</sup> 11/8/01 email from E. Scolnick to D. Greene and B. Goldmann, MRK-ACR0009287. The "data review" probably refers to the Alzheimer's trials data. See 11/07/01 email from E. Scolnick to A. Reicin, MRK-NJ0337634.

<sup>189</sup> 11/8/01 email from E. Scolnick to D. Greene and B. Goldmann, MRK-ACR009287.

<sup>190</sup> See 3/22/05 deposition of E. Scolnick at 162 (Ernst v. Merck & Co, No. 19961\*BH02, Brazoria Cty., TX).

Dr. Scolnick's view, including the data in the Precautions section, by contrast, would enable physicians to do their own risk/benefit analysis in prescribing the drug.

In his reply to Dr. Scolnick's November 8, 2001 email, Dr. Greene stated that a warning "concerning the use of Vioxx in patients with increased cardiac risk" was not supported by the data, but "[a]nother issue is where a balanced and objective DESCRIPTION of the cardiovascular data should appear in the label, as this could go in either precautions or in warnings section."<sup>191</sup> Dr. Scolnick responded that "data from all studies" were acceptable, but "perjorative [sic] words" were not.<sup>192</sup>

Second, the Company's November 6 draft eliminated the references to the naproxen cardioprotection hypothesis that Merck had included in prior proposals.<sup>193</sup> The FDA had expressed skepticism about this hypothesis in communications with Merck representatives. For example, notes taken by Dr. Silverman at an October 2001 meeting with FDA representatives reflect that Dr. Robert Temple\*, Associate Director for Medical Policy at the Center for Drug Evaluation and Research, showed a "lack of total enthusiasm for the Naproxen theory" and that the Agency had "serious concerns that Vioxx may have negative effects."<sup>194</sup> Dr. Silverman also reported what he described as a "very telling remark" by Dr. Bull\*: "When the discussion strayed toward how the

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<sup>191</sup> 11/8/01 email from D. Greene to E. Scolnick, MRK-ACR009287.

<sup>192</sup> 11/8/01 email from E. Scolnick to D. Greene, MRK-ACR009287.

<sup>193</sup> MRL 11/06/01 draft label showing revisions from FDA 10/15/01 draft label, MRK-ABT0002976, at 003.

<sup>194</sup> R. Silverman notes, MRK-ACD0118964, at 64.

alternative hypotheses for the VIGOR CV results might be presented in labeling, she interjected that the labeling will state the facts, not conjectures on mechanisms.”<sup>195</sup>

In view of the FDA’s skepticism about the naproxen cardioprotection hypothesis, Dr. Scolnick on November 1 emailed Ms. Karen Grosser of the labeling team, copying Drs. Kim and Greene, and stated: “We need a statement now that will be a substitute for what the FDA will not relent on i.e. the unknown about CV risks.”<sup>196</sup> Ms. Grosser responded with the following proposed sentence, drafted by Dr. Greene, to be added to the Precautions section:

The basis for the difference in cardiovascular event rates with VIOXX vs. naproxen observed in VIGOR, and the lack of such a difference between VIOXX and placebo or other NSAID comparators in other studies, is not understood.<sup>197</sup>

Merck representatives involved in the labeling negotiations stated that the decision to omit references to the naproxen cardioprotection hypothesis arose out of a desire to advance label negotiations rather than a change in internal opinions about the validity of the theory.

Merck also stated in its November 6, 2001 cover letter that it had adopted the February 2001 FDA Advisory Committee’s view that “the cardiovascular data should be

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<sup>195</sup> R. Silverman notes, MRK-ACD0118964, at 65-66.

<sup>196</sup> 11/1/01 email from E. Scolnick to K. Grosser, MRK-ABH0020144.

<sup>197</sup> 11/1/01 email from K. Grosser to E. Scolnick, MRK-ABH0020143; MRL 11/06/01 draft label showing revisions from FDA 10/15/01 draft label, MRK-ABT0002976, at 003.

presented in the label for prescribers to interpret, rather than providing a conclusion.”<sup>198</sup>

The cover letter noted that, because the VIGOR Trial cardiovascular data “comprise only a fraction of the total cardiovascular safety data available for Vioxx,” cardiovascular data from the ADVANTAGE Trial, the eight Phase IIb/III osteoarthritis studies, and the Alzheimer’s disease trials should also be included.<sup>199</sup>

In comments submitted with the draft label, the Company stated that it opposed re-introducing the aspirin-indicated subgroup analysis because final adjudicated cardiovascular data – which Merck had submitted to the Agency on October 13, 2000 in the VIGOR Safety Update Report – “demonstrate that the relative risk of an event for rofecoxib relative to naproxen is not statistically different between the aspirin-indicated and aspirin-not-indicated sub-populations.”<sup>200</sup>

3. November 28, 2001 Medical Officer Review.

On November 28, 2001, FDA reviewer Dr. Maria Lourdes Villalba\* completed a review of Merck’s response to the April 2001 approvable letter, including the complete report of the ADVANTAGE Trial, the safety update report, safety data from rheumatoid arthritis trials and other data requested by the FDA.<sup>201</sup> Dr. Villalba\* recommended that Merck’s application be approved but stated, that “[u]ntil prospective, randomized, adequately powered studies are performed, rofecoxib should be used with caution in

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<sup>198</sup> 11/6/01 letter from R. Silverman to J. Bull\*, MRK-01420163697, at 99 (attaching MRL’s 11/06/01 draft).

<sup>199</sup> 11/6/01 letter from R. Silverman to J. Bull\*, MRK-01420163697, at 99.

<sup>200</sup> MRL 11/06/01 draft label showing revisions from FDA 10/15/01 draft label, MRK-ABT0002976, at 989-90.

<sup>201</sup> 11/28/01 Medical Officer Review by M.L. Villalba\*, MRK-PUBLIC0002375.

patients with known cardiovascular risk, congestive heart failure and hypertension.”<sup>202</sup>

Dr. Villalba’s\* review found that in the ADVANTAGE Trial, “[c]onsistent with VIGOR, there was a trend of excess in serious cardiac thrombotic events” in the Vioxx group as compared to the naproxen group.<sup>203</sup> Dr. Villalba\* also stated that “[i]f the cardiovascular findings in VIGOR were all explained by naproxen anti-platelet effect, a difference would not be expected between naproxen and rofecoxib in ADVANTAGE, when patients at risk in both treatment groups were already maximally protected by ASA.”<sup>204</sup>

With respect to the safety data, Dr. Villalba\* found that “[t]here is no adequate evidence that rofecoxib has a cardiovascular safety profile similar to placebo or other NSAIDs.”<sup>205</sup> Specifically, Dr. Villalba\* stated that pooled analyses of small studies of different duration, size and design comparing Vioxx to other NSAIDs “can not adequately assess the cardiovascular safety” of Vioxx.<sup>206</sup> The Alzheimer’s disease trials, according to Dr. Villalba\*, provided useful data because of their longer duration (one year), but “were not powered to detect differences in cardiovascular safety between rofecoxib and placebo.”<sup>207</sup> Dr. Villalba\* concluded that, considered as a whole, the data from the ADVANTAGE Trial, the safety update report, and rheumatoid arthritis

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<sup>202</sup> 11/28/01 Medical Officer Review by M.L. Villalba\*, MRK-PUBLIC0002375, at 378.

<sup>203</sup> 11/28/01 Medical Officer Review by M.L. Villalba\*, MRK-PUBLIC0002375, at 383.

<sup>204</sup> 11/28/01 Medical Officer Review by M.L. Villalba\*, MRK-PUBLIC0002375, at 384.

<sup>205</sup> 11/28/01 Medical Officer Review by M.L. Villalba\*, MRK-PUBLIC0002375, at 384.

<sup>206</sup> 11/28/01 Medical Officer Review by M.L. Villalba\*, MRK-PUBLIC0002375, at 385.

<sup>207</sup> 11/28/01 Medical Officer Review by M.L. Villalba\*, MRK-PUBLIC0002375, at 385.

databases “suggest an increased cardiovascular risk” in Vioxx as compared to naproxen.<sup>208</sup>

I. December 2001 Drafts.

1. Negotiation Procedures.

During a November 21, 2001 telephone conference between Dr. Silverman and Drs. Goldkind\*, Villalba\* and Gould\* of the FDA, Dr. Goldkind\* provided feedback on MRL’s November 6 draft and spoke about procedure for the post-VIGOR label negotiations going forward.<sup>209</sup> Dr. Goldkind\* previously had told Dr. Silverman that the FDA would be prepared to begin negotiations the week after receiving Merck’s response to the FDA’s October 15 draft.<sup>210</sup> On the November 21 call, however, Dr. Goldkind\* “requested that the sponsors reconsider their proposal in light of [the FDA’s] comments and resubmit a new proposal” and thus did not set a negotiating schedule.<sup>211</sup>

Dr. Goldkind\* raised a number of substantive areas of disagreement, including Merck’s proposal to include data from Protocol 069 and Merck’s contention that the NSAID template labeling with regard to hypertension and edema was sufficient for

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<sup>208</sup> 11/28/01 Medical Officer Review by M.L. Villalba\*, MRK-PUBLIC0002375, at 386-87.

<sup>209</sup> 12/5/01 memorandum from R. Silverman to J. Bull\*, MRK-AAF0004866; see also R. Silverman meeting notes, MRK-ACD0118964, at 66.

<sup>210</sup> R. Silverman meeting notes, MRK-ACD0118964, at 66.

<sup>211</sup> See FDA, “Sequence of Events with VIOXX, since opening of IND” at 3, [http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1\\_04\\_E-FDA-TAB-C.htm](http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_04_E-FDA-TAB-C.htm). (“In view of the extent of the lack of agreement a telecom was arranged with the sponsor and the division . . . requested that the sponsors reconsider their proposal in light of our comments and resubmit a new proposal.”)

Vioxx.<sup>212</sup> He did not object to Merck's proposal to move the language regarding cardiovascular issues from the Warnings section to the Precautions section.<sup>213</sup>

Dr. Goldkind\* suggested that to expedite the process, Merck should reconsider its November 6 proposal and submit a new draft label prior to beginning formal negotiations during the week of December 17, 2001.<sup>214</sup>

2. December 5, 2001 Draft.

Merck submitted a revised label proposal on December 5, 2001.<sup>215</sup> The November 6, 2001 draft and December 5, 2001 draft differed principally in three respects.<sup>216</sup> Most significantly, Merck's December 5, 2001 draft added a statement in the Dosage and Administration section of the label that "Chronic use of VIOXX 50 mg daily is not recommended."<sup>217</sup> The FDA had requested this language out of concern that patients seeking faster or stronger pain relief would increase the dosage and perhaps even exceed the maximum prescribed dosage – a phenomenon known as "dosage creep."<sup>218</sup>

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<sup>212</sup> The template language for NSAID labels includes the following text in the Precautions section: "Fluid retention and edema have been observed in some patients taking NSAIDs. Therefore as with other NSAIDs, TRADENAME should be used with caution in patients with fluid retention, hypertension, or heart failure." Proposed NSAID Package Insert Labeling Template (Revised 12/19/96), [http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1\\_03\\_D-FDA-TAB-B.pdf](http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_03_D-FDA-TAB-B.pdf).

<sup>213</sup> 11/21/01 notes of R. Silverman, MRK-ACD0118947, at 950, 952.

<sup>214</sup> 11/21/01 notes of R. Silverman, MRK-ACD0118947.

<sup>215</sup> 12/5/01 letter from R. Silverman to J. Bull\*, MRK-AAF0004866.

<sup>216</sup> 12/5/01 letter from R. Silverman to J. Bull\*, MRK-AAF0004866; 11/6/01 draft label, MRK-ABT0002976 and 12/5/01 draft, MRK-AFZ0002671; see also 12/5/01 email from D. Chitty to D. Benezra-Kurshan et al., MRK-ABS0342587 (noting the changes made to the 11/6/01 draft).

<sup>217</sup> MRL 12/5/01 draft showing revisions from 10/15/01 draft label, MRK-ADM0093198, at 238.

<sup>218</sup> 12/5/01 VP Approval form summarizing changes to label, MRK-ACD0018353; Notes on FDA's comments to MRL's 11/6/01 label draft, MRK-AAF0004852. As mentioned in Appendix D, the

Merck's December 5, 2001 submission made two other minor changes from the previous draft. First, it "slightly reworded" the "Geriatric Use" section under "Precautions" to "de-emphasize any safety comparison between Protocol 058 and other protocols."<sup>219</sup> Second, the December 5, 2001 draft reinstated the FDA's proposed language in the "Information for Patients" section: "Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding."<sup>220</sup>

3. Evolution of Cardiovascular Precautions Language: December 2001.

The FDA submitted a responsive label draft on December 21, 2001.<sup>221</sup> The parties' respective proposals with regard to the cardiovascular Precaution are excerpted below.

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decision to use 50 mg dose in the VIGOR Trial was prompted by the FDA's desire to test the drug at a higher dose in part because of concerns about dosage creep.

<sup>219</sup> Compare 11/6/01 draft label, MRK-ABT0002976, at 3009, and 12/5/01 draft label, MRK-AFZ0002671, at 2706; see also 12/5/01 VP Approval form summarizing changes to label, MRK-ACD0018353. Protocol 058 was one of the eight Phase IIb/III osteoarthritis studies, was performed elderly patients, and allowed the use of low dose aspirin.

<sup>220</sup> Compare 11/6/01 draft label, MRK-ABT0002976, at 3005, with 12/5/01 draft label, MRK-AFZ0002671, at 2702.

<sup>221</sup> 12/21/01 facsimile from B. Gould\* to R. Silverman, MRK-AAF0005071 (attaching FDA 12/21/01 draft label).

<p><b>Merck December 5, 2001 Draft Precaution</b><sup>222</sup></p> <p>The risk of developing a serious cardiovascular thrombotic event in the VIGOR study was significantly different in patients treated with VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA) as compared to patients treated with Naproxen 500 mg twice daily (common therapeutic dose). This was largely due to the significant difference in the incidence of myocardial infarction between patients taking Vioxx 50 mg once daily (.5%) and naproxen 500 mg twice daily (.1%). (See CLINICAL STUDIES, Special Studies, VIGOR.)</p> <p>In all other controlled clinical trials, the incidence of all serious cardiovascular thrombotic events, including myocardial infarction, was similar between VIOXX and placebo and between VIOXX and the nonselective NSAID comparators studied (ibuprofen, diclofenac and nabumetone). The basis for the difference in cardiovascular event rates with VIOXX versus naproxen observed in VIGOR, and the lack of such a difference between VIOXX and placebo or other NSAID comparators in other studies, is not understood. Prospective, well powered, long term studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators or placebo have not been performed.</p> <p>Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. While low dose aspirin may be used concomitantly with VIOXX, such concomitant use may result in an increased rate of GI ulceration or other complications, compared to the use of VIOXX alone. (See CLINICAL STUDIES, Special Studies, Use with Aspirin and Platelets, PRECAUTIONS, Drug Interactions, Aspirin.)</p>	<p><b>FDA December 21, 2001 Draft Precaution</b><sup>223</sup></p> <p>In the VIGOR study there was a statistically significant higher incidence of cardiovascular thrombotic events associated with the use of VIOXX 50 mg daily compared to naproxen 1000 mg daily (See Special Studies, VIGOR). The difference was largely due to the significantly higher incidence of myocardial infarction in patients taking VIOXX 50 mg compared to naproxen. (See Special studies, VIGOR.) The relative risk was even higher in the subgroup of patients retrospectively identified as having one or more indications for cardiovascular prophylaxis with aspirin.</p> <p>The finding was consistent in a smaller and shorter study that showed five myocardial infarctions in the VIOXX 25mg group compared to one myocardial infarction in the naproxen group. (See Special Studies, ADVANTAGE). Prospective, well powered, long term studies required to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators other than naproxen or placebo have not been performed.</p> <p>Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. The impact of VIOXX on the cardiovascular prophylactic benefit of ASA is unknown. (See Special Studies, Platelets: PRECAUTIONS, Drug Interactions, Aspirin). VIOXX should be used with caution in patients at risk of developing cardiovascular thrombotic events such as those with a history of myocardial infarction and angina, and in patients with pre-existent hypertension and congestive heart failure.</p>
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<sup>222</sup> FDA 12/21/01 draft label showing revisions from previous draft, MRK-AFZ0002671, at 700.

<sup>223</sup> FDA 12/21/01 draft label, MRK-AAF0005072, at 085.

In its December 21 label proposal (excerpted above), the FDA placed the discussion of cardiovascular risk in the Precautions section, where Merck's December 5 draft had placed it.<sup>224</sup> Although the discussion of cardiovascular events remained in Precautions throughout the remainder of the label negotiations, the FDA's December 21 draft made a number of changes to the description of that data. For example, the FDA:

- Moved the discussion of cardiovascular events to the top of the Precautions list;
- Characterized the between-treatment difference in cardiovascular events in the VIGOR Trial as a “significantly higher incidence” in the Vioxx group, while Merck had described it as a “significant difference”;
- Deleted Merck's statement that “all other controlled clinical trials” showed similar rates of serious cardiovascular events between Vioxx and placebo or comparator NSAIDs, as well as Merck's statement that the reason for the difference in cardiovascular event rates in the VIGOR Trial was “not understood”;<sup>225</sup>
- Reintroduced the aspirin-indicated subgroup analysis in the Clinical Studies section (stating that patients “retrospectively identified as having one or more indications for cardiovascular prophylaxis with aspirin” had a higher risk of heart attack in the VIGOR Trial);<sup>226</sup>
- Cited myocardial infarction data from the ADVANTAGE Trial, which showed five heart attacks in the Vioxx group compared to one in the naproxen group;

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<sup>224</sup> FDA 12/21/01 draft label, showing revisions from previous draft, MRK-AFZ0002671, at 697.

<sup>225</sup> Similar language would reappear in the final label. See 4/11/02 approved Vioxx product label, MRK-ABT0015889, at 97.

<sup>226</sup> The FDA's draft also reintroduced the aspirin-indicated subgroup analysis in the Clinical Studies section. FDA 12/21/01 draft label, MRK-AAF0005072, at 078.

- Deleted references to use of Vioxx with aspirin and stated that Vioxx should be used with caution in patients at risk for cardiovascular thrombotic events as well as those with “pre-existent hypertension and congestive heart failure.”

J. January 2002 Negotiations.

On January 7, 2002, Merck submitted a revised label responding to the FDA’s December 21 proposal.<sup>227</sup> The FDA submitted another draft to Merck on January 29, 2002.<sup>228</sup> Merck and the FDA held teleconferences to discuss the drafts on January 30 and February 8, 2002.<sup>229</sup> The parties’ label proposals and negotiations are discussed below.

1. Merck’s January 7, 2002 Draft Label.

a. Gastrointestinal data.

In its January 7 proposal, Merck proposed adding to the gastrointestinal Warning a discussion of the results of upper gastrointestinal endoscopy studies that had demonstrated a reduction in gastroduodenal ulcers in patients taking Vioxx as compared to comparator NSAIDs, with the following introductory statement: “Although the risk of GI toxicity is not completely eliminated with VIOXX, the results of the VIOXX GI outcomes research (VIGOR) study and of the upper GI endoscopy studies in

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<sup>227</sup> 1/7/02 letter from R. Silverman to J. Bull\*, MRK-AAF0005183 (attaching MRL 1/7/02 draft label).

<sup>228</sup> 1/29/02 facsimile from B. Gould\* to R. Silverman, MRK-AAF0005350 (attaching FDA 1/29/02 draft).

<sup>229</sup> Minutes of 1/30/02 MRL/FDA teleconference, MRK-AAF0008509; minutes of 2/8/02 MRL/FDA teleconference, MRK-AAF008513.

[osteoarthritis] and [rheumatoid arthritis] patients show that the risk of GI toxicity for VIOXX is significantly less than for naproxen or ibuprofen.”<sup>230</sup>

b. Cardiovascular data.

(i) Cardiovascular data from trials other than VIGOR.

In its January 7 proposal, as well as at the January 30 teleconference, Merck proposed including references to cardiovascular data from the ongoing placebo-controlled Alzheimer’s trials and the pooled Phase IIb/III osteoarthritis studies.<sup>231</sup>

The FDA rejected these proposals for the following reasons:

- The Agency objected to inclusion of the Alzheimer’s disease trials prior to their completion and suggested that Merck submit the data as a labeling supplement once the trials were complete.<sup>232</sup>
- With respect to pooled osteoarthritis data, the FDA stated that pooled analyses of studies of varying duration, dose and indication are “inherently difficult to interpret” and maintained that “the level of confidence with meta-analysis does not rise to the level of a prospectively designed, well-controlled, study of adequate duration, and size for a given dose.”<sup>233</sup>
- The FDA again rejected Merck’s proposal to include cardiovascular data from Phase IIb/III studies on the

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<sup>230</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346420, at 446.

<sup>231</sup> FDA 12/21/01 draft label with MRL proposals, MRK-ABS0346473, 5515, 6517; minutes of 1/30/02 MRL/FDA teleconference, MRK-AAF0008509.

<sup>232</sup> Minutes of 1/30/02 MRL/FDA teleconference, MRK-AAF0008509, at 11.

<sup>233</sup> Minutes of 1/30/02 MRL/FDA teleconference, MRK-AAF0008509, at 11.

ground that those studies involved trials of different design,  
size and duration.<sup>234</sup>

(ii) Cardiovascular precaution.

The drafts of the cardiovascular precaution that Merck and the FDA exchanged in January in large part reflected the same disagreements as had the December drafts. Merck continued to propose references to cardiovascular data from clinical trials other than the VIGOR Trial that had shown no increased cardiovascular risk for Vioxx versus comparators. Merck also proposed that the VIGOR Trial cardiovascular data be described as having demonstrated a “significantly different . . . risk” between treatment groups in contrast to the FDA’s proposal of a “significantly higher incidence” on Vioxx.<sup>235</sup> Merck also proposed moving the discussion of the VIGOR Trial cardiovascular events from the Clinical Studies section (near the beginning of the label) to the Adverse Reactions section (near the end of the label), with the rationale that this section is “where prescribers will expect to find” general safety information.<sup>236</sup> Whereas the FDA continued to advocate for a cautionary statement extending to patients at risk for cardiovascular thrombotic events or with hypertension or congestive heart failure, Merck proposed the narrower statement that “[c]aution should be exercised in patients with a medical history of ischemic heart disease.”<sup>237</sup>

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<sup>234</sup> Minutes of 2/8/02 MRL/FDA teleconference, MRK-AAF008513, at 14.

<sup>235</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346473, at 6498.

<sup>236</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346473, at 483; 1/7/02 letter from R. Silverman to J. Bull\*, MRK-AAF0005183, at 84 (attaching MRL 1/07/02 draft label).

<sup>237</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346473, at 498.

In its January 7 proposal, Merck continued to oppose the inclusion of references to the aspirin-indicated subgroup analysis. Merck's internal comments on the FDA's December 21 draft included two rationales for the deletion of the subgroup analysis. First, a statistical test (called the subgroup interaction test) determined that the two subgroups - aspirin-indicated and non-aspirin-indicated - were not sufficiently different in terms of the Vioxx versus naproxen relative risk for thrombotic events to justify drawing any conclusions.<sup>238</sup> Second, because the VIGOR Trial protocol sought to exclude patients indicated for low-dose aspirin, study participants who fell into this category may not have been representative of aspirin-indicated patients in the general population.<sup>239</sup> Nonetheless, the FDA's January 29 draft maintained the aspirin-indicated subgroup analysis.<sup>240</sup>

c. Use of Vioxx with aspirin.

With regard to concomitant use of Vioxx and aspirin, Merck's January 7 draft proposed: (i) a description in the Clinical Studies section of the results of Protocols 058, 085, 090 and the ADVANTAGE Trial (on gastrointestinal impact of concomitant use of Vioxx plus aspirin) in the Clinical Studies section, and (ii) a statement in the Patient Information section that "Vioxx can be used concomitantly with low-dose aspirin."<sup>241</sup> In its notes to the FDA accompanying the proposed draft, Merck argued that "the experience

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<sup>238</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346420, at 432.

<sup>239</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346420, at 432.

<sup>240</sup> FDA 1/29/02 draft label, MRK-AAF0005353, at 356, 361.

<sup>241</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346473, at 494, 503.

of patients taking VIOXX concomitantly with aspirin has surpassed that noted in current labeling” for other NSAIDs.<sup>242</sup> During the February 8, 2002 teleconference, the FDA stated that the short-term studies (the six-week studies and the 12-week ADVANTAGE Trial) submitted by Merck were insufficient to establish safe co-administration of aspirin with Vioxx.<sup>243</sup> Merck’s January 7 draft and the FDA’s January 29 response are reproduced on the table below:

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<sup>242</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346473, at 494. For example, the Celebrex label stated that 440 of 4,000 patients enrolled in four of the five 12- to 24-week endoscopy studies were taking aspirin daily. 2001 approved Celebrex product label, MRK-AAF0007539, 548. The number of patients taking aspirin concomitantly with Vioxx in Protocols 058, 085, 090 and ADVANTAGE was 516. Id. at MRK-ABS0346494. The Celebrex label stated that “CELEBREX can be used with low-dose aspirin.” 2001 approved Celebrex product label, MRK-AAF0007539, 554.

<sup>243</sup> Minutes of 2/8/02 MRL/FDA teleconference, MRK-AAF008513, at 14.

<b>Merck January 7, 2002 Draft<sup>244</sup></b> <i>Cardiovascular Effects</i>	<b>FDA January 29, 2002 Draft<sup>245</sup></b> <i>Cardiovascular Effects</i>
<p>In the VIGOR study, the risk of developing a serious cardiovascular thrombotic event was significantly different in patients treated with VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA and RA) as compared to patients treated with naproxen 500 mg twice daily (common therapeutic dose). This was primarily due to the significant difference in the incidence of myocardial infarction between patients taking VIOXX 50 mg once daily (0.5%) and naproxen 500 mg twice daily (0.1%). (See CLINICAL STUDIES, Special Studies, VIGOR and ADVERSE REACTIONS, Cardiovascular Safety, RA Studies). In all other controlled clinical trials, the incidence of serious cardiovascular thrombotic events was similar between VIOXX and the nonselective NSAID comparators studied other than naproxen (ibuprofen, diclofenac, and nabumetone).</p> <p>NSAIDs that selectively inhibit COX-2 are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Because VIOXX, a member of this class, does not inhibit platelet aggregation, antiplatelet therapies should not be discontinued and if indicated should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events (see Clinical Studies, Special Studies, Platelets and PRECAUTIONS, Drug Interactions, Aspirin). Caution should be exercised in patients with a medical history of ischemic heart disease because of the pharmacodynamic profile of NSAIDs that selectively inhibit COX-2 as noted above.</p>	<p>In the VIGOR study, there was a statistically significant higher incidence of cardiovascular thrombotic events associated with the use of VIOXX 50 mg once daily (twice the recommended dose for OA and RA) compared to patients treated with naproxen 500 mg twice daily. The difference was largely due to the significantly higher incidence of non-fatal myocardial infarction in patients taking VIOXX 50 mg (n=17) compared to naproxen (n=0). The risk of cardiovascular thrombotic events in the VIOXX treated group was five-fold higher than naproxen in the subgroup of patients retrospectively identified as having one or more indications for aspirin prophylaxis. The risk was almost twice higher among those with no prior cardiovascular history in the VIOXX group, as compared to the naproxen group. (See CLINICAL STUDIES, Special Studies, VIGOR, Cardiovascular Safety.) The reason for this finding is unclear. Prospective, well-powered, long term studies required to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators other than naproxen or placebo have not been performed.</p> <p>Because of its lack of platelet effect, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. The impact of VIOXX on the cardiovascular prophylactic benefit of ASA is unknown. (See special studies, Platelets; PRECAUTIONS, Drug Interactions, Aspirin). VIOXX should be used with caution in patients at risk of developing cardiovascular thrombotic events such as those with a history of myocardial infarction and angina and in patients with pre-existent hypertension and congestive heart failure.</p>

<sup>244</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346473, at 498.

<sup>245</sup> FDA 1/29/02 draft label, MRK-AAF0005353, at 361.

d. Renal events.

In its January 7 draft label, Merck objected to the FDA's proposed references in the Warnings and Precautions sections to post-marketing incidences of renal failure, heart failure and edema, on the basis that the labels of other NSAIDs included this information in the less serious Adverse Reactions section of the label, as Merck had proposed.<sup>246</sup> Merck did, however, agree to include in the Precautions section references to higher incidences of hypertension in patients taking Vioxx as compared to naproxen in rheumatoid arthritis trials.<sup>247</sup>

The FDA's January 29 draft deleted references to post-marketing events of renal failure in the Warnings section as Merck had requested but preserved these references – as well as references to post-marketing events of congestive heart failure and edema – in the Precautions section.<sup>248</sup> At the February 8 teleconference, Merck again objected to including in the Precautions section references to post-marketing adverse events on the ground that this was a departure from the labeling of other NSAIDs.<sup>249</sup> The FDA ultimately agreed to delete the references to post-marketing events.

2. Cardiovascular Events Memorandum.

On January 21, 2002, Merck submitted to the FDA a memorandum summarizing “relevant pre-clinical, clinical pharmacology, epidemiologic and clinical trial data”

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<sup>246</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346473, at 497, 500.

<sup>247</sup> MRL 1/7/02 draft label showing revisions from 12/21/01 draft, MRK-ABS0346473, at 500.

<sup>248</sup> FDA 1/29/02 draft label, MRK-AAF0005353, at 361, 362.

<sup>249</sup> Minutes of 2/8/02 MRL/FDA teleconference, MRK-AAF008513, at 14.

concerning the cardiovascular effects of Vioxx.<sup>250</sup> Dr. Temple\* had expressed interest in a summary of these data in a conversation with Dr. Goldman.<sup>251</sup> The memorandum examined four different theories to explain the cardiovascular events in the VIGOR Trial: (i) a prothrombotic effect of selective Cox-2 inhibitors as a class; (ii) “[m]echanism-based” toxicity of Vioxx greater than other Cox-2 inhibitors caused by the degree of selectivity for Cox-2; (iii) “[m]olecule specific and non-mechanism-based toxicity” of Vioxx; and (iv) “[r]elative cardioprotective benefit of naproxen.”<sup>252</sup>

The memorandum concluded that the fourth theory was the “most plausible explanation . . . given the totality of available data.”<sup>253</sup> In a December 12, 2004 internal email, Dr. Braunstein wrote that the purpose of the memorandum was to “address specific counter arguments [by the FDA] about the interpretation of the data by setting up straw men and shooting [them] down.”<sup>254</sup>

K. February 2002 Drafts.

1. Drafts and Teleconference.

Merck responded to the FDA’s January 29 draft on February 15, 2002.<sup>255</sup> Among other things, Merck’s February 15 proposal reflected a number of changes to the

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<sup>250</sup> 1/21/02 letter from R. Silverman to J. Bull\*, MRK-02420000100.

<sup>251</sup> 1/21/02 letter from R. Silverman to J. Bull\*, MRK-02420000100, at 100.

<sup>252</sup> Cardiovascular events memorandum, MRK-ABA0020279.

<sup>253</sup> Cardiovascular events memorandum, MRK-ABA0020279, at 279.

<sup>254</sup> 12/12/04 email from N. Braunstein to J. Van Adelsberg et al., MRK-AFK0196588.

<sup>255</sup> See 2/19/02 email from D. Chitty to D. Altarac et al., MRK-AAZ0006721 (attaching copy of 2/15/02 draft label). Merck’s official submission of this draft was on February 19, 2002. See 2/19/02 letter from R. Silverman to L. Simon\*, MRK-ABS0323433.

cardiovascular Precautions language, including a description of cardiovascular events and mortality experience from the Alzheimer's disease trials.<sup>256</sup> The FDA and Merck held a teleconference on February 20 to discuss the draft.<sup>257</sup> Merck emailed proposed revisions addressing comments raised in the teleconference on February 25, 2002.<sup>258</sup> That day, Dr. Scolnick emailed Drs. Goldmann, Greene, and Kim that the latest Merck proposal was "just plain terrific" and that it would be a "miracle" if the FDA approved it.<sup>259</sup>

## 2. Gastrointestinal Data.

In the February 15 draft, Merck agreed to delete from the gastrointestinal Warning its detailed descriptions of gastrointestinal outcomes in the VIGOR Trial and the endoscopy studies and instead proposed adding just two sentences to the existing

Warning:

Although the risk of GI toxicity is not completely eliminated with VIOXX, the results of the VIOXX GI outcomes research (VIGOR) study in RA patients showed that the risk of GI toxicity with VIOXX 50 mg once daily was significantly less than with naproxen 500 mg twice daily . . . Similar results have been seen in OA patients.<sup>260</sup>

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<sup>256</sup> MRL 2/15/02 draft showing revisions from 1/29/02 draft, MRK-AAZ0006722, at 742. Merck updated proposed cardiovascular Precaution language in a February 20, 2002 email to the FDA. 2/20/02 email from R. Silverman to B. Gould\*, MRK-AAF0005536, at 37.

<sup>257</sup> Minutes of 2/20/02 MRL/FDA teleconference, Plaintiff Exhibit 1198 in Ernst v. Merck & Co. (No. 19961\*BH02, Tex. Dist. Ct.).

<sup>258</sup> 2/25/02 email from R. Silverman to B. Gould\*, MRK-AAF0005583 (attaching draft label); 2/25/02 draft label, MRK-ADM0042344.

<sup>259</sup> 2/25/02 email from E. Scolnick to B. Goldmann, D. Greene, P. Kim, MRK-ACR0009297.

<sup>260</sup> MRL 2/15/02 draft showing revisions from 1/29/02 draft, MRK-AAZ0006722, at 739.

The FDA objected to the second sentence, and Merck deleted it in its proposed

February 25 draft.

3. Cardiovascular Data.

In the February 15 draft, Merck made several changes to the format of the cardiovascular precaution from the FDA's January 29 proposal:

- Merck added a sentence stating that the mortality rates in the VIGOR Trial were similar between the Vioxx and naproxen groups.
- Merck added cardiovascular data from the Alzheimer's disease trials in the text of the precaution.<sup>261</sup> A comparison of the February 15 draft with the approved label text is shown below:

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<sup>261</sup> In its February 25 draft, Merck agreed to revise the discussion of the Alzheimer's trials to include references to Protocols 078 and 091 only. MRL 2/15/02 draft label with revisions based on 2/20/02 MRL/FDA teleconference, MRK-AAF0006094, 6116. At the February 20 teleconference, the FDA had objected to the inclusion of Protocol 126 because it was prematurely terminated and to Protocol 078 because it was still ongoing and blinded, but later agreed to allow inclusion of Protocol 078. Minutes of 2/20/02 MRL/FDA teleconference, Plaintiff Exhibit 1198 in Ernst v. Merck & Co. (No. 19961\*BH02, Tex. Dist. Ct.).

<b>Merck February 15, 2002 Draft<sup>262</sup></b>	<b>Final April 11, 2002 Label<sup>263</sup></b>
<p><i>Cardiovascular Effects</i></p> <p>In the VIGOR study, the risk of developing a serious cardiovascular thrombotic event was significantly higher in patients treated with VIOXX 50 mg once daily as compared to patients treated with naproxen 500 mg twice daily.</p> <p>In VIGOR, cardiovascular mortality was similar between the treatment groups. (See CLINICAL STUDIES, <i>Special Studies, VIGOR, Cardiovascular Safety.</i>)</p> <p>In a placebo-controlled trials database derived from 3 studies in elderly patients with a mean duration of exposure of 1 year, serious cardiovascular thrombotic events and cardiovascular mortality were similar between patients treated with VIOXX 25 mg once daily and placebo (serious cardiovascular thrombotic events 25 vs. 39; cardiovascular mortality 10 vs. 6, VIOXX vs. placebo, respectively)</p> <p style="text-align: center;">* * *</p>	<p><i>Cardiovascular Effects</i></p> <p>The information below should be taken into consideration and caution should be exercised when VIOXX is used in patients with a medical history of ischemic heart disease.</p> <p>In VIGOR, a study in 8076 patients (mean age 58; VIOXX n=4047, naproxen n=4029) with a median duration of exposure of 9 months, the risk of developing a serious cardiovascular thrombotic event was significantly higher in patients treated with VIOXX 50 mg once daily (n=45) as compared to patients treated with naproxen 500 mg twice daily (n=19).</p> <p>In VIGOR, mortality due to cardiovascular events (7 vs. 6, VIOXX vs. naproxen respectively) was similar between the treatment groups. (See CLINICAL STUDIES, <i>Special Studies, VIGOR, Other Safety Findings: Cardiovascular Safety.</i>)</p> <p>In a placebo-controlled database derived from 2 studies with a total of 2142 elderly patients (mean age 75; VIOXX n=1067, placebo n=1075) with a median duration of exposure of approximately 14 months, the number of patients with serious cardiovascular thrombotic events was 21 vs. 35 for patients treated with VIOXX 25 mg once daily versus placebo, respectively. In these same 2 placebo-controlled studies, mortality due to cardiovascular thrombotic events was 8 vs. 3 for VIOXX versus placebo, respectively. The significance of the cardiovascular findings from these 3 studies (VIGOR and 2 placebo-controlled studies) is unknown. * * *</p>

In the February 15 draft, Merck again omitted all references to the aspirin-indicated subgroup analysis in the Precautions and Clinical Studies sections of the

<sup>262</sup> As revised in 2/20/02 email from R. Silverman to B. Gould\*, MRK-AAF0005536, at 37-38.

<sup>263</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 36.

label.<sup>264</sup> The FDA ultimately agreed to exclude discussion of the aspirin-indicated subgroup, and the analysis did not appear in the final label.<sup>265</sup>

L. Display of Cardiovascular Data.

The main point of contention in the last month of label negotiations concerned the question of whether the risk of cardiovascular events – *i.e.*, the “hazard ratio” – in the VIGOR Trial increased over time and should be presented as such on the label. In March 2002, the FDA proposed including in the label a Kaplan-Meier curve to illustrate the rate of cardiovascular events at different temporal intervals in the VIGOR Trial. As explained in Appendix E, a Kaplan-Meier plot records the cumulative incidence rate of an event over time – *i.e.*, the number of events divided by the number of study participants during that period. Merck had included a Kaplan-Meier plot of serious cardiovascular events in the VIGOR Trial with its initial submission of VIGOR Trial data to the FDA in March 2000,<sup>266</sup> and in the supplemental New Drug Application submitted to the FDA on June 29, 2000,<sup>267</sup> but not in the proposed label submitted with supplemental New Drug Application.<sup>268</sup>

As discussed in Appendices E and I, in the Kaplan-Meier plot of serious adverse cardiovascular experiences in the VIGOR Trial prepared by Merck in March 2000 (and

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<sup>264</sup> As revised in 2/20/02 email from R. Silverman to B. Gould\*, MRK-AAF0005536, at 37-38.

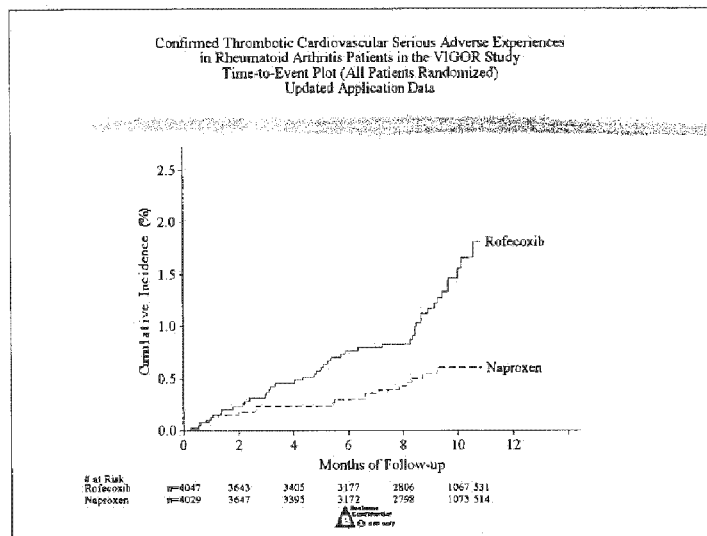
<sup>265</sup> 4/11/02 approved Vioxx product label, MRK-ABT0015886, at 897.

<sup>266</sup> 3/23/00 preliminary VIGOR report to FDA, MRK-ABD0001909, at 919 (attached to 3/23/00 email from G. Noonan to D. Blois, MRK-ABD0001894).

<sup>267</sup> 6/29/00 sNDA Cardiovascular Events Analysis, MRK-00420018004, 8030.

<sup>268</sup> MRL 6/30/00 draft label, MRK-00420008089.

reproduced below), the curves for the naproxen and Vioxx groups appeared to separate in the latter months of the study and to separate dramatically after the eighth month of treatment. This suggested that risk of a cardiovascular event might have increased with longer exposure to Vioxx.



The significance of the visual separation was not entirely clear, however, given the small number of events at issue toward the end of the study, when the patient population was smaller.<sup>269</sup>

Merck’s representatives at the label negotiations argued that the step increase in cardiovascular events depicted in the Kaplan-Meier curve after the eighth month of treatment was an optical effect not supported by the data, and Merck proposed instead that the cardiovascular events should be presented in a chart of events per 100 patient

<sup>269</sup> Thus, on 3/23/00, Dr. George Williams stated to Dr. Reicin that the “numbers [in the VIGOR Trial] are small, and we may be overinterpreting fluctuations in the curves.” 3/23/00 email from G. Williams to A. Reicin, MRK-ABT0022799.

years, a format that assumes a constant hazard ratio across time. The following section summarizes the parties' negotiations regarding this issue.

1. Analysis of Hazard Ratio Prior to Label Negotiations.

a. February 2001 Advisory Committee Meeting.

As discussed in Appendix I, at the February 8, 2001 Advisory Committee meeting, FDA statisticians suggested that the hazard ratio for cardiovascular events in the VIGOR Trial may have increased over time. As part of a presentation on statistical issues relating to MRL's cardiovascular meta-analysis, FDA statistician Dr. Qian Li\* noted that the VIGOR Trial time-to-event curves for cardiovascular events "start[ed] to diverge at six weeks . . . and . . . further separated after the treatment."<sup>270</sup> According to Dr. Li\*, this suggested that "the risk ratio [for Vioxx 50 mg versus naproxen 1000 mg was] not constant over time."<sup>271</sup>

Several external experts challenged this suggestion during the question and answer portion of the meeting. Dr. Nissen\* asked "how much confidence the [FDA] reviewers" had that the apparent inflection point in cardiovascular event data beginning at eight months was "a real phenomenon as opposed to just sort of an anomaly of the statistics."<sup>272</sup> Dr. Scott Zeger\*, Chair of the Department of Biostatistics at Johns Hopkins University and a consultant for Merck, stated that he had reviewed the data himself and

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<sup>270</sup> Transcript of the 2/8/01 Arthritis Advisory Committee meeting, MRK-AAF0003438, at 3552.

<sup>271</sup> Transcript of the 2/8/01 Arthritis Advisory Committee meeting, MRK-AAF0003438, at 3552.

<sup>272</sup> Transcript of the 2/8/01 Arthritis Advisory Committee meeting, MRK-AAF0003438, at 3572.

found “no evidence that there [was] a meaningful change” over time in hazard ratio.<sup>273</sup>

By contrast, FDA statistician Dr. Stan Lim\* stated that the analysis of data six months or longer did suggest an increased cardiovascular risk over time, although noting that the FDA had not looked into this issue in depth.<sup>274</sup>

Dr. Zeger\* agreed that the data were inconclusive:<sup>275</sup>

DR. ZEGGER: I just wanted to make the point that I was not saying this proves that there is no change. I was just trying to be responsive to the question. Is there strong evidence in the data of a change, and my answer to that is no.

Following this exchange, Dr. Frank Harrell\*, a consultant to the advisory committee, suggested the following<sup>276</sup>:

DR. HARRELL: On that point, I think if today and yesterday we never saw a single point estimate or a single p value or a single power calculation but only saw confidence intervals we would be so much better off than we are right now. But on this particular graph what we need to see is a confidence band for the hazards ratio over time. It is a real easy graph to make and I hope somebody has made it.

Merck held a follow-up consultation with Dr. Harrell\* on March 4, 2001 to discuss performing additional analyses of the hazard ratio.<sup>277</sup>

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<sup>273</sup> Transcript of the 2/8/01 Arthritis Advisory Committee meeting, MRK-AAF0003438, at 3573.

<sup>274</sup> Transcript of the 2/8/01 Arthritis Advisory Committee meeting, MRK-AAF0003438, at 3576.

<sup>275</sup> Transcript of the 2/8/01 Arthritis Advisory Committee meeting, MRK-AAF0003438, at 3576.

<sup>276</sup> Transcript of the 2/8/01 Arthritis Advisory Committee meeting, MRK-AAF0003438, at 3576-577.

b. Analysis by Drs. Shapiro and Mukhopadhyay.

Drs. Shapiro and Mukhopadhyay conducted three separate statistical analyses, including one recommended by Dr. Harrell\*, regarding the hazard ratio. They concluded that, while Kaplan-Meier plots gave the appearance of an increased rate of cardiovascular events after eight months, their analyses “consistently suggested that there was not any strong evidence” to suggest a change in hazard ratio over time for confirmed thrombotic cardiovascular events.<sup>278</sup>

Drs. Shapiro and Mukhopadhyay suggested an alternative explanation for the apparent spike in the Vioxx hazard ratio at the eight month mark of the VIGOR Trial Kaplan-Meier plot. A comparison of the risk of cardiovascular events between Vioxx and naproxen over the course of the VIGOR Trial favored naproxen from the beginning of the study up to month eight, but then briefly switched to favor Vioxx before switching back to favor naproxen.<sup>279</sup> One of Dr. Shapiro’s slides illustrating this change in the risk ratio is reproduced below (with Treatment Group “R” signifying rofecoxib, or Vioxx):<sup>280</sup>

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<sup>277</sup> 3/19/02 memorandum from D. Shapiro, S. Mukhopadhyay to R. Silverman, MRK-AFK0196692, at 92.

<sup>278</sup> 5/29/01 memorandum from D. Shapiro, S. Mukhopadhyay to R. Silverman and A. Reicin, MRK-NJ0203555, at 55.

<sup>279</sup> 5/29/01 memorandum from D. Shapiro, S. Mukhopadhyay to R. Silverman and A. Reicin, MRK-NJ0203555, at 56.

<sup>280</sup> 9/4/01 slide presentation of D. Shapiro to Research Management Committee, “Cardiovascular Hazard Rates,” MRK-NJ0203565, at 70.

**Events by Time Interval**

Interval	Tmt Grp	Cases	PYR	Rate	Risk Ratio (N/R)
Total	R	64	2695	2.37	
	N	32	2696	1.19	0.50
Mo. 1-2	R	12	648	1.85	
	N	9	648	1.39	0.75
Mo. 3-4	R	14	584	2.40	
	N	5	583	0.86	0.36
Mo. 5-6	R	11	545	2.02	
	N	5	544	0.92	0.46
Mo. 7-8	R	6	510	1.18	
	N	7	511	1.37	1.16
Mo. > 8	R	21	407	5.16	
	N	6	410	1.46	0.28

These data showed that at months five to six there were 11 cardiovascular events in the Vioxx group of the study and 5 cardiovascular events in the naproxen group. At months seven to eight, there were 6 events in the Vioxx group and 7 in the naproxen group. After month eight, there were 21 cardiovascular events in the Vioxx group and 6 in the naproxen group. When plotted on the Kaplan-Meier curve, this meant that the cumulative incidence rates converged before month eight, then diverged sharply. According to Drs. Shapiro and Mukhopadhyay’s analysis, this change in risk ratios gave the appearance of an increase in the hazard ratio, “when in fact the relative risk [was] merely returning to its previous level.”<sup>281</sup>

At her presentation to the Research Management Committee, Dr. Shapiro pointed out that, while the difference in event rates appeared “more extreme” after month eight,

<sup>281</sup> 5/29/01 memorandum from D. Shapiro, S. Mukhopadhyay to R. Silverman and A. Reicin, MRK-NJ0203555, at 556.

this was also an effect of the reduced number of study participants.<sup>282</sup> If three events were switched from the Vioxx group to the naproxen group, the risk ratio would be “almost identical” with the rate observed over the entire course of the study.<sup>283</sup> In a presentation to the biostatistics group a few weeks later, Dr. Shapiro stated that the members of the Research Management Committee “were unconvinced” by her explanation of the data and remained concerned about the appearance of the curves.<sup>284</sup>

c. Myocardial infarction hazard ratio.

MRL scientists also investigated whether the risk of myocardial infarction, as opposed to thrombotic events generally, increased over time in the VIGOR Trial. After the Research Management Committee presentation, Dr. Kenneth Truitt and Dr. Christopher Brett of the Clinical Sciences Department analyzed whether there was any difference in the types of cardiovascular events that occurred earlier, as opposed to later, in the VIGOR Trial.<sup>285</sup>

On September 27, 2001, Dr. Truitt circulated a draft memorandum regarding his analysis and noted in his cover email that, while his analysis did not show any difference in types of cardiovascular events that occurred early or late in the VIGOR Trial,

[i]n looking at the MIs (alone), one might conclude  
(correctly or incorrectly) that the risk increases over time,  
based on relatively constant numbers of events – even at

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<sup>282</sup> 9/4/01 slide presentation of D. Shapiro to Research Management Committee, “Cardiovascular Hazard Rates,” MRK-NJ0203565, at 70.

<sup>283</sup> 9/4/01 slide presentation of D. Shapiro to Research Management Committee, “Cardiovascular Hazard Rates,” MRK-NJ0203565, at 70.

<sup>284</sup> Slide presentation of D. Shapiro, “VIGOR – Review Lessons; New Results,” MRK-NJ0066164, 194.

<sup>285</sup> 9/27/01 draft memorandum from K. Truitt and C. Brett to “RMC Members,” MRK-ABH0001559.

longer exposures, corresponding to fewer patients. I do not bring this up in the memo but point it out here so we can be ready with a response, should someone bring up the issue.<sup>286</sup>

Dr. Mukhopadhyay proposed a meeting of Merck biostatisticians to “discuss whether there is any scientific merit to look at MI separately . . . or can we justify that there is not enough number of events to address each of them separately?”<sup>287</sup>

Dr. Capizzi responded that, regardless of the number of events at issue, since Dr. Mukhopadhyay had already determined that there was no evidence of an increased hazard ratio in overall cardiovascular events, there was no reason to do a separate analysis of myocardial infarctions “unless there is [a] sound clinical rationale why you would expect differential results among the components” of the global analysis.<sup>288</sup>

Dr. Oppenheimer agreed with Dr. Capizzi’s view and also stated that Dr. Truitt’s graphs were “deficient” because they did not include information regarding the number of study participants over time.<sup>289</sup>

Dr. Oppenheimer wrote to Dr. Truitt and Mr. Bolognese that Dr. Truitt should not “purposefully exclude the info of declining numbers at risk at later time points” and suggested “providing data (with patient [years] of exposure) broken down in 4 month blocks.”<sup>290</sup> Dr. Oppenheimer stated, however, that “the most relevant analysis for

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<sup>286</sup> 9/27/01 email from K. Truitt to B. Gertz et al., MRK-AFO0118946.

<sup>287</sup> 9/27/01 email from S. Mukhopadhyay to D. Shapiro, MRK-NJ0128029.

<sup>288</sup> 9/27/01 email from T. Capizzi to S. Mukhopadhyay, D. Shapiro, MRK-NJ0128028.

<sup>289</sup> 9/28/01 email from L. Oppenheimer to T. Capizzi et al., MRK-NJ0128028.

<sup>290</sup> 9/28/01 email from L. Oppenheimer to K. Truitt, MRK-AFO0119021.

addressing changes over time is to examine ALL EVENTS pooled” rather than analyzing specific cardiovascular events:

Once you start breaking this up into sub categories you need to take into account the following:

- nothing was seen overall thus is there a clinical/scientific rational to look at these sub-categories.

- the sub group analyses [sic] suffers from multiplicity and very small numbers of events.

- since we saw a slight trend in the over eight category (but not statistically compelling) we would expect some of the sub categories to be more extreme, some less extreme in the >8 month time interval.<sup>291</sup>

Dr. Truitt revised his memorandum as Dr. Oppenheimer had proposed, and included a table of specific cardiovascular event types in the VIGOR Trial by time intervals.<sup>292</sup>

With respect to myocardial infarctions, the table showed seven events at 0-4 months, five events at 4-8 months, and eight events at 8-12 months as reflected in Table 2 below:<sup>293</sup>

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<sup>291</sup> 9/28/01 email from L. Oppenheimer to K. Truitt, MRK-AFO0119021.

<sup>292</sup> 9/27/01 draft memorandum from C. Brett, K. Truitt to “RMC Members,” MRK-NJ0141263.

<sup>293</sup> 9/27/01 draft memorandum from C. Brett, K. Truitt to “RMC Members,” MRK-NJ0141263, at 264.

Table 2

Summary of Specific Cardiovascular Events in the VIGOR Trial,  
Categorized by Exposure Time (at Occurrence) and Treatment Group

	0 - 4 months		4 - 8 months		8 - 12 months	
	VIOXX	naproxen	VIOXX	naproxen	VIOXX	naproxen
Myocardial infarction	7	3	5	1	8	0
Unstable angina	4	2	1	0	0	1
Non-hemorrhagic stroke	3	3	4	4	3	1
TIAs	1	0	0	0	1	0
Hemorrhagic stroke	1	0	1	1	0	0
Peripheral thromboses	1	1	2	0	3	0
Sudden, unexplained death	1	1	1	1	1	3

Dr. Truitt also listed the number of patients in each treatment group at these time points, as reflected in Table 3:<sup>294</sup>

Table 3

Number of Patients in VIGOR Trial at Different Time Points

Month	Rofecoxib (N=4047)	Naproxen (N=4029)	Total (N=8076)
	n (%)	n (%)	n (%)
2	3645 (90.1)	3647 (90.5)	7292 (90.3)
4	3407 (84.2)	3395 (84.3)	6802 (84.2)
6	3181 (78.6)	3173 (78.8)	6354 (78.7)
8	2806 (69.3)	2800 (69.5)	5606 (69.4)
9	2026 (50.1)	2039 (50.6)	4065 (50.3)
10	1072 (26.5)	1074 (26.7)	2146 (26.6)
11	440 (10.9)	432 (10.7)	872 (10.8)
12	57 (1.4)	60 (1.5)	117 (1.4)

Note: The number of patients at each time point represents the number of patients completing through the previous time point and at risk at the beginning of the period immediately preceding the indicated time point.

Read together, the data in the two tables indicate that the number of myocardial infarctions in the Vioxx group continued to increase, even after the number of patients in the study dropped dramatically between 8 and 12 months. Dr. Truitt's revised draft of

<sup>294</sup> 9/27/01 draft memorandum from C. Brett, K. Truitt to "RMC Members," MRK-NJ0141263, at 265.

the memorandum did not discuss this result, but referred to Dr. Shapiro's and Dr. Mukhopadhyay's analysis and commented that "small numbers of specific event types, in one or both treatment groups, precludes meaningful comparative analyses based on individual adverse experience terms."<sup>295</sup>

Mr. Bolognese forwarded Dr. Truitt's revised draft to Dr. Oppenheimer for approval.<sup>296</sup> Mr. Bolognese noted that the revised draft "included a summary of the events by time interval" and stated that "[g]iven the small numbers of events, I don't think percents based on total numbers of events observed in the various time intervals by treatment will be informative."<sup>297</sup> Mr. Bolognese also edited the conclusion section of Dr. Truitt's memorandum to reflect the increased number of myocardial infarctions in month 8 through 12, writing that "no *differential* clustering of different specific thromboembolic experiences (based on adjudicated term) occurred early vs. late in the trial, and "[n]o temporal *differential* clustering *across the different events* was observed in patients with specific underlying risk factors"<sup>298</sup> (changes in italics). Dr. Oppenheimer approved the revised draft,<sup>299</sup> and the memorandum was circulated to the Research Management Committee on October 3, 2001.<sup>300</sup>

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<sup>295</sup> 9/27/01 draft memorandum from C. Brett, K. Truitt to "RMC Members," MRK-NJ0141263, at 273.

<sup>296</sup> 9/28/01 email from J. Bolognese to L. Oppenheimer et al., MRK-NJ0141273 (attaching 9/27/01 draft memorandum from C. Brett, K. Truitt, MRK-NJ0141274).

<sup>297</sup> 9/28/01 email from J. Bolognese to L. Oppenheimer et al., MRK-NJ0141273.

<sup>298</sup> 9/27/01 draft memorandum from C. Brett, K. Truitt, MRK-NJ0141274, at 275.

<sup>299</sup> 10/1/01 email from L. Oppenheimer to J. Bolognese, K. Truitt, MRK-AFO0079462.

<sup>300</sup> 10/3/01 email from K. Truitt to D. Merrill, MRK-NJ0141297.

## 2. Discussion of Hazard Ratio During Label Negotiations.

In light of these analyses, Merck objected to the Agency's proposal that a Kaplan-Meier curve of cardiovascular events be included in the label. At a March 7, 2002 teleconference, however, FDA representatives stated that they were "not comfortable with Merck's conclusion that the hazard ratio of CV thrombotic events is constant over time."<sup>301</sup> The Agency did not argue that the VIGOR Trial data definitively showed an increase in hazard ratio, but rather contended that the presentation of the VIGOR Trial cardiovascular data in a Kaplan-Meier curve would most appropriately address the "issue of potential change in hazard rate over time."<sup>302</sup> When Merck objected that its analysis showed no statistically significant evidence of an increase in hazard ratio, the FDA responded that the failure to show a statistically significant difference did not prove that the hazard ratio was constant.<sup>303</sup>

After the teleconference, Dr. Shapiro – who had attended the teleconference along with other representatives from Clinical Biostatistics – asked Dr. Joshua Chen to generate a Kaplan-Meier plot for confirmed thrombotic event data in the Alzheimer's disease trials, Protocols 078 and 091. Dr. Shapiro stated that if the FDA wanted a Kaplan-Meier curve of the VIGOR Trial data, Merck would seek to include one for the Alzheimer's trials as well.<sup>304</sup>

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<sup>301</sup> Minutes of 3/7/02 MRL/FDA teleconference, MRK-AAF0006080, at 81.

<sup>302</sup> Minutes of 3/7/02 MRL/FDA teleconference, MRK-AAF0006080, at 81.

<sup>303</sup> Minutes of 3/7/02 MRL/FDA teleconference, MRK-AAF0006080, at 81.

<sup>304</sup> 3/8/02 email from J. Bolognese to J. Chen, MRK-YAB0002586 ("This is actually Deborah writing on Jim's email since he has his laptop connected.").

On March 13, 2002, Merck submitted a revised draft label in which it continued to propose that the cardiovascular data be expressed as rates per 100 patient years as in its previous proposals.<sup>305</sup>

On March 18, 2002, Ms. Barbara Gould\*, Project Manager at the Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products, emailed to Drs. Silverman and Braunstein a March 14, 2002 memorandum addressing the cardiovascular hazard ratio in the VIGOR Trial prepared by Dr. M. F. Huque\* of Division of Biometrics, Center for Drug Evaluation and Research.<sup>306</sup> Dr. Huque\* concluded that the Vioxx group in the VIGOR Trial “tends to show a different hazard rate pattern than the Naproxen group . . . during the 8-12 month interval” and that this finding “cast[s] doubt on the constant hazard rate assumption for the Rofecoxib group.”<sup>307</sup>

On March 19, 2002, Drs. Shapiro and Mukhopadhyay submitted to Dr. Silverman an update of their May 2001 hazard ratio analysis, including investigator-reported as well

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<sup>305</sup> 3/13/02 draft label, MRK-ACD0039092, at 9102 (attached to 3/13/02 email from D. Chitty to R. Silverman, N. Braunstein, MRK-ACD0039091). This draft also reflected several minor changes in the form of rearranging paragraphs and words in the Precautions section relating to cardiovascular effects and fluid retention, edema and hypertension.

<sup>306</sup> 3/18/02 email from B. Gould\* to R. Silverman, MRK-AAF0005765; 3/14/02 memorandum from M. Huque\* to L. Goldkind\*, MRK-AAF0005766.

<sup>307</sup> 3/14/02 memorandum from M. Huque\* to L. Goldkind\*, MRK-AAF0005766, at 766.

as confirmed cardiovascular events.<sup>308</sup> Drs. Shapiro and Mukhopadhyay again concluded that there was no evidence of an increased hazard ratio in either category.<sup>309</sup>

On March 20, 2002, Merck and the FDA again discussed the hazard ratio issue during a teleconference.<sup>310</sup> The FDA stated that displaying cardiovascular data in a table of events per 100 patient years was inappropriate because this presentation assumed risk remained constant over time.<sup>311</sup> The FDA maintained that its analyses, including Dr. Huque's\* March 14 memorandum, "strongly suggest[ed]" that the hazard ratio did in fact increase with time.<sup>312</sup> The Agency acknowledged, however, that because the VIGOR Trial was not designed to show statistically significant changes in hazard ratios for cardiovascular events, it was difficult to draw definitive conclusions from the data.<sup>313</sup> Merck proposed submitting a table of cumulative incidence rates as an alternative to the Kaplan-Meier curve.<sup>314</sup> The FDA responded that such a table was preferable to a table

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<sup>308</sup> 3/19/02 memorandum from D. Shapiro, S. Mukhopadhyay to R. Silverman, MRK-AFK0196692. In the VIGOR Trial, all investigator-reported cardiovascular and gastrointestinal events were submitted to an external adjudication committees for review. The term "investigator-reported events" refers to all events reported by investigators including those confirmed and those not confirmed by the adjudicators.

<sup>309</sup> 3/19/02 memorandum from D. Shapiro, S. Mukhopadhyay to R. Silverman, MRK-AFK0196692, at 92.

<sup>310</sup> Minutes of 3/20/02 MRL/FDA teleconference, MRK-AAF0006083.

<sup>311</sup> Minutes of 3/20/02 MRL/FDA teleconference, MRK-AAF0006083, at 6084.

<sup>312</sup> Minutes of 3/20/02 MRL/FDA teleconference, MRK-AAF0006083, at 6085.

<sup>313</sup> Minutes of 3/20/02 MRL/FDA teleconference, MRK-AAF0006083, at 6084.

<sup>314</sup> Minutes of 3/20/02 MRL/FDA teleconference, MRK-AAF0006083, at 6085. Merck's earlier drafts of the label had included incidence rates rather than cumulative rates of the VIGOR Trial gastrointestinal and cardiovascular data, because in Merck's view, "cumulative rates are generally less clinically meaningful because they can only be interpreted in relation to a specific duration of therapy and because they can underestimate risk over longer-term periods by not accounting for dropouts." Report, MRK-AFT0006828, at 830 (attached to 3/5/02 letter from R. Silverman\* to L. Simon\* ,

showing the rate per 100 patient years, but “still is not the optimal way to present the data” because it did not account for potential changes in the hazard ratio.<sup>315</sup>

The following day, on March 21, Dr. Silverman submitted a letter to the FDA that argued in favor of presenting the data in rates per 100 patient years as opposed to cumulative incidence rates.<sup>316</sup> In support of Merck’s position, Dr. Silverman submitted Kaplan-Meier plots from the two ongoing Alzheimer’s trials (Protocols 078 and 091), which indicated that, in those trials, the hazard ratio for cardiovascular events on Vioxx remained constant over a period of 30 months.<sup>317</sup> Dr. Silverman opposed the inclusion in the label of Kaplan-Meier plots or tables showing cumulative incidence rates of cardiovascular events in the VIGOR Trial on the ground that “there is no statistical evidence for a change in either relative risk or hazard over time.”<sup>318</sup>

The letter also pointed out what Merck viewed as a flaw in the FDA’s analysis of the hazard ratio. Merck noted that the Agency’s Vioxx analysis in its first table used confirmed thrombotic event data while the naproxen analysis in this table represented a mixture of confirmed and investigator-reported data.<sup>319</sup> The second table in the Agency’s

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MRK-AFT0006825). Nevertheless, in a March 5, 2002 letter, Merck accepted the FDA’s request to use cumulative rates in the Vioxx product label because the “differences between cumulative incidences and incidence rates [were] small and [did] not influence the understanding of the relative risks for the various events [GI and CV] between the treatment groups” in the VIGOR Trial. 3/5/02 letter from R. Silverman to L. Simon\*, MRK-AFT0006828, at 830.

<sup>315</sup> Minutes of 3/20/02 MRL/FDA teleconference, MRK-AAF0006083 at 85.

<sup>316</sup> 3/21/02 letter from R. Silverman to L. Simon\*, MRK-02420000407, at 09.

<sup>317</sup> 3/21/02 letter from R. Silverman to L. Simon\*, MRK-02420000407, at 10.

<sup>318</sup> 3/21/02 letter from R. Silverman to L. Simon\*, MRK-02420000407, at 07.

<sup>319</sup> 3/21/02 letter from R. Silverman to L. Simon\*, MRK-02420000407, at 07.

analysis, however, used investigator-reported cardiovascular events for both the Vioxx and naproxen analyses.<sup>320</sup> In its letter, Merck explained that because confirmed thrombotic events were the prespecified endpoints agreed upon between Merck and the Agency, the analysis of confirmed events in the first table was more relevant and in fact supported Merck's conclusion that hazard ratio in the VIGOR Trial was constant over time.<sup>321</sup> The letter also pointed out that the Agency chose 0-4, 4-8, and 8-12 month intervals for its analysis while Merck's analysis included additional intervals including "a more stringent analysis" of 0-8 months vs. >8 months.<sup>322</sup> None of Merck's analyses demonstrated statistical evidence for a change in risk ratios over time.<sup>323</sup>

Later that day, Merck submitted a revised draft label that included "a new table of cardiovascular thrombotic events in VIGOR that we believe addresses the Agency's requests to show cumulative incidence rates over time."<sup>324</sup> The proposed table showed serious cardiovascular events that occurred after 4, 8 and 10 ½ months of exposure in the VIGOR Trial, the number of patients remaining in the study at each interval, and the

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<sup>320</sup> 3/21/02 letter from R. Silverman to L. Simon\*, MRK-02420000407, at 07.

<sup>321</sup> 3/21/02 letter from R. Silverman to L. Simon\*, MRK-02420000407, at 07.

<sup>322</sup> 3/21/02 letter from R. Silverman to L. Simon\*, MRK-02420000407, at 08.

<sup>323</sup> 3/21/02 letter from R. Silverman to L. Simon\*, MRK-02420000407, at 08.

<sup>324</sup> 3/21/02 letter from R. Silverman to L. Simon\*, MRK-AAF0005794 (attaching draft label).

Kaplan-Meier cumulative rate.<sup>325</sup> The FDA accepted this resolution of the hazard ratio discussions.<sup>326</sup>

M. April 2002: Final Drafts and Approved Label.

1. Drafts and Teleconferences.

Although Merck and the FDA had resolved all major issues pertaining to the revised label by the beginning of April 2002, they continued to exchange drafts concerning minor changes to the text of the label. In an April 3, 2002 teleconference, the FDA requested changes to the wording of the portions of the label describing the VIGOR Trial, the cardiovascular precaution and recommendations against chronic use of Vioxx at the 50 mg dose.<sup>327</sup> Merck submitted a revised draft label to the FDA on the same day incorporating most of these changes.<sup>328</sup>

For example, in the Precautions section, Merck accepted the FDA's proposal to state "[t]he significance of the cardiovascular findings from [the VIGOR Trial and the two Alzheimer's disease trials] is unknown," as opposed to stating that the "interpretation" of the cardiovascular findings from these studies "has not been established."<sup>329</sup> In addition, Merck agreed to specify that fluid retention, edema and hypertension occurred with increased frequency with chronic use of Vioxx "at daily

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<sup>325</sup> MRL 3/21/02 draft label with FDA 4/3/02 proposals, MRK-ACM0000080, at 89.

<sup>326</sup> This issue resurfaced after withdrawal, in preparation for the February 2005 Arthritis Advisory Committee meeting. 12/4/04 email from N. Braunstein to J. Van Adelsberg *et al.*, MRK-AFK0196588.

<sup>327</sup> See MRL 3/21/02 draft label with FDA 4/3/02 proposals, MRK-ACM0000080, at 89, 98.

<sup>328</sup> 4/3/02 letter from R. Silverman to L. Simon\*, MRK-02420002560, at 561.

<sup>329</sup> MRL 3/21/02 draft label with FDA 4/3/02 proposals, MRK-ACM0000080, at 97.

doses of 50 mg,” while the previous draft had stated that these side effects occurred with increased frequency “at doses above the 12.5 to 25 mg range.”<sup>330</sup> Merck also accepted the FDA’s proposed revisions to changes in the tables of cumulative incidence rates submitted in the March 21, 2002 draft, including deletion of the sentence, “There was no statistically significant change in rates of events over time.”<sup>331</sup>

The FDA submitted its final counterproposal on April 9.<sup>332</sup> In a teleconference that day, Merck accepted all of the Agency’s proposed changes.<sup>333</sup> The following day, Merck submitted a revised label incorporating these changes, which included specifying that the serious cardiovascular events in the VIGOR Trial included sudden death, myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack, and peripheral venous and arterial thromboses.<sup>334</sup> Merck also accepted the FDA’s request to relocate cautionary language concerning use of Vioxx by patients with a medical history of ischemic heart disease from the end of the cardiovascular precaution to the beginning.<sup>335</sup> On April 11, 2002, the FDA approved the revised label, as well as the rheumatoid arthritis indication.<sup>336</sup>

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<sup>330</sup> MRL 3/21/02 draft label with FDA 4/3/02 proposals, ACM0000080, at 98.

<sup>331</sup> MRL 3/21/02 draft label with FDA 4/3/02 proposals, ACM0000080, at 89.

<sup>332</sup> 4/10/02 letter from N. Braunstein to L. Simon\*, MRK-AFV0041337, at 337.

<sup>333</sup> 4/10/02 letter from N. Braunstein to L. Simon\*, MRK-AFV0041337, at 337.

<sup>334</sup> 4/9/02 draft label, MRK-AFV0041357, at 365.

<sup>335</sup> 4/9/02 draft label, MRK-AFV0041357, at 373.

<sup>336</sup> Vioxx Label Change Q & A, MRK-ABX0022610.

## 2. Approved Label.

In the approved VIGOR label, Merck did not achieve its objective of eliminating the NSAID-class gastrointestinal safety warning but succeeded in obtaining revisions to the warning reflecting the trial results. The final label was a product of negotiations between Merck and the FDA on issues such as the description of the cardiovascular hazard ratio and the deletion of the naproxen cardioprotection hypothesis. Merck's proposed statements that Vioxx could safely be used with aspirin were also omitted.<sup>337</sup>

Specifically, the approved label, in the Clinical Studies section, under subheading "Special Studies," described the VIGOR Trial followed by the gastrointestinal data and cardiovascular data.<sup>338</sup> The description of the study design and the cardiovascular findings are reproduced below:<sup>339</sup>

VIOXX® (rofecoxib tablets and oral suspension)

9183810

### *Special Studies*

The following special studies were conducted to evaluate the comparative safety of VIOXX.

#### *VIOXX GI Clinical Outcomes Research (VIGOR Study)*

##### *Study Design*

The VIGOR study was designed to evaluate the comparative GI safety of VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA and RA) versus naproxen 500 mg twice daily (common therapeutic dose). The general safety and tolerability of VIOXX 50 mg once daily versus naproxen 500 mg twice daily was also studied. VIGOR was a randomized, double-blind study (median duration of 9 months) in 8076 patients with rheumatoid arthritis (RA) requiring chronic NSAID therapy (mean age 58 years). Patients were not permitted to use concomitant aspirin or other antiplatelet drugs. Patients with a recent history of myocardial infarction or stroke and patients deemed to require low-dose aspirin for cardiovascular prophylaxis were to be excluded from the study. Fifty-six percent of patients used concomitant oral corticosteroids. The GI safety endpoints (confirmed by a blinded adjudication committee) included:

PUBs-symptomatic ulcers, upper GI perforation, obstruction, major or minor upper GI bleeding.

Complicated PUBs (a subset of PUBs)-upper GI perforation, obstruction or major upper GI bleeding.

<sup>337</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 30.

<sup>338</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 31-32.

<sup>339</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 31-32 (including information in Tables 4 and 5).

**Other Safety Findings: Cardiovascular Safety**

The VIGOR study showed a higher incidence of adjudicated serious cardiovascular thrombotic events in patients treated with VIOXX 50 mg once daily as compared to patients treated with naproxen 500 mg twice daily (see Table 2). This finding was largely due to a difference in the incidence of myocardial infarction between the groups. (See Table 3.) (See PRECAUTIONS, *Cardiovascular Effects*.) Adjudicated serious cardiovascular events (confirmed by a blinded adjudication committee) included: sudden death, myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack and peripheral venous and arterial thromboses.

Table 4

VIGOR-Summary of Patients with Serious Cardiovascular Thrombotic Adverse Events Over Time: Comparison to Naproxen

Treatment Group	Patients Randomized		4 Months <sup>2</sup>	8 Months <sup>3</sup>	10 ½ months <sup>4</sup>
VIOXX 50 mg	4047	Total number of events	17	29	45
		Cumulative Rate <sup>†</sup>	0.46%	0.82%	1.81%*
Naproxen 1000 mg	4029	Total number of events	9	15	19
		Cumulative Rate <sup>†</sup>	0.23%	0.43%	0.60%

Table 5

VIGOR Trial Serious Cardiovascular Thrombotic Adverse Events

	VIOXX 50 mg N <sup>2</sup> =4047 n <sup>3</sup>	Naproxen 1000 mg N <sup>2</sup> =4029 n <sup>3</sup>
Any CV thrombotic event:	45 *	19
Cardiac events	28**	10
Fatal MI/Sudden death	5	4
Non-fatal MI	18**	4
Unstable angina	5	2
Cerebrovascular	11	8
Ischemic stroke	9	8
TIA	2	0
Peripheral	6	1

In addition, the Warnings section, among other things, provided information for patients with Advanced Renal Disease.<sup>340</sup> The relevant portions are reproduced below<sup>341</sup>:

<sup>340</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 35.

<sup>341</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 35.

## WARNINGS

### *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation*

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Although the risk of GI toxicity is not completely eliminated with VIOXX, the results of the VIOXX GI outcomes research (VIGOR) study demonstrate that in patients treated with VIOXX, the risk of GI toxicity with VIOXX 50 mg once daily is significantly less than with naproxen 500 mg twice daily. (See CLINICAL STUDIES, *Special Studies, VIGOR*.)

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Previous studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

### *Advanced Renal Disease*

Treatment with VIOXX is not recommended in patients with advanced renal disease. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, *Renal Effects*).

The Precautions section included the cardiovascular data as well as data related to renal toxicity, fluid retention, edema and hypertension.<sup>342</sup> The relevant portions are reproduced below:<sup>343</sup>

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<sup>342</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 36.

<sup>343</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 36.

## PRECAUTIONS

### *General*

VIOXX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

### *Cardiovascular Effects*

The information below should be taken into consideration and caution should be exercised when VIOXX is used in patients with a medical history of ischemic heart disease.

In VIGOR, a study in 8076 patients (mean age 58; VIOXX n=4047, naproxen n=4029) with a median duration of exposure of 9 months, the risk of developing a serious cardiovascular thrombotic event was significantly higher in patients treated with VIOXX 50 mg once daily (n=45) as compared to patients treated with naproxen 500 mg twice daily (n=19). In VIGOR, mortality due to cardiovascular thrombotic events (7 vs 6, VIOXX vs naproxen, respectively) was similar between the treatment groups. (See CLINICAL STUDIES, *Special Studies, VIGOR, Other Safety Findings: Cardiovascular Safety.*) In a placebo-controlled database derived from 2 studies with a total of 2142 elderly patients (mean age 75; VIOXX n=1067, placebo n=1075) with a median duration of exposure of approximately 14 months, the number of patients with serious cardiovascular thrombotic events was 21 vs 35 for patients treated with VIOXX 25 mg once daily versus placebo, respectively. In these same 2 placebo-controlled studies, mortality due to cardiovascular thrombotic events was 8 vs 3 for VIOXX versus placebo, respectively. The significance of the cardiovascular findings from these 3 studies (VIGOR and 2 placebo-controlled studies) is unknown. Prospective studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators or placebo have not been performed.

**Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis.** Therefore, in patients taking VIOXX, antiplatelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis. (See CLINICAL STUDIES, *Special Studies, Platelets; PRECAUTIONS, Drug Interactions, Aspirin.*) Prospective, long-term studies on concomitant administration of VIOXX and aspirin evaluating cardiovascular outcomes have not been conducted.

### *Fluid Retention, Edema, and Hypertension*

Fluid retention, edema, and hypertension have been reported in some patients taking VIOXX. In clinical trials of VIOXX at daily doses of 25 mg in patients with rheumatoid arthritis the incidence of hypertension was twice as high in patients treated with VIOXX as compared to patients treated with naproxen 1000 mg daily. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg in patients with osteoarthritis have shown effects on hypertension and edema similar to those observed with comparator NSAIDs; these occurred with an increased frequency with chronic use of VIOXX at daily doses of 50 mg. (See ADVERSE REACTIONS.) VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

### *Renal Effects*

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Caution should be used when initiating treatment with VIOXX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIOXX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS, *Advanced Renal Disease*).

The Adverse Events section, among other things, included cardiovascular adverse event data as well as clinical adverse event data in the rheumatoid arthritis Phase III

studies and rheumatoid arthritis and osteoarthritis studies with Vioxx 50 mg dose.<sup>344</sup> The relevant portions are reproduced below:<sup>345</sup>

The following serious adverse events have been reported rarely (estimated <0.1%) in patients taking VIOXX, regardless of causality. Cases reported only in the post-marketing experience are indicated in italics.

*Cardiovascular:* cerebrovascular accident, congestive heart failure, deep venous thrombosis, myocardial infarction, *pulmonary edema*, pulmonary embolism, transient ischemic attack, unstable angina.

***Rheumatoid Arthritis***

Approximately 1,100 patients were treated with VIOXX in the Phase III rheumatoid arthritis efficacy studies. These studies included extensions of up to 1 year. The adverse experience profile was generally similar to that reported in the osteoarthritis studies. In studies of at least three months, the incidence of hypertension in RA patients receiving the 25 mg once daily dose of VIOXX was 10.0% and the incidence of hypertension in patients receiving naproxen 500 mg twice daily was 4.7%.

***Clinical Studies in OA and RA with VIOXX 50 mg (Twice the highest dose recommended for chronic use)***

In OA and RA clinical trials which contained VIOXX 12.5 or 25 mg as well as VIOXX 50 mg, VIOXX 50 mg QD was associated with a higher incidence of gastrointestinal symptoms (abdominal pain, epigastric pain, heartburn, nausea and vomiting), lower extremity edema, hypertension, serious adverse experiences and discontinuation due to clinical adverse experiences compared to the recommended chronic doses of 12.5 and 25 mg (see DOSAGE AND ADMINISTRATION).

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<sup>344</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 41.

<sup>345</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 41-42.

Finally, the Dosage and Administration section indicated that the lowest dose of Vioxx should be sought for each patient and recommended against chronic usage of the 50 mg dose.<sup>346</sup> The relevant portions are reproduced below:<sup>347</sup>

**DOSAGE AND ADMINISTRATION**

VIOXX is administered orally. The lowest dose of VIOXX should be sought for each patient.  
*Osteoarthritis*

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

*Rheumatoid Arthritis*

The recommended dose is 25 mg once daily. The maximum recommended daily dose is 25 mg.

*Management of Acute Pain and Treatment of Primary Dysmenorrhea*

The recommended dose of VIOXX is 50 mg once daily. The maximum recommended daily dose is 50 mg. Use of VIOXX for more than 5 days in management of pain has not been studied. Chronic use of VIOXX 50 mg daily is not recommended. (See ADVERSE REACTIONS, *Clinical Studies in OA and RA with VIOXX 50 mg*).

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<sup>346</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 42.

<sup>347</sup> 4/11/02 approved Vioxx product label, MRK-ABH0022928, at 42.