

understands all of the clinical data about Vioxx, dose-related effects on blood pressure and edema, upset stomachs that occurred in patients so that they accurately presented all that information when the drug was eventually approved.”<sup>253</sup>

Also, in November 1998, Dr. Scolnick wrote to Dr. Beth Seidenberg, head of the Pulmonary/Immunology Department, Clinical Sciences, MRL, that Merck should be ready to conduct head-to-head studies of Vioxx and Celebrex “[t]he VERY FIRST day they have [Celebrex] in a drugstore.”<sup>254</sup> Dr. Scolnick also noted that “renal safety [was] going to be an issue to explain to doctors, and to agencies”<sup>255</sup> and stated: “we MUST debunk the edema issue right away and destroy their credibility. If we are wrong we need to know.”<sup>256</sup> Appendix C discusses MRL’s and the FDA’s review of the pre-1998 New Drug Application renal data on Vioxx.

H. The May 1998 Board of Scientific Advisors Meeting.

In May 1998, MRL held the annual meeting of the Merck Institute Board of Scientific Advisors, a board which at the time consisted of 23 external scientists and was chaired by Dr. Douglas A. Greene\*, Chief, Division of Endocrinology and Metabolism, University of Michigan School of Medicine, and Director, Michigan Diabetes Research

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<sup>253</sup> 3/22/05 deposition of E. Scolnick at 309-310 (*Ernst v. Merck & Co.*, 19961\*BH02, Tex. Dist. Ct.). Dr. Scolnick also has testified that the reference to “pimples” did not relate to the FitzGerald prostacyclin hypothesis or a concern that Vioxx might increase the risk of thrombotic cardiovascular events. *Id.* (“Q. Well, the pimples you were worried about at this time period included the effect on heart attacks and strokes; true? A. No. Quite not true.”).

<sup>254</sup> 11/19/98 email from E. Scolnick to B. Goldmann, MRK-ABI0001586, at 86.

<sup>255</sup> 11/19/98 email from E. Scolnick to B. Goldmann, MRK-ABI0001586, at 86.

<sup>256</sup> 11/98 email chain between E. Scolnick and B. Seidenberg, MRK-ABH0014364, at 64.

and Training Center.<sup>257</sup> The purpose of the meeting was to discuss with consultants the various development programs on which MRL was working and to receive input and advice about particular issues. According to Dr. Oates\*, who chaired the Board of Scientific Advisors in the 1980s and then again in 1996, 1997 and 2000,<sup>258</sup> the meetings generally included 8 to 10 presentations by MRL scientists followed by a closed deliberation session among the consultants.<sup>259</sup> Dr. Oates\* stated that Messrs. Gilmartin and Frazier, Senior Vice President and General Counsel at Merck, generally joined for part of the discussion at the end of the Board of Scientific Advisors' meetings.

In advance of the May 1998 meeting, MRL sent to the members of the Board of Scientific Advisors background materials for topics on that year's agenda, which included Vioxx. The background material on Vioxx had been prepared by Dr. Nies, with

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<sup>257</sup> Background Materials for the 5/98 BSA meeting, MRK-AGG0002839, at 839, 842-43, 847-48.

Other members of the BSA were Henry G. Bone, III\*, M.D., Michigan Bone & Mineral Clinic, P.C.; Barbara J. McNeil\*, M.D., Ph.D., Harvard Medical School; Herbert Y. Meltzer\*, M.D., Vanderbilt University School of Medicine; John Mendelsohn\*, M.D., President, The University of Texas, Anderson Cancer Center; William W. Muir III\*, DVM, Ph.D., Veterinary Hospital; Jeremy Nathans\*, M.D., Ph.D., Johns Hopkins University; John A. Oates\*, M.D., Vanderbilt University; Sir. Keith Peters\*, M.D., Addenbrooke's Hospital; Donald L. Price\*, M.D., Johns Hopkins University; David Robertson\*, M.D., Vanderbilt University; P. Frederick Sparling\*, M.D., The University of North Carolina at Chapel Hill; Andrew Tait\*, Ph.D., University of Glasgow; Carol A. Tamminga\*, M.D., Maryland Psychiatric Research Center, University of Maryland; Myron L. Weisfeldt\*, M.D., Columbia Presbyterian Medical Center; Scott L. Zeger\*, Johns Hopkins University; and Huda Y. Zoghbi\*, M.D., Howard Hughes Medical Institute. Agenda and Background Information sent to the BSA, MRK-AGG0002839, at 852-57.

<sup>258</sup> Dr. Oates\* affiliations are discussed in text accompanying n.212 above.

<sup>259</sup> 3/2/05 deposition of A. Nies at 201 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.) (stating that Merck employees were not present during the Board's "executive sessions").

Dr. Scolnick's sign-off.<sup>260</sup> In the document, Dr. Nies reviewed the status of the Vioxx development program and the existing gastrointestinal, renal, bone turnover and articular cartilage safety data.<sup>261</sup> The background document also informed the Board of Scientific Advisors about the prostacyclin metabolite findings in Protocol 023, stating that the results were "entirely unexpected" because "[c]urrent knowledge would suggest that Cox-2 is not an important enzyme in the synthesis of prostacyclin by normal endothelium."<sup>262</sup> The document stated that "additional experimentation was required to understand" those findings.<sup>263</sup> The document also stated that Dr. Watson's blinded analysis of cardiovascular events in the Vioxx database (discussed in Section F of this Appendix) did "not suggest a concern."<sup>264</sup>

When the Board of Scientific Advisors met, the majority of the Vioxx-related discussion focused on the effect of Vioxx on the risk of cardiovascular events<sup>265</sup> and the FitzGerald prostacyclin hypothesis was discussed "extensively."<sup>266</sup>

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<sup>260</sup> 3/12/98 email from A. Nies to E. Scolnick, MRK-ABH0014093, at 93 ("I am attaching my summary/update of the VIOXX program for the board of advisors meeting . . . I want to strike the correct balance of update and issues that I would like to present to the board without including information that is too speculative or sensitive for other reasons.").

<sup>261</sup> Background Materials for the 5/98 BSA meeting, MRK-AGG0002839, at 858-867.

<sup>262</sup> Background Materials for the 5/98 BSA meeting, MRK-AGG0002839, at 867-68.

<sup>263</sup> Background Materials for the 5/98 BSA meeting, MRK-AGG0002839, at 868.

<sup>264</sup> Background Materials for the 5/98 BSA meeting, MRK-AGG0002839, at 868.

<sup>265</sup> 4/1/05 deposition of A. Nies at 412 (*In re Vioxx Litig.*, No. 619, N.J. Super. Ct. Law Div.) ("It's unusual to spend that much time on one topic, but this [the effect of Vioxx on the risk of cardiovascular events] was an important topic.").

<sup>266</sup> 8/23/05 deposition of A. Nies at 697 (*In re Vioxx Litig.*, No. 619, N.J. Super. Ct. Law Div.).

1. The Board of Scientific Advisors' Post-meeting Report on Vioxx.

Following general practice, at the conclusion of the meeting, the Board of Scientific Advisors issued a report to Dr. Scolnick summarizing the Board's views on topics discussed at the meeting. At the May 1998 meeting, Dr. Greene<sup>\*</sup>, in his capacity as Chairman, appointed Dr. Oates<sup>\*</sup> to coordinate and oversee preparation of the report section on Vioxx in part because of Dr. Oates's<sup>\*</sup> expertise in prostanoids.

The 12-page report on Vioxx summarized the Board of Scientific Advisors' views about the general progress of the Vioxx development program and the questions raised in Dr. Nies' background document. It included a seven-page subsection on "Cardiovascular Pathophysiology,"<sup>267</sup> which underscored the fact that the science about selective Cox-2 inhibitors was new and developing and noted that selective Cox-2 inhibitors might affect positively or negatively or not at all the multi-step process that leads to coronary ischemic events.<sup>268</sup>

The Board of Scientific Advisors noted that, on the one hand, it was possible that Cox-2 inhibitors (both selective Cox-2 inhibitors, like Vioxx, and non-selective ones, like aspirin) might be cardioprotective, because "a growing body of evidence indicat[ed] that inflammatory disease [was] a risk factor for myocardial infarction" and inhibition of Cox-2 reduced inflammation.<sup>269</sup> The Board of Scientific Advisors also noted that, on the

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<sup>267</sup> 5/98 "Programmatic Review: Vioxx Program," MRK-AEI0002734, at 736.

<sup>268</sup> 5/98 "Programmatic Review: Vioxx Program," MRK-AEI0002734, at 736-42.

<sup>269</sup> 5/98 "Programmatic Review: Vioxx Program," MRK-AEI0002734, at 736.

other hand, selective Cox-2 inhibitors might increase the risk of thrombotic events if they inhibited prostacyclin biosynthesis in the vasculature without blocking platelet production of thromboxane.<sup>270</sup>

With respect to Protocol 023 and the FitzGerald prostacyclin hypothesis, the Board of Scientific Advisors' report concluded that "[m]ore information [was] clearly needed to address these hypotheses and the other questions related to the possible influences of a COX-2 inhibitor on coronary morbidity and mortality."<sup>271</sup>

On this background of information regarding the anti-platelet and anti-fibrillatory effects of prostacyclin and its vascular localization, it has been found that Vioxx reduces the urinary excretion of the prostacyclin metabolite, 2,3-dinor-6-keto-PGF<sub>1α</sub>. This is important data but it is not a basis for any conclusion. Rather, it should be taken as a basis for hypotheses that should be actively pursued.

One hypothesis would be that the excretion of the prostacyclin metabolite, 2,3-dinor-6-keto-PGF<sub>1α</sub>, does not reflect systemic/vascular prostacyclin biosynthesis. An alternative hypothesis is that prostacyclin biosynthesis in the vasculature is inhibited by Vioxx (without blocking production of thromboxane A<sub>2</sub> by the platelet). By removing this potent inhibitor of platelet aggregation, the probability that a coronary plaque rupture would lead to myocardial infarction or ischemic ventricular fibrillation is enhanced.

<sup>270</sup> 5/98 "Programmatic Review: Vioxx Program," MRK-AEI0002734, at 738.

<sup>271</sup> 5/98 "Programmatic Review: Vioxx Program," MRK-AEI0002734, at 738.

The Board of Scientific Advisors' report stressed that scientific data developed in the future likely would answer some of these hypothesized questions, but that there was "a strong mandate for introduction of Vioxx into medical practice as soon as is feasible."<sup>272</sup>

The above considerations regarding hypothetical adverse effects and potential unexpected therapeutic benefits of Vioxx are part of the scientific intelligence gathering appropriate to the development of any truly novel pharmacological entity, and should be addressed in parallel with the conclusion of the process of acquisition and analysis of the data that will place this drug in the hands of patients. The gain in safety achieved by the elimination of serious and fatal gastrointestinal toxicity will free patients from one of the most serious adverse effects in current drug therapy. Thus, there is a strong mandate for introduction of Vioxx into medical practice as soon as is feasible.

With respect to the point made in Dr. Nies' background document that Vioxx might affect only the metabolism as opposed to the biosynthesis of prostacyclin, the Board of Scientific Advisors found that "theoretically" Dr. Nies could be correct.<sup>273</sup> With respect to the question of whether the urinary PGI-M "derived principally from the kidney," the Board of Scientific Advisors noted that such a question "could be asked," but expressed its belief, based on the existing evidence, that urinary PGI-M derived from

<sup>272</sup> 5/98 "Programmatic Review: Vioxx Program," MRK-AEI0002734, at 742.

<sup>273</sup> 5/98 "Programmatic Review: Vioxx Program," MRK-AEI0002734, at 739.

prostacyclin that was synthesized throughout the body.<sup>274</sup> This advice was consistent with the opinion that Dr. Oates\* had expressed in his November 17, 1997 letter to Dr. Gertz (discussed in Section E.5 of this Appendix).<sup>275</sup>

## 2. The Board of Scientific Advisors' Recommendations.

The Board of Scientific Advisors recommended several studies that MRL might conduct to address the various hypotheses and other questions related to the possible influences of selective Cox-2 inhibition on cardiovascular adverse events. These studies are discussed in Section J of this Appendix, along with other study proposals that MRL received from its consultants in the wake of Protocol 023 findings.

The Board of Scientific Advisors also advised Merck to examine cardiovascular events in all clinical trials of Vioxx and Arcoxia. Although MRL routinely analyzed the rates of adverse events, including cardiovascular events, in each of its clinical trials, the Board of Scientific Advisors noted that individual Vioxx trials would be unlikely to have sufficient power to determine whether cardiovascular events were “increased or decreased” by selective Cox-2 inhibition because each trial would have too few events to provide a statistically significant result (*i.e.*, a result that was unlikely to have occurred by chance alone).<sup>276</sup> Therefore, the Board of Scientific Advisors recommended that Merck

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<sup>274</sup> 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 740 (“All this together argues against the predominant amount of urinary [PGI-M] being derived from nonvascular sites in the kidney.”).

<sup>275</sup> 11/17/97 letter from J. Oates\* to B. Gertz, MRK-ABC0002119, at 19 (“In summary, it seems quite unlikely that [PGI-M] in the urine is derived predominantly from the kidney.”).

<sup>276</sup> 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 739. The concept of statistical power is discussed in detail in Exhibit 3.

collect and pool the cardiovascular data from all clinical trials of Vioxx and the other selective Cox-2 inhibitors<sup>277</sup> to determine if any signal of cardiovascular risk or benefit could be discerned.

To ensure the feasibility of the pooled analysis and enhance its validity, the Board of Scientific Advisors recommended that Merck institute a procedure whereby investigator-reported cardiovascular adverse events in clinical trials of Vioxx and other selective Cox-2 inhibitors would be assessed by a blinded expert committee under a prespecified uniform set of criteria. In general, adverse events that occur in a clinical trial are diagnosed and reported by individual investigators (i.e., physicians interacting with the patients enrolled in the trial). The investigators may have varying levels of expertise with the type of adverse event at issue – for example, a rheumatologist acting as investigator in a Vioxx trial would not be expected to have expertise in diagnosing cardiovascular events. As a result, individual investigators may apply varying criteria to their diagnoses and sometimes misdiagnose events.

Under the standard procedure recommended by the Board of Scientific Advisors, an independent expert committee would re-evaluate (or “adjudicate”) investigator-reported cardiovascular adverse events based on its review of the underlying medical reports. Such adjudication would be conducted on a blinded basis, meaning that the committee members would not know whether any given patient had taken the selective Cox-2 inhibitor, an active comparator, or placebo. In its report, the Board of

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<sup>277</sup> 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 739.

Scientific Advisors noted: “Knowledge that this plan [to conduct a meta-analysis of cardiovascular events pursuant to the recommended procedures] is in place should be reassuring to the FDA as they consider the prostacyclin biosynthesis question.”<sup>278</sup>

I. The Cardiovascular Adjudication Standard Operating Procedure and the Program-wide Cardiovascular Data Analysis Plan.

In May 1998, based on the Board of Scientific Advisors’ advice, MRL began to develop what later became known as “The Standard Operating Procedure for the Surveillance, Monitoring, and Adjudication of Acute Thromboembolic Events in Clinical Trials of COX-2 Specific Inhibitors” (the “Cardiovascular Adjudication SOP”).<sup>279</sup> Pursuant to the Cardiovascular Adjudication SOP, which was in place by mid-February 1999, investigator diagnoses of specified cardiovascular adverse experiences from trials that were four weeks or longer and began in the second quarter of 1998 or later<sup>280</sup> were referred to an independent committee for blinded adjudication.<sup>281</sup> This Section describes how the Cardiovascular Adjudication SOP was prepared and approved, what the SOP mandated, and how it was implemented.

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<sup>278</sup> 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 739.

<sup>279</sup> Some Merck documents refer to certain cardiovascular events as “thrombotic.” Other Merck documents refer to the same events as “thromboembolic.” Although there is a clinical difference, witnesses and Merck internal documents used these terms interchangeably to refer to cardiovascular events caused by a clot, such as a myocardial infarction or stroke, and we do not distinguish between them for purposes of these Appendices.

<sup>280</sup> 2/16/99 First Approved Draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 76.

<sup>281</sup> This meant that Protocol 078 (assessing efficacy of Vioxx in the prevention of Alzheimer’s disease in patients with mild cognitive impairment), which had started in April 1998, and the VIGOR Trial (assessing the gastrointestinal safety of Vioxx), which started in January 1999, would be among the first trials subject to the Cardiovascular Adjudication SOP.

1. Chronology.

After the May 1998 Board of Scientific Advisors meeting, Dr. Nies asked Dr. Watson to lead the effort to prepare the Cardiovascular Adjudication SOP.<sup>282</sup> On May 20, 1998, a task force formed to assist in that effort held its first meeting.<sup>283</sup> The task force included Dr. Eliav Barr, Cardiovascular Clinical Research, MRL, Dr. Daniels from Clinical Sciences,<sup>284</sup> Mr. Bolognese, a biostatistician, and Dr. Gregory Geba, Associate Medical Director, Clinical Development Program, Medical and Scientific Affairs, U.S. Human Health.<sup>285</sup>

The Clinical Development Oversight Committee oversaw preparation of the Cardiovascular Adjudication SOP. On June 10, 1998, the Committee endorsed the task force's proposed plan (i) to include Vioxx and Arcoxia trials of at least four weeks duration conducted by MRL, Merck's Clinical Development Program ("CDP") and Merck's Clinical Development Studies Program ("CDSP"),<sup>286</sup> (ii) to include arterial and

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<sup>282</sup> Minutes of 5/12/98 Vioxx Project Team meeting, MRK-ABF0002399, at 05.

<sup>283</sup> 5/20/98 memorandum from D. Watson to J. Anderson et al., MRK-AFO0023534, at 34.

<sup>284</sup> Although Dr. Daniels was a member of the task force, he did not attend the May 1998 taskforce meeting. 5/20/98 memorandum from D. Watson to J. Anderson et al., MRK-AFO0023534, at 34 (Dr. Daniels not listed on the attendee list).

<sup>285</sup> 5/20/98 memorandum from D. Watson to J. Anderson et al., MRK-AFO0023534, at 34.

<sup>286</sup> Minutes of 6/10/98 CDOC meeting, MRK-ABP0003616, at 22-23.

The CDP and CDSP Departments conducted clinical trials in addition to and largely separate from those conducted by MRL. Their studies were post-marketing studies, i.e., studies conducted after products were approved for marketing, in support of approved indications.

venous cardiovascular, cerebrovascular, and peripheral vascular events, and (iii) to establish three subspecialty adjudication committees.<sup>287</sup>

In the ensuing months, Dr. Watson and his colleagues worked on developing further the Cardiovascular Adjudication SOP, including the adjudication guidelines and a list of investigator-reported terms that would be eligible for adjudication. On November 24, 1998, Dr. Watson forwarded to the Clinical Development Oversight Committee a nearly final draft of the Cardiovascular Adjudication SOP.<sup>288</sup> On December 3, 1998, Dr. Seidenberg, head of the Pulmonary Immunology Department at the time, requested that clinical monitors of all relevant trials (i.e., trials of selective Cox-2 inhibitors of at least four weeks) be notified about the Cardiovascular Adjudication SOP and that the SOP be “noted in the protocol[s] + [when revised and approved] attached as an appendix to the protocol[s]” for those studies.<sup>289</sup> On December 16, 1998, Merck submitted to the FDA final protocol for the VIGOR Trial (discussed in detail in Appendices D and E), which stated that “[c]ardiovascular thrombotic or embolic [serious adverse events] will be adjudicated [in the VIGOR Trial] by an independent committee as a part of a combined analysis with other [Vioxx] clinical studies” and that “[h]andling of these acute thrombotic or embolic vascular [serious adverse events] will be defined in a

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<sup>287</sup> Minutes of 6/10/98 CDOC meeting, MRK-ABP0003616, at 22-23; see also 6/98 slide presentation of D. Watson to CDOC, “Strategies for Surveillance, Monitoring, and Adjudication of Acute Thrombotic/Embolic Vascular Events in COX-2 Clinical Trials,” MRK-ABP0003649, at 63-64.

<sup>288</sup> 11/24/98 memorandum from D. Watson to CDOC, MRK-AJA0071487, at 87 (attaching a draft of the Cardiovascular Adjudication SOP).

<sup>289</sup> 12/3/98 handwritten note from B. Seidenberg to S. Harper, MRK-ABS0209917, at 17.

separate document.”<sup>290</sup> The Clinical Development Oversight Committee considered the draft at its December 3, 1998 meeting,<sup>291</sup> and Dr. Watson circulated an approved draft that incorporated suggested changes on February 16, 1999.<sup>292</sup>

2. Summary of the Cardiovascular Adjudication SOP.

The 49-page approved Cardiovascular Adjudication SOP set forth the purpose and scope of the procedure and specified the process for identifying eligible investigator-reported adverse events and collecting the underlying medical paperwork.<sup>293</sup> The Cardiovascular Adjudication SOP also stated who was eligible to serve on the adjudication committee and specified the responsibilities of that committee.

a. Purpose and scope of the Cardiovascular Adjudication SOP.

The Cardiovascular Adjudication SOP stated that the “background” for the SOP was the findings of Protocol 023 and the FitzGerald prostacyclin hypothesis.<sup>294</sup> It stated

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<sup>290</sup> Final protocol for the VIGOR Trial, MRK-I8940042886, at 932 (attached to 12/16/98 letter from R. Silverman to R. DeLap\*, MRK-AAD0009576, at 76 (stating that “[t]he cardiovascular thrombotic and embolic adverse event adjudication has been added” to the protocol)); see also 8/16/99 letter from E. Floyd\*, Associate Director, Regulatory Affairs, MRL, to K. Midthun\*, FDA, MRK-AAF0002256 (attaching a copy of the Cardiovascular Adjudication SOP as Appendix 6 to third amended Protocol for the VIGOR Trial, MRK-I8940053317, at 321, 366-67 & 409).

<sup>291</sup> Minutes of 12/3/98 CDOC meeting, MRK-ABP0004935, at 39; see also 12/98 slide presentation of D. Watson to CDOC, “Standard Operating Procedure for the Surveillance, Monitoring, and Adjudication of Acute Thrombotic/Embolic Vascular Events in Clinical Trials of COX-2 Agents,” MRK-ABP0005034-61.

<sup>292</sup> 2/16/99 email from D. Moyer to G. Block et al., MRK-ACV0020567, at 67 (attaching 2/11/99 memorandum from D. Watson and L. Nelsen, MRK-ACV0020568, at 68 (listing changes requested by CDOC); 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570-618).

<sup>293</sup> 2/16/99 first approved draft of Cardiovascular Adjudication SOP, MRK-ACV0020570-618.

<sup>294</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 574.

that “[t]he clinical implications of partially inhibiting the production of [prostacyclin] without inhibiting thromboxane [were] unknown.”<sup>295</sup> The document also stated that the purpose of the procedure was “to provide standardized data for pooled analyses of the incidence of vascular events in patients treated with a [selective] COX-2 compound, compared with that of patients treated with one or more comparator agents.”<sup>296</sup>

The Cardiovascular Adjudication SOP applied to all trials of Vioxx, Arcoxia and “future” selective Cox-2 compounds of at least four weeks<sup>297</sup> that began after the first quarter of 1998.<sup>298</sup> The Cardiovascular Adjudication SOP also prespecified a set of approximately 100 adverse events that, if reported by an investigator, would be eligible for adjudication.<sup>299</sup>

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<sup>295</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 574.

<sup>296</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 574.

<sup>297</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 573.

<sup>298</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 576.

<sup>299</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 587 (Appendix B, listing terms eligible for adjudication).

The Cardiovascular Adjudication SOP called for adjudication of all such events that occurred while a patient was on study treatment or within 14 days following a patient’s discontinuation of study treatment (e.g., due to an adverse reaction). 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 573. This 14-day follow-up period is a standard approach commonly used in clinical drug trials. When the goal of the investigation is to assess the drug’s immediate or acute effect, the 14-day approach is preferred because including in the analysis events that occurred long after discontinuation might dilute any effect seen while or soon after patients were using the drug.

An alternative approach, known as the “intention-to-treat” method, would have been to collect and adjudicate events that occurred during the entire length of the trial even if a patient dropped out while the trial was ongoing and even if a patient never received the treatment. <http://www.clinicaltrials.gov/ct/info/glossary>. The intention-to-treat approach is generally followed when the goal of the investigation is to assess long-term effects of a drug. It is not clear whether

b. Implementation of the Cardiovascular Adjudication SOP.

Merck's Epidemiology Department, which was part of Biostatistics and Research Decision Sciences, MRL, was responsible for overall administration of the Cardiovascular Adjudication SOP.<sup>300</sup> Other Merck personnel involved in the implementation of the SOP were members of the Worldwide Product Safety and Epidemiology Department and clinical monitors for the studies, who, depending on the study, could be members of MRL, the Clinical Development Program or the Clinical Development Studies Program.<sup>301</sup>

The Worldwide Product Safety and Epidemiology Department was responsible for monitoring adverse event reports from clinical trials of Vioxx and Arcoxia and identifying those cardiovascular adverse events that were potentially eligible for adjudication.<sup>302</sup> Clinical monitors were then responsible for requesting the underlying medical paperwork for the identified events from the investigators.<sup>303</sup> When doing so,

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MRL scientists preparing the Cardiovascular Adjudication SOP considered using an "intention-to-treat" approach. According to Dr. Barr, however, the risk hypothesized by Dr. FitzGerald\* in 1997 would be expected to materialize, if at all, shortly after patients began treatment because effects on platelet function (a basis of Dr. FitzGerald's\* hypothesis), if clinically significant, were known to have an immediate effect on clinical outcomes. As discussed in Appendix R, after Vioxx was withdrawn from the market, Merck collected follow-up data from patients randomized into the APPROVe Trial in order to explore whether the increased relative risk on Vioxx seen in the APPROVe Trial persisted more than 14 days after patients discontinued treatment and, if so, for how long. The primary analysis conducted on that data was an intention-to-treat analysis.

<sup>300</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 573.

<sup>301</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 573.

<sup>302</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 573.

<sup>303</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 573.

clinical monitors remained blinded to the treatment allocation of the particular patient.<sup>304</sup>

After the paperwork necessary for adjudication was assembled, it was forwarded to the adjudication committee.<sup>305</sup>

c. The blinded adjudication committee.

The adjudication committee (referred to in the SOP as “the Vascular Event Committee”) was composed of three specialty subcommittees for cardiac, cerebrovascular, and peripheral (pulmonary, abdominal/pelvic, and extremities) events.<sup>306</sup> These subcommittees included external cardiologists, neurologists, and vascular medicine internists, respectively.<sup>307</sup> Members of the Vascular Event Committee could not be employees of Merck, investigators for any of the clinical trials covered by the Cardiovascular Adjudication SOP or involved in such trials in any capacity.<sup>308</sup>

When adjudication packages (i.e., the underlying medical documentation obtained from the field) were forwarded to the relevant adjudication subcommittee, the packages did not reveal the study in which the patient was enrolled or any treatment information about the particular patient.<sup>309</sup> This meant that the adjudicators did not know whether a

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<sup>304</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 573.

<sup>305</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 573.

<sup>306</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 573.

<sup>307</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 573.

<sup>308</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 574.

<sup>309</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 576 (stating that after the Worldwide Product Safety and Epidemiology Department identified potentially eligible events and before the relevant clinical monitor was notified, an “Epidemiology staff member

particular patient had taken a selective Cox-2 inhibitor, an active comparator or placebo.

Such “blinding” was meant to eliminate the possibility of bias in the adjudication process.

Upon receiving the adjudication package, each member of the relevant subcommittee performed a preliminary adjudication and decided, based on his or her evaluation of the underlying medical documentation, whether the event met the prespecified criteria for a thrombotic event, such as a myocardial infarction or a stroke.<sup>310</sup> If the event did not meet the prespecified criteria, but the adjudicators thought that “the clinical picture was strongly suggestive of an event of interest,” they could “use good clinical judgment to classify the event as meeting the criteria.”<sup>311</sup> Alternatively, they could classify the event as non-thrombotic or refer the event for adjudication by a different specialty subcommittee. In cases where preliminary adjudications were not unanimous, final adjudication was reached by majority vote.<sup>312</sup>

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who [had] no responsibility to the [Adjudication Committee] or for adjudication procedures” would “mask” “patient and treatment identifiers” on the Worldwide Adverse Experience System report).

<sup>310</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 606.

<sup>311</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 606.

<sup>312</sup> 2/16/99 first approved draft of the Cardiovascular Adjudication SOP, MRK-ACV0020570, at 576-77. The Cardiovascular Adjudication SOP was revised several times, including in January 2000. The January 2000 revision included an amendment to remove from the 134-term list of terms eligible for adjudication several terms that had been determined to have “a low likelihood of being thromboembolic events.” 1/4/00 memorandum from D. Watson and L. Nelsen, MRK-ABC0000027, at 27 (attaching revisions to the Cardiovascular Adjudication SOP, MRK-ABC0000030, at 34-35). Those removed terms were: aortic atherosclerosis, aortic disorder, asystole, atherosclerosis, atrial fibrillation, atrial flutter, cardiac aneurysm, cardiac dykinesia, cardiac output low, cardiomyopathy, congestive heart failure, cor pulmonale, electromechanical dissociation, idioventricular rhythm, incomplete left bundle branch block, left bundle branch block, peripheral atherosclerosis, pulmonary edema, varicosity, venous insufficiency.

According to Dr. Watson, once the Cardiovascular Adjudication SOP went into effect in late 1998 and

### 3. Program-wide Cardiovascular Data Analysis Plan.

Simultaneously with the development of the Cardiovascular Adjudication SOP, the Clinical Development Oversight Committee and the Cardiovascular Adjudication SOP task force began discussing a data analysis plan that would specify the statistical analyses for future pooled analyses of events confirmed as thrombotic events pursuant to the Cardiovascular Adjudication SOP.<sup>313</sup> At MRL, data analysis plans were prepared by statisticians in conjunction with personnel from Clinical Sciences, Epidemiology and other departments and had to be approved by the Clinical Development Oversight Committee.<sup>314</sup> According to Merck's internal policy, a data analysis plan was required

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clinical monitors (including Dr. Reicin, the Clinical Monitor for the VIGOR Trial, which began in early 1999) began to request from the field and review medical reports associated with the investigator-reported events, they determined that some of the events, although prespecified as eligible for adjudication in the Cardiovascular Adjudication SOP, did not appear, based on the medical reports, to be the types of events that might be confirmed by the Cardiovascular Adjudication Committee as thromboembolic in nature. As a result, the clinical monitors and members of MRL's Cardiovascular Clinical Sciences group decided that adjudication of such events was not necessary and suggested that these events be removed from the list of events eligible for adjudication. See 8/4/05 deposition of D. Watson at 404 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.) (testifying that he "agreed with the removal" of terms).

Merck continued, however, to monitor and report to the FDA the investigator-reported events removed from the adjudication list, and these events were later available for analyses of investigator-reported (as opposed to adjudicated and confirmed) events. 8/4/05 deposition of D. Watson at 598 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>313</sup> Minutes of 5/15/98 Cox-2 Cardiovascular SAE Surveillance Task Force meeting, MRK-AFO0023534, at 35 ("Associated data analysis plans will describe the methods for pooled analyses of confirmed events."); 6/98 slide presentation of D. Watson to CDOC, MRK-ABP0003649, at 65 (stating that the proposed analysis would "[e]stimate and compare incidence of acute thrombotic/embolic vascular events with COX-2 compounds and comparators" and "[e]stimate difference (and 95% CIs) with Cox-2 vs. one or more pooled NSAIDs (and [placebo] if possible)").

<sup>314</sup> Merck's Medical Affairs Procedures and Policies – Procedure 38: The Data Analysis Plan (showing revisions effective as of Jan 1, 1999), MRK-NJ0083053, at 57, 59. More specifically, it describes the variables measured for efficacy and safety; when and how efficacy and safety variables will be measured; the statistical methods used for efficacy and safety analysis; data handling convention in the analysis; rules for identifying protocol violators; and rules for inclusion and exclusion of protocol

for “[a]ll Phase IIb/III trials, ‘mega’ trials and Phase IV/V clinical trials sponsored by [Merck] that involve[d] a new indication or that [were] planned to support a substantive label change.”<sup>315</sup> Merck’s policy required that a data analysis plan be prepared before unblinding of any of the data that would be analyzed pursuant to the data analysis plan.<sup>316</sup> Merck policy also required submission of data analysis plans intended to support a label change to the FDA for information, review and comment.<sup>317</sup> The reason for this practice was to avoid any appearance of bias in the analyses done after the data were unblinded.

Minutes of the June 10, 1998 Clinical Development Oversight Committee meeting, at which Dr. Watson discussed the task force’s proposed scope and implementation for the Cardiovascular Adjudication SOP, state that “CDOC . . . raised some concerns with timing for notification to regulatory agencies of our intent to monitor and adjudicate these events (e.g., submission of DAP).”<sup>318</sup> Witnesses could not recall to what discussion the quoted statement from the minutes referred.

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violators in an analysis. Merck’s Medical Affairs Procedures and Policies – Procedure 38: The Data Analysis Plan (showing revisions effective as of Jan 1, 1999), MRK-NJ0083053, at 57.

<sup>315</sup> Merck’s Medical Affairs Procedures and Policies – Procedure 38: The Data Analysis Plan (showing revisions effective as of Jan 1, 1999), MRK-NJ0083053, at 56.

<sup>316</sup> Merck’s Medical Affairs Procedures and Policies – Procedure 38: The Data Analysis Plan (showing revisions effective as of Jan 1, 1999), MRK-NJ0083053, at 59.

<sup>317</sup> Merck’s Medical Affairs Procedures and Policies – Procedure 38: The Data Analysis Plan (showing revisions effective as of Jan 1, 1999), MRK-NJ0083053, at 59. The policy was amended in 1999 to provide that “Exceptions to sending a DAP to the FDA must be approved by [Regulatory Affairs, Domestic].” Id.

<sup>318</sup> Minutes of 6/10/98 CDOC meeting, MRK-ABP0003616, at 23.

At the December 3, 1998 Clinical Development Oversight Committee meeting, the Committee asked Dr. Watson to present “a preliminary analysis plan including hypothesis and power considerations at the [next] CDOC meeting.”<sup>319</sup> On January 6, 1999, Dr. Watson presented an outline of a proposed data analysis plan for the pooled analysis.<sup>320</sup> In his presentation, Dr. Watson stated that “[a] formal data analysis plan [would] be drafted in 1999 and approved before the first analysis is conducted.”<sup>321</sup> Dr. Watson’s proposed plan stated that “the statistical analyses” would “estimate the incidence of serious thromboembolic events in patients treated with [Vioxx and Arcoxia] compared to patients that have received comparator NSAIDs” and that “[s]ummary statistics and the incidence rates in each treatment group and their rate differences (and 95% [confidence intervals]) [would] be calculated.”<sup>322</sup> Dr. Watson’s proposed plan stated, however, that “no formal statistical hypothesis testing” would be done,<sup>323</sup> meaning that “the rates . . . that were calculated would not be compared to each other in a formal

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<sup>319</sup> 2/11/99 memorandum from D. Watson, L. Nelsen to “RIBL,” MRK-ACV0020568, at 68.

<sup>320</sup> Minutes of 1/6/99 CDOC meeting, MRK-NJ0120180, at 81-82.

<sup>321</sup> Background memorandum for D. Watson’s presentation at 1/6/99 CDOC meeting, MRK-NJ0120174, at 74.

<sup>322</sup> Minutes of 1/6/99 CDOC meeting, MRK-NJ0120180, at 81. As mentioned above, a confidence interval is a range of values that is likely to cover the true parameter (e.g., relative risk of adverse events between two drugs). It quantifies the margin of error for the observed result and thus indicates how precise the observed result is.

<sup>323</sup> Minutes of 1/6/99 CDOC meeting, MRK-NJ0120180, at 81

way using statistical methods”<sup>324</sup> “to try to rule out or to try to address a particular hypothesis.”<sup>325</sup>

Dr. Watson proposed to combine and analyze studies in three blocks: (i) Arcoxia trials; (ii) placebo-controlled Vioxx trials; and (iii) active comparator-controlled Vioxx trials. He also listed primary, secondary and tertiary event types,<sup>326</sup> and noted that the analyses for any block of studies would be powered to detect a 2- to 3-fold higher rate in primary events in patients treated with Vioxx or Arcoxia and a 3- to 5-fold higher rate for secondary and tertiary event types combined. This meant that if there were a 2- to 3-fold or greater increase in the rate of primary events occurring on Vioxx, such an increase would be statistically significant. On the other hand, these blocks of studies would have no power to detect at a statistically significant level a less than 2-fold increase in the rate of primary events.<sup>327</sup>

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<sup>324</sup> 8/4/05 deposition of D. Watson at 426 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>325</sup> 8/4/05 deposition of D. Watson at 427-28 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>326</sup> Proposed primary type events were fatal and non-fatal myocardial infarction, unstable angina pectoris, fatal and non-fatal ischemic stroke. Proposed secondary type events were fatal and non-fatal arterial thromboembolism, sudden cardiac death/resuscitated cardiac arrest, and transient ischemic attack. Proposed tertiary type events were fatal and non-fatal pulmonary embolism, fatal and non-fatal venous thrombosis and cardiac (atrial or ventricular) thrombosis. Minutes of 1/6/99 CDOC meeting, MRK-NJ0120180, at 81-82. The events were grouped in the three groups “according to whether they are primarily mediated by platelet aggregation (primary and tertiary events of interest more so than tertiary), and by the certainty with which the diagnosis could be said to represent an acute platelet-mediated event (primary > secondary > tertiary).” Background memorandum for D. Watson’s presentation at 1/6/99 CDOC meeting, MRK-NJ0120174, at 74.

<sup>327</sup> Background memorandum for D. Watson’s presentation at 1/6/99 CDOC meeting, MRK-NJ0120174, at 76.

At the January 6, 1999 meeting, the Clinical Development Oversight Committee agreed with Dr. Watson's proposed analysis strategy but stated that, to increase the power of the primary analysis, the analysis should look at the primary, secondary and tertiary event types combined.<sup>328</sup> As discussed in Exhibit 3 to the Report, whether a particular analysis is able (or powered) to detect a difference in relative risk between two treatments at a statistically significant level depends in part on the overall number of adverse events at issue. The power of the analysis increases as the overall number of the relevant adverse events goes up. In addition, the Clinical Development Oversight Committee decided that the analyses for Vioxx and Arcoxia should be done separately, rather than together.<sup>329</sup>

At the January 6, 1999 meeting, the Clinical Development Oversight Committee also assigned Mr. Bolognese, an MRL biostatistician, to prepare and present to the Committee a formal data analysis plan "as early as feasible" and before any analyses were completed.<sup>330</sup> By September 1999, however, Mr. Bolognese had not yet finalized a

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<sup>328</sup> Minutes of 1/6/99 CDOC meeting, MRK-NJ0120180, at 82. Dr. Spector stated that the reason for combining the events for primary analysis was to increase the power of the analysis. Dr. Spector stated that, once a secondary analysis is prespecified in a data analysis plan, it will be done regardless of the results of the primary analysis.

<sup>329</sup> Minutes of 1/6/99 CDOC meeting, MRK-NJ0120180, at 82.

<sup>330</sup> Minutes of 1/6/99 CDOC meeting, MRK-NJ0120180, at 82. Dr. Spector stated that, by January 1999, conversations about a cardiovascular DAP had been ongoing for quite some time and that he felt it was about time a DAP was finally developed, which is why the minutes refer to a request for a presentation of a DAP "as soon as feasible."

Mr. Bolognese stated that he did not read the instruction to prepare the data analysis plan "as early as feasible" as having an unusual sense of urgency. Mr. Bolognese indicated that, if the assignment had to be done very quickly, CDOC would have specified a particular deadline. Instead, the instruction

draft of such a data analysis plan, and, around that time, members of the Clinical Development Oversight Committee instructed Mr. Bolognese not to continue his work on the project.<sup>331</sup> The collection and adjudication of cardiovascular events, however, continued without interruption.

It is not entirely clear why Mr. Bolognese was instructed to defer his work on the cardiovascular data analysis plan. The decision appears to have been based in part on the fact that there was no plan to obtain a statement in the label based on the planned pooled cardiovascular analysis and thus no need to have the data analysis plan finalized and submitted to the FDA before any of the underlying data were unblinded.<sup>332</sup> Moreover, it was understood that the first block of data would not be available for an analysis for another two years,<sup>333</sup> if not longer, and there remained ample time to prepare the data

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was to complete the assignment as early as it could be done consistently with Mr. Bolognese's other responsibilities.

<sup>331</sup> 1/22/00 email from D. Watson to G. Block, *et al.*, MRK-AJA0128613, at 14 (“Based on discussions at CDOC, it was decided that there will be no DAP for the CV SOP, and no formal comparisons of the incidence rates for CV events among the treatment groups. The statistical analysis section has been rewritten to reflect this decision.”); 1/17/00 email from T. Capizzi to A. Reicin, D. Watson, MRK-NJ0120261, at 61 (“after CDOC decided that there should be no DAP for GI events, we received senior management approval not to pursue a CV DAP”).

<sup>332</sup> 9/14/99 email from J. Bolognese to R. Silverman, MRK-ACD0021447, at 47 (“[B]ased on the CDOC action on the post-filing PUB’s DAP [to not have a post-NDA PUB DAP], it appears to CBARDs that a DAP for the CV events monitoring is not needed, also, since there are no formal hypotheses to test. Furthermore, it seems that CV events are more remotely important to the VIOXX development than PUB events are. Thus, if no DAP is needed for post-filing PUBs, none would seem to be needed for the CV events.”); *see also* 3/14/00 email from L. Oppenheimer to A. Reicin *et al.*, MRK-NJ0121093 (“As you recall – the . . . draft PUB meta-analysis DAP was reviewed at CDOC and it was decided not to pursue based on the availability of VIGOR. Following that decision – it was also decided outside of CDOC not to write a DAP for the adjudicated cardiovascular AEs.”).

<sup>333</sup> Background memorandum for D. Watson’s presentation at 1/6/99 CDOC meeting, MRK-NJ0120174, at 75 (stating that the two Vioxx blocks of studies would not be completed until the fourth quarter of 2001 and the fourth quarter of 2003).

analysis plan before any analyses could be conducted.<sup>334</sup> In a January 14, 2000 email, Dr. Watson also noted that the “strategy” not to develop a data analysis plan and not to compare rates among the treatments was also “consistent with the idea that the data are being collected for internal consumption only until such time it is requested of us or we decide to make it public.”<sup>335</sup> The cardiovascular data analysis plan was developed in the second half of 2000, as discussed in Appendix F.

J. Research Conducted to Investigate the Protocol 023 Findings.

1. Studies Conducted by MRL.

In 1998/1999, MRL conducted several studies intended to answer some of the questions raised by Protocol 023 with regard to Vioxx’s impact on urinary excretion of PGI-M, a prostacyclin metabolite. Specifically, Merck investigated:

- whether doses of Vioxx lower than the 50 mg dose used in Protocol 023 also suppressed the urinary excretion of PGI-M;
- whether Vioxx inhibited urinary PGI-M through its inhibition of Cox-2 or some other property of the Vioxx molecule;

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<sup>334</sup> See 8/4/05 deposition of D. Watson at 423-24 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.) (“My understanding at the time was that the procedure would generate data . . . that could be used in an analysis in the future. That analysis would occur when it was . . . determined that there were enough events according to a prespecified plan to analyze them. And at that time I had no idea of when . . . adequate number of events would occur. We were just starting to carry out the adjudication process and trials were ongoing, and so . . . I knew that at some point in time there would be enough events but I didn’t know when.”).

<sup>335</sup> 1/14/00 email from D. Watson to A. Reicin et al., MRK-NJ0120172, 72 (“Jim [Bolognese] had the assignment to develop a DAP for the analysis. Since then we (Jim and I) have been instructed by CDOC and senior management to not do so, and that comparisons with other treatments are not to be made.”). Dr. Watson has testified that he did not recall whether he had been told about the reasons for the decision not to develop a data analysis plan at the time. 8/4/05 deposition of D. Watson at 464 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

- whether Vioxx suppressed prostacyclin metabolism or its renal clearance, as opposed to its synthesis;
- whether prostacyclin production in rabbit aortas was mediated by Cox-2 or Cox-1; and
- whether acetaminophen, which was believed to have no effect on the risk of cardiovascular events, suppressed, as did Vioxx, the urinary PGI-M excretion without suppressing thromboxane.<sup>336</sup>

These studies are discussed below. Merck subsequently conducted and funded several additional studies, which, like the rabbit study, explored the contribution of Cox-2 to vascular production of prostacyclin. Those subsequent studies are discussed in Appendix J.

a. Study to assess the effect of lower doses of Vioxx on the urinary excretion of PGI-M in humans.

As mentioned above, the dose of Vioxx used in Protocol 023 was 50 mg, and it was not clear what effect, if any, lower doses of Vioxx (including 12.5 mg and 25 mg – the expected clinical doses for the treatment of osteoarthritis) would have on the urinary excretion of PGI-M. In February 1998, Merck completed Protocol 061, a pharmacological study, which, among other things, showed that Vioxx at 12.5 mg and 25 mg also reduced the excretion of PGI-M.<sup>337</sup> The results of Protocol 061 are reflected in the table below:

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<sup>336</sup> “Dr. Alan Nies’ Writeup for Meeting of Board of Scientific Advisors,” MRK-NJ0162361, at 370; see also Wong E, Huang JQ, Tagari P, Riendeau D. Effects of COX-2 inhibitors on aortic prostacyclin production in cholesterol-fed rabbits. Atherosclerosis. 2001;157:393-402.

<sup>337</sup> Van Hecken \* A, Schwartz JI, Depré \* M, et al. Comparative inhibitory activity of rofecoxib, meloxicam, diclofenac, ibuprofen, and naproxen on COX-2 versus COX-1 in healthy volunteers. J Clin Pharmacol. 2000;40:1109-1120, at 1112-13; see also Protocol 061 Clinical Study Report, MRK-ABJ0026211, at 281.

Table 4

Protocol 061 – Analysis of Change from Baseline on Day 6  
for Urinary PGI-M (pg/mg Creatinine)

Treatment	N	Baseline Mean (SD)	Day 6 Mean (SD)	Mean Change (SD)	LS Mean Change (SB) *
Placebo	15	193.57 (60.17)	184.34 (69.53)	-9.23 (64.47)	-7.27 (10.91)
Vioxx (12.5 mg)	12	176.93 (88.09)	94.34 (25.22)	-82.58 (76.16) <sup>†</sup>	-92.70 (12.24) <sup>‡</sup>
Vioxx (25 mg)	12	205.98 (84.99)	97.27 (49.68)	-108.70 (77.76) <sup>†</sup>	-97.75 (12.25) <sup>‡</sup>
Between-Treatment Comparison			Difference in LS Mean	90% CI for Difference	p-Value
Vioxx (12.5 mg) versus placebo			-85.4	(-112.4, -58.4)	<0.001
Vioxx (25 mg) versus placebo			-90.5	(-117.5, -63.5)	<0.001
<sup>†</sup> Univariate within-treatment p-value ≤ 0.050.				<sup>*</sup> Adjusted for baseline levels.	
<sup>‡</sup> ANCOVA within-treatment p-value ≤ 0.050.					

A subsequent analysis of results of Protocol 023 and Protocol 061 showed that the effect of Vioxx on PGI-M decreased with lower doses, but such dose response was relatively shallow, meaning that there was not much differences in the effect among the three doses.<sup>338</sup> For the 50 mg dose, mean differences from placebo observed in Protocol 023 on day 13 of dosing were -60.79% (90% confidence interval, -83.83% to -37.75%).<sup>339</sup> In comparison, for the 25 mg and 12.5 mg doses, mean differences from placebo observed in Protocol 061 on day 6 of dosing were -45.47% (90% confidence interval, -61.16% to -29.79%) and -40.66% (90% confidence interval, -56.35% to -24.98%), respectively.<sup>340</sup>

<sup>338</sup> 3/14/00 memorandum from P. Larson to B. Gertz, MRK-ABC0037091, at 92.

<sup>339</sup> 3/14/00 memorandum from P. Larson to B. Gertz, MRK-ABC0037091, at 92.

<sup>340</sup> 3/14/00 memorandum from P. Larson to B. Gertz, MRK-ABC0037091, at 92.

b. Study of other Cox-2 selective inhibitors' effect  
on urinary prostacyclin metabolites in dogs.

As mentioned above, it was not clear from Protocol 023 whether the effect of Vioxx on urinary excretion of PGI-M was caused through inhibition of Cox-2 (and thus a class effect shared by all Cox-2 inhibitors) or through some other property of the Vioxx molecule.<sup>341</sup> To help answer this question, in 1998, Merck Frosst undertook a urinary prostaglandin study in dogs.<sup>342</sup> In the study, dogs were given Celebrex and two other non-Vioxx selective Cox-2 inhibitors for five days.<sup>343</sup> The results, which became available in October 1998, showed that all selective Cox-2 inhibitors inhibited urinary excretion of PGI-M.<sup>344</sup> This result suggested that the effect of Vioxx on PGI-M was caused by the suppression of Cox-2.<sup>345</sup>

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<sup>341</sup> Although Dr. FitzGerald\* conducted the McAdam Study around the same time that he conducted Protocol 023, it appears that MRL scientists did not know about the results of the McAdam Study (and that Celebrex, like Vioxx, appeared to suppress PGI-M, suggesting the effect was a class effect) until January 1999, when the McAdam Study was published.

<sup>342</sup> 10/22/98 memorandum from D. Riendeau to D. Nicholson and M. Gresser, MRK-ABC0006422-25; see also 2/5/98 email from P. Tagari to A. Nies *et al.*, MRK-ABC0002155, at 55 (stating that the study objective was "Demonstration that inhibition of [PGI-M] excretion is a class effect of COX-2 inhibitors in . . . dogs").

<sup>343</sup> 10/22/98 memorandum from D. Riendeau to D. Nicholson and M. Gresser, MRK-ABC0006422, at 22.

<sup>344</sup> 10/22/98 memorandum from D. Riendeau to D. Nicholson and M. Gresser, MRK-ABC0006422, at 23.

<sup>345</sup> 10/06/05 transcript of *Humeston v. Merck & Co.*, ATL-L-2272-03 MT, N.J. Super. Ct. Law Div., at 3247 (Testimony of B. Morrison: "So the conclusion then is that what we saw in patients is not a chemical thing of Vioxx it is actually due to its mechanism, so we rule out that possibility."). In addition to conducting the animal study discussed in the text, in 2000/2001, Merck conducted two studies comparing the effect of two-week treatment with Vioxx 25 mg daily, Celebrex 200 mg twice daily and Arcoxia 90 mg daily on the urinary excretion of PGI-M in elderly volunteers (*i.e.*, healthy patients). The studies showed that all three selective Cox-2 inhibitors caused a similar reduction (close to 60% from baseline) in the urinary excretion of PGI-M, further confirming that the effect on

c. Studies to assess the effect of selective Cox-2 inhibition  
on metabolism and renal clearance of prostacyclin.

Scientists at MRL believed, and the Board of Scientific Advisors agreed, that Protocol 023 did not rule out the possibility that the observed reduction in the urinary excretion of PGI-M reflected a reduction in the renal clearance and/or metabolism of prostacyclin into PGI-M and not an inhibition in the biosynthesis of prostacyclin. To exclude these possibilities, in 1998/early 1999, Merck Frosst conducted two different studies. The first study involved infusing dogs with radio-labeled hydrolysis product of prostacyclin and measuring their excretion of radioactive urinary PGI-M. In the study, the levels of excretion of radioactive urinary PGI-M did not vary significantly between the dogs in which Cox-2 was inhibited (via administration of Celebrex) and their controls, and thus produced no evidence that Cox-2 inhibited renal clearance of prostacyclin.<sup>346</sup>

The second study explored whether selective inhibition of Cox-2 inhibited suppressed the metabolism of prostacyclin into PGI-M in the rat, dog and human liver. This study produced no evidence that selective Cox-2 inhibition affected metabolism of prostacyclin in the liver.<sup>347</sup>

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PGI-M was a class effect. Schwartz JI, Vandormael\* K, Tach\* C, et al. Effect of rofecoxib, etoricoxib, celecoxib, and naproxen on urinary excretion of prostanoids in elderly volunteers. J Am Soc Nephrol. 14:2003 (abstract presented at the 36th Annual Meeting of the American Society of Nephrology, San Diego, November 2003), MRK-ADY0007320, at 20.

<sup>346</sup> 3/8/99 memorandum from J. Falguyret and D. Percival (Biochemistry and Molecular Biology at Merck Frosst) to D. Reindeau (cc: A. Nies, B. Gertz et al.), MRK-ABC0006396, at 402.

<sup>347</sup> 10/6/05 transcript of Humeston v. Merck & Co., ATL-L-2272-03 MT, N.J. Super. Ct. Law Div., at 3251-52 (testimony of B. Morrison).

These studies failed to produce any support for the hypothesis that Vioxx affected prostacyclin metabolism or its renal clearance, and thus suggested that Vioxx, in fact, suppressed prostacyclin biosynthesis.<sup>348</sup> These studies did not produce any evidence, however, on the issue of where in the body (lungs, vasculature and/or elsewhere) prostacyclin production was catalyzed by Cox-2 and suppressed by Vioxx.<sup>349</sup>

d. Study to assess contribution of Cox-2 to prostacyclin production in rabbit aortas.

As mentioned above, MRL scientists believed that even if PGI-M were an index of extra-renal production of prostacyclin, it was not clear that the suppression in urinary PGI-M caused by Vioxx signified a reduction in vascular production of prostacyclin (as opposed to a reduction in prostacyclin production by some other part of the body, e.g., the lungs). It was also unclear whether vascular production of prostacyclin was mediated by Cox-1, Cox-2, or both. In 1998, scientists at Merck Frosst conducted a study in rabbits to evaluate the contribution of Cox-2 to prostacyclin production in aortic tissue. The study assessed the effects of four drugs (three selective Cox-2 inhibitors and one non-selective NSAID) on prostacyclin synthesis (stimulated by infused arachidonic acid) in aortic tissue taken from euthanized rabbits, some of which had been healthy and some

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<sup>348</sup> 8/27/03 deposition of B. Gertz at 59 (Younge v. Merck & Co., No. 03-CV-00125M, S.D. Ala.) (“We did not find an alternative explanation. So I would say that [the reduction in PGI-M] does reflect a reduction of prostacyclin above the kidney.”); id. at 171 (“We spent extensive amount of studies to try to [see if PGI-M was coming from the kidneys only]. We did not show it.”).

<sup>349</sup> E. Scolnick, “Scientific Review,” at 5 (“Studies conducted at Merck Frosst were not able to determine the source in animals of this prostacyclin metabolite.”), [http://www.merck.com/newsroom/vioxx\\_withdrawal/pdf/VIOXX\\_scientific\\_review.pdf](http://www.merck.com/newsroom/vioxx_withdrawal/pdf/VIOXX_scientific_review.pdf).

of which had been in early stages of atherosclerosis.<sup>350</sup> The aortic tissue was also analyzed for the presence of Cox-1 and Cox-2.

The results, which became available in March 1999,<sup>351</sup> showed that in both healthy rabbits and rabbits with atherosclerosis, Vioxx and another highly selective Cox-2 inhibitor called DFP had no effect on prostacyclin synthesis. However, both Celebrex, which was known to inhibit Cox-1 at least to some extent, and indomethacin (a non-selective NSAID) inhibited the tissue's ability to synthesize prostacyclin. Further, Cox-1 was found to be expressed in the aortas and platelets of both healthy and atherosclerotic rabbits, but Cox-2 was not detected in any of the rabbit aortas.

The article about the study, which was published in Atherosclerosis in 2001, stated that “[t]hese data suggest that vascular [prostacyclin] synthesis is primarily dependent on the activity of COX-1 and not COX-2” in both normal rabbits and rabbits with atherosclerosis.<sup>352</sup>

The article concluded: “The current study suggests that the aorta is not a tissue that plays a major role in systemic COX-2 dependent prostacyclin production.”<sup>353</sup> The article referenced other evidence that under certain conditions, prostacyclin production

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<sup>350</sup> Wong E, Huang JQ, Tagari P, Riendeau D. Effects of COX-2 inhibitors on aortic prostacyclin production in cholesterol-fed rabbits. Atherosclerosis. 2001;157:393-402, at 394.

<sup>351</sup> 3/16/99 memorandum from E. Wong to D. Riendeau (cc: B. Gertz, A. Nies, et al.), MRK-ABC0006410-15 (reporting results of the study).

<sup>352</sup> Wong E, Huang JQ, Tagari P, Riendeau D. Effects of COX-2 inhibitors on aortic prostacyclin production in cholesterol-fed rabbits. Atherosclerosis. 2001;157:393-402, at 399.

<sup>353</sup> Wong E, Huang JQ, Tagari P, Riendeau D. Effects of COX-2 inhibitors on aortic prostacyclin production in cholesterol-fed rabbits. Atherosclerosis. 2001;157:393-402, at 400.

can be mediated by Cox-2 in inflammatory macrophages that may infiltrate the artery wall and “endothelial [vessel wall] cells and vascular smooth muscle cells following the activation of these cells with various stimuli.”<sup>354</sup>

- e. Study to assess the effect of acetaminophen  
on prostacyclin and thromboxane metabolites.

In 1998, MRL funded a study to test the findings by scientists at Sweden’s Karolinska Institute, published in the Prostaglandins journal in 1989, that a single dose of acetaminophen 500 mg “caused a pronounced reduction” of the excretion of PGI-M but had “no effect on the thromboxane synthesis,” as measured by the urinary excretion of TX-M.<sup>355</sup> These findings, if true, would (i) mean that Vioxx and acetaminophen had the same or similar effect on the urinary excretion of prostacyclin and thromboxane metabolites; and (ii) tend to undermine the FitzGerald prostacyclin hypothesis because acetaminophen had been on the market for years and was considered safe and without cardiovascular risk.

In a January 12, 1998 email to Dr. Anthony Ford-Hutchinson, co-chair of the Vioxx Project Team, Dr. Gertz wrote:

Alan [Nies] had found a paper which aledged [sic] to have shown that [acetaminophen] produces a sharp reduction in urinary PGI-M. John Oates in his review of the paper

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<sup>354</sup> Wong E, Huang JQ, Tagari P, Riendeau D. Effects of COX-2 inhibitors on aortic prostacyclin production in cholesterol-fed rabbits. Atherosclerosis. 2001;157:393-402, at 400 (citations omitted).

<sup>355</sup> Green\* K, Drvota\* V, Vesterqvist\* O. Pronounced reduction of in vivo prostacyclin synthesis in humans by acetaminophen (paracetamol). Prostaglandins. 1989;37:311-15, MRK-NJ0017635, at 636; 1/12/98 email from B. Gertz to A. Ford-Hutchinson, MRK-ADL0001533, at 33 (“we are going to see if we can replicate the clinical result [of the Karolinska Institute Study]”).

commented that it looked real to him thogh [sic] Garret  
[FitzGerald] was less impressed. Clearly if this was real  
we would be less worried.<sup>356</sup>

Because the Karolinska Institute Study involved very few patients and  
Dr. FitzGerald\* had stated that his data showed that acetaminophen decreased both  
prostacyclin and thromboxane metabolites,<sup>357</sup> Merck decided to undertake its own  
acetaminophen study “to see if [one could] replicate the . . . result [of the Karolinska  
Institute Study].”<sup>358</sup> MRL scientists asked Dr. Ford-Hutchinson to conduct such a study  
or find an outside researcher who would do so.<sup>359</sup> In a January 13, 1998 email to  
Dr. Ford-Hutchinson and Dr. Bennett Shapiro, Executive Vice President, Basic Research,  
MRL, Dr. Scolnick wrote:<sup>360</sup>

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<sup>356</sup> 1/12/98 email from B. Gertz to A. Ford-Hutchinson, MRK-ADL0001533, at 33. Although Dr. Gertz’s email did not explain why Dr. FitzGerald\* was “less impressed” with the Karolinska Study, a subsequent memorandum from Dr. FitzGerald\* stated that he “[had] data that [did] not confirm [the Karolinska Study] results” and that “[i]n [his] experience, [acetaminophen] is a weak, non-selective [i.e., dual] [Cox] inhibitor. Therefore, it decreases both prostacyclin (PGI-M) and thromboxane (Tx-M) biosynthesis.” 2/17/98 letter from G. FitzGerald\* and F. Catella-Lawson\* to B. Morrison, MRK-NJ0017825, at 26.

<sup>357</sup> 2/17/98 letter from F. Catella-Lawson\*, G. FitzGerald\* to B. Morrison, MRK-NJ0017825, at 26 (“[W]e have data that do not confirm [the Karolinska Institute Study] results. In our experience, [acetaminophen] is a weak, non-selective [Cox] inhibitor. Therefore, it decreases both prostacyclin (PGI-M) and thromboxane (Tx-M) biosynthesis.”).

<sup>358</sup> 1/12/98 email from B. Gertz to A. Ford-Hutchinson, MRK-ADL0001533, at 33.

<sup>359</sup> 1/12/98 email from B. Gertz to A. Ford-Hutchinson, MRK-ADL0001533, at 33.

<sup>360</sup> 1/13/98 email from E. Scolnick to A. Ford-Hutchinson, MRK-ABH0014002, at 02.

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From: Scolnick, Edward M.  
Sent: Tuesday, January 13, 1998 11:22 AM  
To: Ford-Hutchinson, Anthony  
Cc: Shapiro, Bennett M.  
Subject: Tylenol and cox 2  
Importance: High

Tony and ben we all know what the issues are about MK 966 and prostacyclin and throboxane based on the urinary metabolite data. I assume we are working VERY hard to clarify this in montreal. Reynold/ Barry found a paper which purports that tylenol alos knocks down prostacyclin in urine ands not thromboxane. NO ONE knows how tylenol works: Does it inhbit cox 2 directly? probab;ly not. Does a metabokliute inhbiti cox 2? does it block induction of cox 2? The data on prostacyclin in man seems clear. can we try in animals? if it is true we MUST find out how it works.We can discuss at rmc wed/ ed

In the summer of 1998, Merck funded and MRL scientists helped to design a study to assess the effects on PGI-M and TX-M excretion of (i) single dose of acetaminophen 1000 mg; and (ii) five-day treatment with acetaminophen 1000 mg taken three times daily.<sup>361</sup> The PGI-M results, which became available on September 8, 1999,<sup>362</sup> showed that single and multiple doses of acetaminophen significantly reduced PGI-M relative to placebo.<sup>363</sup> The TX-M results, which became available on October 12, 1999, showed that (i) single doses of acetaminophen 1000 mg “significantly reduced [TX-M] relative to placebo”;<sup>364</sup> and (ii) after five days of dosing, the extent to which acetaminophen 1000 mg reduced TX-M relative to placebo was not

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<sup>361</sup> 10/12/99 memorandum from B. Musser to J. Schwartz, MRK-ADL0001407, at 07.

<sup>362</sup> 9/8/99 memorandum from B. Musser to J. Bolognese, et al., MRK-NJ0184716, at 16.

<sup>363</sup> 9/8/99 memorandum from B. Musser to J. Bolognese, et al., MRK-NJ0184716, at 16. The single dose peak inhibition (from day 1 baseline) mean difference from placebo of PGI-M was 22.2% (95% confidence interval, 7.7%, 33.1%). After five days of dosing, the peak inhibition (from baseline) mean difference from placebo of PGI-M was 15.7% (95% confidence interval, 5.3%, 23.7%).

<sup>364</sup> The single dose peak inhibition (from day 1 predose) mean difference from placebo was 29.1% for acetaminophen (95% confidence interval: 11.7%, 42.2%) and 70.4% for indomethacin (95% confidence interval: 66.2%, 73.6%). 10/12/99 memorandum from B. Musser to J. Schwartz, MRK-ADL0001407, at 07.

statistically significant.<sup>365</sup> The single-dose TX-M results differed from the results obtained in the Karolinska Study because, in that study, a single dose of acetaminophen 500 mg had “no effect” on TX-M,<sup>366</sup> whereas, in the Merck-funded study, single doses of acetaminophen 1000 mg “significantly reduced [TX-M] relative to placebo.”<sup>367</sup>

MRL scientists collaborating on the study found the TX-M results somewhat “surpris[ing]” because they did not expect acetaminophen to have any effect on the thromboxane metabolite.<sup>368</sup> Thus, in discussing the study in a poster presented at the March 2000 conference of the American Society for Clinical Pharmacology and Therapeutics, the study’s authors stated:

Acetaminophen has not previously been reported to affect the biosynthesis of [thromboxane] *in vivo*; though this present study does show some effect on urinary excretion of its metabolite [TX-M] on Day 1, but clearly less than indomethacin.

\* \* \*

These results are in partial, but not complete agreement with the previous literature – the effect of acetaminophen

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<sup>365</sup> After five days of dosing, the mean difference from placebo in peak inhibition was 12.3% for acetaminophen (95% confidence interval: -4.5%, 24.3%) and 46.4% for indomethacin (95% confidence interval: 43.4%, 48.5%). 10/12/99 memorandum from B. Musser to J. Schwartz, MRK-ADL0001407, at 07.

<sup>366</sup> Green \* K, Drvota \* V, Vesterqvist \* O. Pronounced reduction of in vivo prostacyclin synthesis in humans by acetaminophen (paracetamol). Prostaglandins. 1989;37:311-15, at 312. MRK-NJ0017635, at 636.

<sup>367</sup> 10/12/99 memorandum from B. Musser to J. Schwartz, MRK-ADL0001407, at 07.

<sup>368</sup> Undated memorandum from J. Schwartz to H. Greenberg, MRK-ADL0001344, at 44-45 (“As you know from my comments earlier there is some surprise with the [thromboxane] data. . . . [T]he data for single dose and steady state are not consistent and it is questionable if there is a true effect of acetaminophen on [thromboxane] suppression.”).

on [thromboxane] differs from the literature, as this study shows some reduction on its urinary metabolite [TX-M] on Day 1. Further investigation is warranted to confirm our findings.<sup>369</sup>

(Citations omitted).

## 2. Other Research Proposals.

Between October 1997 and September 1998, MRL scientists solicited the advice of MRL's consultants, including Dr. Oates\*, Dr. FitzGerald\*, and the Board of Scientific Advisors, with regard to what research could be done to shed further light on the findings of Protocol 023. As discussed above, Merck undertook some of the studies recommended by its consultants (including the institution of the Cardiovascular Adjudication SOP and a study to assess the effect of selective Cox-2 inhibition on the metabolism of prostacyclin), and Drs. Scolnick, Spector, Nies and Gertz considered and decided not to conduct certain other studies recommended by the consultants.<sup>370</sup> Dr. Nies has testified that MRL scientists decided not to conduct some of the studies because they thought that the proposed studies would not answer directly or conclusively the fundamental questions posed by the findings of Protocol 023, namely: (i) whether Vioxx suppressed prostacyclin production in human blood vessels; and (ii) whether Vioxx

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<sup>369</sup> See 2/28/00 draft of the 3/00 ASCPT poster at 20; see also Greenberg\* H, Schwartz J, Waldman\* A, et al. Acetaminophen (A) inhibits prostacyclin (PGI<sub>2</sub>) synthesis *in vivo* [abstract PIII-89]. American Society for Clinical Pharmacology and Therapeutics, 2000 Annual Meeting, Los Angeles, CA, March 2000.

<sup>370</sup> 9/29/98 handwritten memorandum from A. Nies to B. Gertz, R. Spector, B. Seidenberg, MRK-ABK0311068, 68 ("I told [Dr. Oates\* that MRL] would not be doing any clinical studies at this time."); see also 3/2/05 deposition of A. Nies at 145-48 (*In re Vioxx Litig.*, No. 619, N.J. Super. Ct. Law Div.) (stating that these proposals were discussed at a meeting).

increased the risk of cardiovascular events in humans.<sup>371</sup> The proposals that MRL scientists considered but did not undertake are summarized below.

a. Proposed studies in patients with elevated thromboxane/prostacyclin metabolite levels.

Protocol 023 had measured urinary metabolites in healthy patients. Drs. Oates\*, FitzGerald\* and Patrono\* independently suggested studying Vioxx in patients with vascular injury (such as patients with peripheral vascular disease, atherosclerosis, scleroderma, homocysteinemia, and smokers), who had been found to have elevated urinary PGI-M and TX-M levels.<sup>372</sup>

Dr. Oates\* wrote to Dr. Nies that measuring “the effect of Cox-2 inhibitor induced prostacyclin reduction of thromboxane metabolite excretion” would generate information on “the possible importance of prostacyclin production on platelet activation,” stating that “[a] slight decrease in thromboxane metabolite excretion would be difficult to interpret, but an actual increase would be cause for concern.”<sup>373</sup>

Dr. FitzGerald\* proposed assessing the effect of low-dose aspirin and a selective Cox-2 inhibitor on the urinary TX-M and PGI-M in patients with peripheral vascular

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<sup>371</sup> 4/1/05 deposition of A. Nies at 405 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>372</sup> 9/29/98 handwritten memorandum from A. Nies to B. Gertz, R. Spector, B. Seidenberg, MRK-ABK0311068, at 68 (stating that Dr. Oates\* contacted Dr. Nies “wanting to study Vioxx in patients with atherosclerosis/hyperlipidemia [and] elevated [thromboxane] metabolite excretion”); Undated (~9/98) letter from C. Patrono\* to M. Laurenzi, MRK-ABK0311070, at 71.

<sup>373</sup> 10/21/97 draft letter from J. Oates\* to A. Nies, OATES-001405, at 05; 10/27/97 letter from J. Oates\* to A. Nies, MRK-NJ0152620, at 22.

disease.<sup>374</sup> Dr. FitzGerald's\* proposal consisted of two parts. The first part would involve assessing the effect of low-dose aspirin on the urinary excretion of PGI-M to test the hypothesis that the elevated levels of urinary PGI-M in these patients reflected elevated levels of vascular biosynthesis of prostacyclin. Low-dose aspirin was known to inhibit platelet-derived thromboxane and have little effect, if any, on prostacyclin. If low-dose aspirin suppressed not only urinary TX-M but also urinary PGI-M in these patients, that (i) would suggest that elevated prostacyclin levels in these patients were the body's response to the elevated production of thromboxane; and (ii) tend to support the hypothesis that the elevated urinary PGI-M levels in these patients reflected elevated biosynthesis of prostacyclin in the vasculature.

The second part of Dr. FitzGerald's\* proposal was to assess the effect of a selective Cox-2 inhibitor on the urinary metabolites of such patients. Dr. FitzGerald\* noted that a selective Cox-2 inhibitor would not be expected to have any effect on thromboxane production but assessing its effect on the PGI-M "increment" would "nail the site of drug impact on [prostacyclin] as cleanly as you can hope to do in a patient population."<sup>375</sup> It appears that, while the study would have provided further evidence on selective Cox-2 inhibitors' effect on PGI-M, it would not have conclusively established whether selective Cox-2 inhibitors suppressed production of prostacyclin in the vasculature or elsewhere in the body.

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<sup>374</sup> 10/24/97 email from G. FitzGerald\* to A. Nies, MRK-NJ0051533, at 33.

<sup>375</sup> 10/24/97 email from G. FitzGerald\* to A. Nies, MRK-NJ0051533, at 33.

In its May 1998 Report (discussed in Section H of this Appendix), the Board of Scientific Advisors (which included Dr. Oates<sup>\*</sup>) also recommended that MRL study the effect of Vioxx on urinary metabolites in patients with elevated thromboxane metabolite levels. The Board of Scientific Advisors' report noted that if Vioxx administration led to a further increase of thromboxane metabolites (suggesting that prostacyclin was an important restraint on platelets in such patients), "MRL should be the first to know, and thereby be able to take the lead in developing the obvious strategy of the combination of very low-dose aspirin . . . with a Cox-2 inhibitor."<sup>376</sup>

Similarly, in September 1998, Dr. Patrono<sup>\*</sup>, an MRL consultant and a world-renowned Italian expert on prostaglandins and antiplatelet agents, offered to develop a formal proposal for a study to assess urinary thromboxane metabolite levels in patients with cardiovascular disease to assess the effect of Cox-2 derived prostacyclin on platelets in patients with cardiovascular disease.<sup>377</sup>

b. Proposed study regarding impact of  
blood flow on vascular Cox-2 and prostacyclin.

Dr. FitzGerald<sup>\*</sup> also suggested studying the effect of blood flow dynamics on expression of Cox-2 and prostacyclin in vitro.<sup>378</sup> A study by James Topper<sup>\*</sup> and colleagues published in the Proceedings of the National Academy of Sciences in 1996,

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<sup>376</sup> 5/98 "Programmatic Review: Vioxx Program," MRK-AEI0002734, at 42.

MRL's efforts with regard to combination therapy of low-dose aspirin and Vioxx, as well as other potential combination therapies, are discussed in Appendix L.

<sup>377</sup> Undated (~9/98) letter from C. Patrono<sup>\*</sup> to M. Laurenzi, MRK-ABK0311070, at 71.

<sup>378</sup> 10/24/97 email from G. FitzGerald<sup>\*</sup> to A. Nies, MRK-NJ0051533, at 33.

showed that certain kinds of flow dynamics induced Cox-2 expression in the vascular wall in vitro, suggesting that such types of blood flow might induce Cox-2 in vivo (the “Topper Study”).<sup>379</sup> The article about the Topper Study also noted that such Cox-2 induction occurred in areas of blood vessels that tended to be free of atherosclerotic lesions.<sup>380</sup> According to the authors, this “co-localization” of Cox-2 expression with healthy portions of blood vessels suggested that Cox-2 might exert a cardioprotective effect, perhaps by means of Cox-2-dependent production of prostacyclin.<sup>381</sup> In light of Protocol 023’s suggestion that Cox-2 might be responsible for production of prostacyclin, Dr. FitzGerald\* wanted to explore further the relationship between various flow dynamics, Cox-2 and prostacyclin.

c. Proposed studies regarding clinical  
impact of suppressed PGI-M levels.

Dr. FitzGerald\* also proposed to examine the relationship between prostacyclin metabolites and flow-dependent vasodilation, i.e., relaxation of vessel wall muscles, in patients on placebo and various doses of Vioxx. Because Dr. FitzGerald\* believed that

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<sup>379</sup> Topper\* JN, Cai\* J, Falb\* D, Gimbrone\* MAJ. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc Natl Acad Sci USA. 1996;93:10417-22, at 10419-21.

<sup>380</sup> Topper\* JN, Cai\* J, Falb\* D, Gimbrone\* MAJ. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc Natl Acad Sci USA. 1996; 93:10417-22, at 10419-21.

<sup>381</sup> Topper\* JN, Cai\* J, Falb\* D, Gimbrone\* MAJ. Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc Natl Acad Sci USA. 1996; 93:10417-22, at 10419-21.

flow-dependent vasodilation had an impact on clinical cardiovascular outcomes, he thought that the study would provide some evidence on whether depressed PGI-M levels would correlate with clinical outcomes (such as myocardial infarctions).<sup>382</sup>

Finally, Dr. FitzGerald\* suggested that MRL integrate urine collections into its clinical trials of Vioxx and test the urine of all patients who had a cardiovascular event to ascertain the correlation between PGI-M levels and clinical outcomes.<sup>383</sup>

d. MRL consideration of study proposals.

Drs. Scolnick, Spector, Ford-Hutchinson, Nies and Gertz discussed the various study proposals<sup>384</sup> but decided not to undertake them<sup>385</sup> because they believed that such studies would not help “assess the risks and benefits [of Vioxx] in patients” given that each study proposed to look at indirect measurements.<sup>386</sup> With regard to the studies that proposed to measure urinary metabolites, Dr. Nies explained:

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<sup>382</sup> 10/24/97 email from G. FitzGerald\* to A. Nies, MRK-NJ0051533, at 33.

<sup>383</sup> 10/24/97 email from G. FitzGerald\* to A. Nies, MRK-NJ0051533, at 33.

<sup>384</sup> 2/17/98 email from A. Nies to R. Silverman, A. Ford-Hutchinson, G. Gertz, B. Seidenberg et al., MRK-ABC0009243, at 43 (stating that Dr. Nies had “set up a meeting with ed [Scolnick] on Feb 23 to go over issues related to Cox-2/Vioxx”; listing “[r]eduction of urinary excretion of [PGI-M]” as the first item on the agenda; stating that at the meeting, Dr. Nies expected to focus on the PGI-M issue and one other issue).

<sup>385</sup> 3/2/05 deposition of A. Nies at 227 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.) (stating that Merck never did the study in unstable angina patients proposed by Dr. Patrono\*); id. at 228 (stating that Merck did not do the study assessing urinary metabolites in patients with atherosclerosis, hyperlipidemia, and elevated thromboxane metabolite excretion proposed by Dr. Oates\*). According to Dr. Nies, the decision not to do the study in smokers proposed by Dr. Oates\* was a joint decision in which he participated. 8/23/05 deposition of A. Nies at (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

<sup>386</sup> 4/1/05 deposition of A. Nies at 404-05 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.).

These are indirect measures of urinary metabolites of substance that we don't know exactly where it's being made, and I think that it's very difficult to make any specific inferences from the results that you find, and so I think we'd get data that we wouldn't be able to interpret any better than the original data.<sup>387</sup>

K. The Vioxx Cardioprotection Hypothesis.

In addition to the FitzGerald prostacyclin hypothesis, another hypothesis circulating in 1998 and discussed at the May 1998 meeting of the Board of Scientific Advisors was that Vioxx might reduce the risk of cardiovascular events in one or both of two ways. First, some evidence had suggested that atherosclerosis was a consequence of chronic inflammation.<sup>388</sup> If so, it was hypothesized that Vioxx, as well as other anti-inflammatory agents, might provide cardioprotection by inhibiting inflammation and thereby preventing the genesis, progression, and clinical manifestations of atherosclerosis.<sup>389</sup> Second, some studies had suggested that Cox-2 expressed in arterial

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<sup>387</sup> 4/1/05 deposition of A. Nies at 405 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.); see also 8/23/05 deposition of A. Nies at 694 (In re Vioxx Litig., No. 619, N.J. Super. Ct. Law Div.) (stating that Dr. Oates' study "was not to see the effects of Vioxx in smokers[, but] to look at smokers' urine to see whether there was an effect of a metabolite of a prostaglandin").

<sup>388</sup> Background materials for the 3/31/99 consultants' meeting, "Potential Role of Vioxx Treatment in the Prevention of Coronary Ischemic Syndromes," MRK-ABA0004509, at 509 (attached to 3/18/99 memorandum from W. Shaw to J. Anderson et al., MRK-ABA0004507, 507).

<sup>389</sup> Background materials for the 3/31/99 consultants' meeting, "Potential Role of Vioxx Treatment in the Prevention of Coronary Ischemic Syndromes," MRK-ABA0004509, at 510 (attached to 3/18/99 memorandum from W. Shaw to J. Anderson et al., MRK-ABA0004507, 507); Undated (~9/98) letter from C. Patrono\* to M. Laurenzi, MRK-ABK0311070, at 70 (citing a study that suggested that "COX-2-derived eicosanoids may participate in the local inflammatory process of unstable angina and contribute to ischemic complications").

plaques and/or endothelial cells might catalyze some production of vascular thromboxane, which before was believed to be catalyzed only by Cox-1.<sup>390</sup>

1. Studies Supporting the Vioxx Cardioprotection Hypothesis.

Among the studies that led to the Vioxx cardioprotection hypothesis was an observational case control study<sup>391</sup> by Paul M. Ridker\* and his colleagues undertaken to assess whether inflammation increased the risk of a first thrombotic event and whether treatment with aspirin decreased the risk (the “Ridker Study”).<sup>392</sup> The Ridker Study analyzed data for a subset of patients enrolled in a randomized controlled clinical trial designed to assess the efficacy of aspirin in the primary prevention of cardiovascular disease. The subset consisted of 543 apparently healthy men who later had myocardial infarction, stroke or venous thrombosis, and 543 controls who did not report vascular disease during a follow-up period exceeding eight years.

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<sup>390</sup> Undated (~9/98) letter from C. Patrono\* to M. Laurenzi, MRK-ABK0311070, 070 (citing studies that suggested that “COX-2 expressed in plaque monocytes/macrophages is a potential source of aspirin-insensitive TXA<sub>2</sub> production” and that “COX-2 expressed by endothelial cells is a potential source . . . for transcellular biosynthesis of TXA<sub>2</sub> by aspirinated platelets”).

<sup>391</sup> As discussed in Appendix P, case-control studies are used to evaluate the risk factors and potential causes of a particular disease. In a case-control study, a group of subjects with the disease (the cases) are compared with another group of subjects who do not have the disease (the controls) to try to determine whether the particular factor at issue predisposes someone to have the disease.

<sup>392</sup> Ridker\* PM, Cushman\* M, Stampfer\* MJ, Tracy\* RP, Hennekens\* CM. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336:973-79, at 73. The Ridker Study looked at a subset of patients enrolled in the Physicians’ Health Study, a randomized double-blind placebo-controlled two-by-two factorial trial of aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer, which, among other things, showed that aspirin reduced the risk of a first myocardial infarction by 44%. In the Physicians’ Health Study, patients were randomly assigned to receive aspirin (325 mg) on alternate days, beta carotene on alternate days, both, or neither. *Id.* at 974, 978.

The study found that: (i) patients who subsequently had myocardial infarction or ischemic stroke had higher concentrations of plasma C-Reactive Protein (a marker for systemic inflammation) at the beginning of the study than those who did not, which suggested that inflammation increased the risk of a first myocardial infarction or ischemic stroke; (ii) the use of aspirin was associated with a significant reduction in the rate of cardiovascular events; and (iii) this reduction was greater among patients with higher C-Reactive Protein levels, which suggested that the magnitude of the beneficial effect of aspirin in preventing myocardial infarction was directly related to baseline levels of C-Reactive Protein.<sup>393</sup>

The article concluded that the observation that the beneficial effect of low-dose aspirin was greatest in patients with higher baseline levels of C-Reactive Protein “raise[d] the possibility” that aspirin was cardioprotective due to its “anti-inflammatory as well as antiplatelet effects.”<sup>394</sup> The article further stated that “[this] observation also suggest[ed] the possibility that other anti-inflammatory agents [of which Vioxx was one] may have a role in preventing cardiovascular disease.”<sup>395</sup>

In addition to the Ridker Study, pharmacological studies had shown that thromboxane biosynthesis might be mediated in part by Cox-2 (as opposed to only

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<sup>393</sup> Ridker\* PM, Cushman\* M, Stampfer\* MJ, Tracy\* RP, Hennekens\* CM. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336:973-79, at 975-76.

<sup>394</sup> Ridker\* PM, Cushman\* M, Stampfer\* MJ, Tracy\* RP, Hennekens\* CM. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336:973-79, at 78 (emphasis added).

<sup>395</sup> Ridker\* PM, Cushman\* M, Stampfer\* MJ, Tracy\* RP, Hennekens\* CM. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997;336:973-79, at 978-79.

Cox-1), that some thromboxane production might be “aspirin-insensitive,” and that suppression of Cox-2 might slow down atherogenesis, i.e., formation of atheroma important to the pathogenesis of arteriosclerosis.<sup>396</sup> Based on these studies, in September 1998, Dr. Patrono\* asked Dr. Martino Laurenzi, Worldwide Human Health and Marketing, whether MRL would be interested in funding a study to assess the effect of concomitant administration of a selective Cox-2 inhibitor and aspirin in patients with unstable angina. Dr. Patrono\* hypothesized that a selective Cox-2 inhibitor would reduce the number and severity of cardiovascular events because it would reduce thromboxane biosynthesis (beyond the reduction achieved by aspirin) and inhibit inflammation.<sup>397</sup>

2. Consultants’ Views Regarding the Vioxx Cardioprotection Hypothesis.

At the May 1998 meeting of Merck’s Board of Scientific Advisors (also discussed in Section H of this Appendix), the Board opined that it was “appropriate to ask whether COX-2 expression regulate[d] . . . the progression of . . . atherosclerosis . . . either positively or negatively” in light of “a growing body of evidence indicating that inflammatory disease [was] a risk factor for myocardial infarction, and [that] such inflammatory processes almost certainly are accompanied by . . . COX-2 expression.”<sup>398</sup> In its May 1998 report, the Board of Scientific Advisors also stated that “[t]o address the hypothesis that a COX-2 inhibitor might reduce the process of atherosclerosis,” Merck

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<sup>396</sup> Undated (~9/1998) letter from C. Patrono\* to M. Laurenzi, MRK-ABK0311070, at 71. Stedman’s Medical Dictionary (26<sup>th</sup> ed. 1995), at 162.

<sup>397</sup> Undated (~9/1998) letter from C. Patrono\* to M. Laurenzi, MRK-ABK0311070, at 71.

<sup>398</sup> 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 736.

could conduct a study in an animal model with “features resembling human atherosclerosis.”<sup>399</sup>

On March 31, 1999, MRL convened a consultants’ meeting to explore further the hypothesis that Vioxx might be cardioprotective. The consultants included Dr. Garret FitzGerald\*, Dr. Carlo Patrono\*, and Dr. Desmond Fitzgerald\*, Royal College of Surgeons in Ireland.<sup>400</sup> One of the questions discussed at the meeting was whether it was “worthwhile to conduct a pilot clinical trial to investigate a cardioprotective effect of Vioxx.”<sup>401</sup> At the meeting, the clear consensus<sup>402</sup> was that “it [was] not appropriate to perform large clinical trials at [that] point” in the absence of stronger evidence that Vioxx might be cardioprotective.<sup>403</sup>

L. Publication of the Results of Protocol 023.

The results of Protocol 023 were presented at two scientific conferences in 1998 and published in the Journal of Pharmacology and Experimental Therapeutics in May 1999. The results of the McAdam Study, the study on Celebrex that showed that Celebrex also inhibited urinary excretion of PGI-M (a metabolite of prostacyclin), were

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<sup>399</sup> 5/98 “Programmatic Review: Vioxx Program,” MRK-AEI0002734, at 741.

<sup>400</sup> 3/31/99 consultants’ meeting, “Executive Summary,” MRK-ABA0004522, at 522 (attached to 3/18/99 memorandum from W. Shaw to J. Anderson et al., MRK-ABA0004507, at 507).

<sup>401</sup> 3/31/99 consultants’ meeting, “Questions,” MRK-ABA0004517, at 517 (attached to 3/18/99 memorandum from W. Shaw to J. Anderson et al., MRK-ABA0004507, at 507).

<sup>402</sup> See 7/12/01 email from W. Shaw to P. DiBattiste, MRK-NJ0056416, at 16 (referring to “the clear consensus . . . not to proceed at that time”).

<sup>403</sup> 3/31/99 consultants’ meeting, “Executive Summary,” MRK-ABA0004522, at 522 (attached to 3/18/99 memorandum from W. Shaw to J. Anderson et al., MRK-ABA0004507, at 507).

published in the Proceedings of the National Academy of Sciences in January 1999. This Section addresses the discussions between MRL and Drs. FitzGerald\* and Francesca Catella-Lawson\*, Dr. FitzGerald's\* colleague from the University of Pennsylvania and a co-author of the Protocol 023 article,<sup>404</sup> regarding drafts of the article and, in particular, the article's discussion of the PGI-M findings and the FitzGerald prostacyclin hypothesis.

1. Presentation of the Protocol 023 findings at scientific conferences.

In April 1998, an abstract about Protocol 023 was presented at the American Heart Association Vascular Biology Meeting in San Francisco. The abstract was entitled "Selective Inhibition of Cyclooxygenase II in the Elderly: Effects on Hemodynamics, Sodium Balance and Vasoactive Eicosanoids."<sup>405</sup> The abstract reported that, in Protocol 023, "chronic [Vioxx] treatment . . . spar[ed] Cox-1 dependent platelet [thromboxane] formation [and] affected prostacyclin biosynthesis or metabolism as evidenced by a reduction in . . . PGI-M excretion," but did not state expressly the

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<sup>404</sup> Dr. Catella-Lawson's\* title was Assistant Professor, Department of Medicine, and Director, Clinical Investigation Unit and Associate Director, General Clinical Research Center, Hospital of the University of Pennsylvania, Center for Experimental Therapeutics, University of Pennsylvania. 7/98 "Second International Workshop on COX-2," Maui, Hawaii, MRK-ABK0442001, at 266.

<sup>405</sup> Catella-Lawson\* F, McAdam\* B, Morrison B, et al. Selective Inhibition of Cyclooxygenase II in the Elderly: Effects on Hemodynamics, Sodium Balance and Vasoactive Eicosanoids [abstract]. North American Vascular Biology Organization, Vascular Biology (April 15-18, 1998) (submitted to the FDA with the 11/23/98 New Drug Application for Vioxx), MRK-OS420123664, at 66. "Hemodynamics" refers to the dynamics of the blood circulation. Stedman's Medical Dictionary (26<sup>th</sup> ed. 1995), at 777. "Eicosanoids" here refers to prostacyclin and thromboxane. "Vasoactive" means "influencing the tone and caliber of blood vessels." Stedman's Medical Dictionary (26<sup>th</sup> ed. 1995), at 1909.

hypothesis that selective Cox-2 inhibitors might elevate the risk of cardiovascular events.<sup>406</sup>

In July 1998, Dr. Catella-Lawson<sup>\*</sup>, discussed the study at the Second International Workshop on Cox-2 in Maui, Hawaii.<sup>407</sup> The title of Dr. Catella-Lawson's<sup>\*</sup> presentation was: "Renal and Extrarenal Biosynthesis of Prostacyclin During Long-term Cox-2 Inhibition."<sup>408</sup> The slides from Dr. Catella-Lawson's<sup>\*</sup> presentation, which referred to the FitzGerald prostacyclin hypothesis,<sup>409</sup> were distributed to the workshop participants,<sup>410</sup> but were not published in a journal.

## 2. Publication of the McAdam Study.

The McAdam Study was published in the Proceedings of the National Academy of Sciences on January 5, 1999.<sup>411</sup> The article set forth the FitzGerald prostacyclin

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<sup>406</sup> Catella-Lawson<sup>\*</sup> F, McAdam<sup>\*</sup> B, Morrison B, et al. Selective Inhibition of Cyclooxygenase II in the Elderly: Effects on Hemodynamics, Sodium Balance and Vasoactive Eicosanoids [abstract]. North American Vascular Biology Organization, Vascular Biology (April 15-18, 1998) (copy submitted to the FDA), MRK-OS420123665, at 66.

<sup>407</sup> 7/98 "Second International Workshop on COX-2," Maui, Hawaii, MRK-ABK0442001, at 001, 266-274.

<sup>408</sup> 7/98 "Second International Workshop on COX-2," Maui, Hawaii, MRK-ABK0442001, at 267.

<sup>409</sup> 7/98 "Second International Workshop on COX-2," Maui, Hawaii, slides for Dr. Catella-Lawson's<sup>\*</sup> presentation, MRK-ABK0442001, at 274 (citing the Murata knockout mice study and stating that "[i]t remain[ed] to be established whether chronic treatment with [Vioxx] and other selective Cox-2 inhibitors [would] suppress this response [increase in prostacyclin production] during ischemic events in humans" and "[t]he implications of partial suppression of prostacyclin in vivo [were at the time] unclear").

<sup>410</sup> See 7/98 "Second International Workshop on COX-2," Maui, Hawaii, slides for Dr. Catella-Lawson's<sup>\*</sup> presentation, MRK-ABK0442001, at 266-274.

<sup>411</sup> McAdam<sup>\*</sup> BF, Catella-Lawson<sup>\*</sup> F, Mardini<sup>\*</sup> IA, Kapoor<sup>\*</sup> S, Lawson<sup>\*</sup> JA, FitzGerald<sup>\*</sup> GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: The human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci USA. 1999;96:272-277.

hypothesis, *i.e.*, that selective Cox-2 inhibitors could be prothrombotic due to their inhibition of prostacyclin without concomitant inhibition of thromboxane.<sup>412</sup> According to the article, the fact that two selective Cox-2 inhibitors, Vioxx and Celebrex, both inhibited PGI-M suggested that such inhibition was a feature of selective Cox-2 inhibitors – in other words, a “class effect.”<sup>413</sup> The article stated that the study results “clearly implicate[d] COX-2 as a major source of [prostacyclin].”<sup>414</sup> The article also stated that to determine whether the effect on prostacyclin biosynthesis would have any cardiovascular consequences would require studies that were “much larger than those necessary to detect efficacy and safety in arthritis.”<sup>415</sup>

On January 14, 1999, the University of Pennsylvania Medical Center issued a press release entitled “New Cox-2 Inhibitors May Elevate Cardiovascular Risk.”<sup>416</sup> The press release stated that the McAdam Study suggested that “aspects of [selective Cox-2

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<sup>412</sup> McAdam\* BF, Catella-Lawson\* F, Mardini\* IA, Kapoor\* S, Lawson\* JA, FitzGerald\* GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: The human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci USA. 1999;96:272-277, at 276.

<sup>413</sup> McAdam\* BF, Catella-Lawson\* F, Mardini\* IA, Kapoor\* S, Lawson\* JA, FitzGerald\* GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: The human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci USA. 1999;96:272-277, at 276.

<sup>414</sup> McAdam\* BF, Catella-Lawson\* F, Mardini\* IA, Kapoor\* S, Lawson\* JA, FitzGerald\* GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: The human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci USA. 1999;96:272-277, at 276.

<sup>415</sup> McAdam\* BF, Catella-Lawson\* F, Mardini\* IA, Kapoor\* S, Lawson\* JA, FitzGerald\* GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: The human pharmacology of a selective inhibitor of COX-2. Proc Natl Acad Sci USA. 1999;96:272-277, at 276.

<sup>416</sup> 1/14/99 University of Pennsylvania Medical Center press release, “New COX-2 Inhibitors May Elevate Cardiovascular Risk,” MRK-ACZ0029498, at 98.

inhibitors'] action in the body may elevate the risk of heart attacks, strokes, and other adverse cardiovascular events[.]”<sup>417</sup> and quoted Dr. FitzGerald\* as saying:

The clinical trials designed to show that the COX-2 inhibitors work in treating arthritis have not shown evidence of a cardiovascular risk.

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However, they would have been roughly an order of magnitude too small in their sample sizes to detect what we see as a possible problem associated with the use of these drugs. So, the question hangs out there for future experience: Will a cardiovascular risk emerge over time as the COX-2 inhibitors reach more and more patients?<sup>418</sup>

The press release also stated that, according to Dr. FitzGerald\*, “the potential risk factor identified in the experiments done [in the McAdam Study] [was] not a property solely of Celebrex. Results of a study involving Vioxx . . . have shown similar results.”<sup>419</sup>

That same day, Ms. Christine Fanelle of Merck’s Public Affairs Department emailed to Ms. Charlotte McKines, Senior Director, New Products, U.S. Human Health, Dr. Silverman and others a standby statement and a “Q&A” document regarding the publication of the McAdam Study.<sup>420</sup> These documents were prepared to respond to

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<sup>417</sup> 1/14/99 University of Pennsylvania Medical Center press release, “New COX-2 Inhibitors May Elevate Cardiovascular Risk,” MRK-ACZ0029498, at 98.

<sup>418</sup> 1/14/99 University of Pennsylvania Medical Center press release, “New COX-2 Inhibitors May Elevate Cardiovascular Risk,” MRK-ACZ0029498, at 99.

<sup>419</sup> 1/14/99 University of Pennsylvania Medical Center press release, “New COX-2 Inhibitors May Elevate Cardiovascular Risk,” MRK-ACZ0029498, at 99.

<sup>420</sup> 1/14/99 email from C. Fanelle to C. McKines et al., MRK-ADI0023673, at 73.

media inquiries concerning the McAdam Study and the University of Pennsylvania press release and made a number of points:

- The clinical “significance of the U. Penn study results [was] unknown”;
- The incidence of cardiovascular event rates in Merck’s Phase III osteoarthritis studies “was similar across all groups [Vioxx, comparator NSAIDs and placebo]” and included “[high] CV risk patients”;
- “[T]he U. Penn study was designed to measure renal function and arachidonic acid metabolites, not specifically CV risk”;
- “The results [of the University of Pennsylvania study] presented [were] out of context of how the study was designed”; and
- Another hypothesis existed – that Vioxx could be cardioprotective by virtue of its anti-inflammatory effects.<sup>421</sup>

The discussion in the McAdam article and the University of Pennsylvania press release of potential cardiovascular risk from selective Cox-2 inhibitors received some media attention. On January 29, 1999, a Reuters story reported that the McAdam Study raised questions about whether selective Cox-2 inhibitors might increase the risk of heart attacks, strokes, or blood clotting.<sup>422</sup> The article also quoted a Searle representative stating: “We don’t think this is a concern”; “Nothing we’ve seen in our database says it’s a concern”; and “The [University of Pennsylvania] press release doesn’t really reflect

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<sup>421</sup> Draft standby statement and Q&A, MRK-ADI0023670, at 70-72.

<sup>422</sup> Searle Defends Celebrex Safety, Reuters News, Jan. 29, 1999.

what was in the study.”<sup>423</sup> Similarly, on February 1, 1999, the Philadelphia Inquirer ran a story entitled “Penn Study Hints at Risks with Cox-2 Painkillers/The New Drugs May Increase a Patient’s Chances of Getting a Stroke or a Heart Attack.”<sup>424</sup> The article stated in part:

So far, clinical trials have shown no such ill effects of the drugs, but, FitzGerald said, the risks may be so small that they will show up only when many thousands more people begin taking Cox-2 inhibitors.

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FDA officials were aware of Penn’s study, which was funded by Searle Inc., Celebrex’s maker, when they approved the drug, FitzGerald said. “I would fully endorse their decision not to allow this to retard their approval of Celebrex,” he said.<sup>425</sup>

Finally, an April 1999 Better Homes and Gardens article about available treatments for arthritis mentioned the recent approval of Celebrex, the McAdam Study and the fact that

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<sup>423</sup> Searle Defends Celebrex Safety, Reuters News, Jan. 29, 1999. A January 19, 1999 story in the Globe and Mail, a Canadian newspaper, also reported that the McAdam Study raised questions about whether Celebrex “might increase the risk of heart attacks, strokes, and blood clotting.” Carolyn Abraham, New painkiller increases cardiac risk, study shows, The Globe and Mail, Jan. 19, 1999, at C8.

<sup>424</sup> Stacey Burling\*, Penn Study Hints at Risks with Cox-2 Painkillers/The New Drugs May Increase a Patient’s Chances of Getting a Stroke or a Heart Attack, The Philadelphia Inquirer, Feb. 1, 1999, at D12.

<sup>425</sup> Stacey Burling\*, Penn Study Hints at Risks with Cox-2 Painkillers/The New Drugs May Increase a Patient’s Chances of Getting a Stroke or a Heart Attack, The Philadelphia Inquirer, Feb. 1, 1999 (quoting Dr. FitzGerald\* as saying: “The likelihood is, if this is a risk, it will be a small one because our experience to date does not reveal an excess of cardiovascular events.”).

the study “suggest[ed] that COX-2 inhibitors [might] increase the risk of stroke and cardiovascular problems, including heart attack.”<sup>426</sup>

3. Presentation of the Results of Protocol 023  
at the April 1998 Vascular Biology Meeting.

In December 1997, a few months after completing the study, Drs. Catella-Lawson\* and FitzGerald\* informed MRL scientists that they wanted to present the results of Protocol 023 at the April 1998 American Heart Association’s Vascular Biology Meeting in San Francisco, California. Merck had funded Protocol 023, and, under the funding contract, was entitled to “the opportunity to review all proposed abstracts, manuscripts or presentations regarding the study 60 days prior to submission of the publication.”<sup>427</sup> Therefore, in late 1997 and early 1998, Drs. FitzGerald\* and Catella-Lawson\* and MRL scientists worked together on drafting and revising (i) an abstract for submission to the American Heart Association (and eventual inclusion in the abstract book handed out to the Vascular Biology Meeting participants); and (ii) a poster for presentation at the meeting.

The original draft of the abstract was prepared jointly by Dr. Catella-Lawson\* and Dr. Morrison. After Dr. FitzGerald\* approved the draft in December 1997, Dr. Morrison

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<sup>426</sup> Kathleen Heins\*, Composing a Cure for Arthritis, Better Homes and Gardens, April 1999.

<sup>427</sup> 10/30/95 letter from T. Musliner to G. FitzGerald\*, MRK-ACS0009346, 347 (signed by F. Catella-Lawson\*). Further, the contract stated that “[p]ublications derived from this study should include input from . . . MRL personnel” and that “[s]uch input should be reflected in publication authorship.” Id.

forwarded it to other MRL scientists for review.<sup>428</sup> The draft abstract did not state the hypothesis that selective Cox-2 inhibition might increase the risk of cardiovascular events. The draft abstract, however, presumed that the reduction in the urinary excretion of PGI-M signified a reduction in systemic biosynthesis of prostacyclin, concluding that the “[i]nhibition of PGI-M by [Vioxx] implie[d] a major role for Cox-2 in the biosynthesis of systemic prostacyclin.”<sup>429</sup>

After reviewing the draft abstract, Dr. Gertz took the position that “the conclusion[] somewhat overstate[d] the results.”<sup>430</sup> As discussed in Section E.4.b of this Appendix, Drs. Nies and Gertz believed that the reduction in the urinary excretion of PGI-M did not necessarily mean that Vioxx suppressed production of prostacyclin in the body because there were alternative explanations for the observed urinary PGI-M reduction. Dr. Morrison explained to Dr. Catella-Lawson\* Dr. Gertz’s view that the conclusion of the abstract was “not directly supported by the data” because “[i]t [was] possible that [Vioxx] affect[ed] the metabolism of prostacyclin and not its synthesis, and

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<sup>428</sup> 12/29/97 memorandum from B. Morrison to A. Nies and R. Spector, MRK-NJ0017231, at 31 (attaching original draft with revisions, MRK-NJ0017235).

<sup>429</sup> Original draft with revisions, MRK-NJ0017235, at 35 (attached to 12/29/97 memorandum from B. Morrison to A. Nies and R. Spector, MRK-NJ0017231).

<sup>430</sup> 12/29/97 memorandum from B. Morrison to A. Nies and R. Spector, MRK-NJ0017231, at 31 (noting that handwritten notes on draft abstract were made by B. Gertz) (attaching original draft with revisions, MRK-NJ0017235, at 36).

it [was] not clear that the effect [was] mediated by inhibition of Cox-2 as opposed to some other mechanism.”<sup>431</sup>

After receiving Dr. Morrison’s requested changes, Drs. Catella-Lawson\* and FitzGerald\* agreed to remove from the abstract the conclusions that: (i) “Inhibition of PGI-M by [Vioxx] implie[d] a major role for Cox-2 in the biosynthesis of systemic prostacyclin”; and (ii) Vioxx decreased “[s]ystemic biosynthesis of prostacyclin.”<sup>432</sup> The abstract submitted to the American Heart Association reported that Vioxx and indomethacin reduced the urinary excretion of PGI-M and that Vioxx had no effect on thromboxane), concluding that Vioxx “affected prostacyclin biosynthesis or metabolism as evidenced by a reduction in[] PGI-M excretion.”<sup>433</sup>

On March 24, 1998, after the American Heart Association accepted the abstract for presentation at the April 14 – 18, 1998 Vascular Biology Meeting, Dr. Catella-Lawson\* emailed to Dr. Morrison a draft poster (which was a more detailed summary of the study than the already approved abstract) that she wanted to present at

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<sup>431</sup> Memorandum from B. Morrison to F. Catella-Lawson\* regarding revisions to the draft, MRK-NJ0017236, at 36 (attached to 12/29/97 memorandum from B. Morrison to A. Nies and R. Spector, MRK-NJ0017231).

<sup>432</sup> 12/29/97 memorandum from B. Morrison to A. Nies, R. Spector, MRK-NJ0017231, at 31 (noting that “Penn” [i.e., F. Catella-Lawson\* and G. FitzGerald\*] agreed to requested changes) (attaching memorandum from B. Morrison to F. Catella-Lawson\* regarding revisions to the draft, MRK-NJ0017236, at 36).

<sup>433</sup> Catella-Lawson\* F, McAdam\* B, Morrison B, et al. Selective Inhibition of Cyclooxygenase II in the Elderly: Effects on Hemodynamics, Sodium Balance and Vasoactive Eicosanoids [abstract]. North American Vascular Biology Organization, Vascular Biology (April 15-18, 1998) (submitted to the FDA with the 11/23/98 New Drug Application for Vioxx), MRK-OS420123664, at 66 (emphasis added).

the meeting.<sup>434</sup> Upon receiving the draft poster, Dr. Morrison reminded Dr. Catella-Lawson\* that, under the funding contract, MRL was entitled to “the opportunity to review all proposed . . . presentations regarding the study 60 days prior to . . . presentation” and stated that he did not think that “sending the outline for the poster a few days before the presentation [was] acceptable.”<sup>435</sup> Dr. Morrison also noted that, after the MRL co-authors (*i.e.*, Drs. Morrison and Gertz) signed off on the poster, the poster would have to be cleared through MRL’s internal review, which “takes a minimum of 2 weeks.”<sup>436</sup> Under an internal MRL policy, all publications (articles, abstracts, posters and other presentations) co-authored by MRL employees, had to be cleared through an internal review process.<sup>437</sup> Dr. Morrison, however, forwarded the draft poster to his colleagues in an effort to get the poster approved for the presentation.<sup>438</sup>

In the “Results” section, the draft poster prepared by Dr. Catella-Lawson\* reported both the renal and the urinary metabolite results of the study.<sup>439</sup> In the

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<sup>434</sup> 3/24/98 email from F. Catella-Lawson\* to B. Morrison, FITZG-002564, at 64.

<sup>435</sup> 3/24/98 email from B. Morrison to F. Catella-Lawson\*, FITZG-002564, at 64.

<sup>436</sup> 3/24/98 email from B. Morrison to F. Catella-Lawson\*, FITZG-002564, at 64.

<sup>437</sup> See 4/14/98 memorandum from V. Aymer to B. Morrison, MRK-NJ0017792, at 92.

<sup>438</sup> Undated (~3/98) memorandum from B. Morrison to B. Seidenberg, MRK-NJ0002566, at 66 (“[Dr. Catella-Lawson\*] will hopefully respond Monday. You can than [sic] work your magic to get it approved. If not, I will leave it to you to speak to her.”).

<sup>439</sup> Draft poster, MRK-NJ0002571, at 77-79 (attached to undated (~3/98) memorandum from B. Morrison to B. Seidenberg, MRK-NJ0002566).

“Conclusions” section, the draft concluded that Cox-2 was the “predominant isozyme which accounts for biosynthesis of prostacyclin under physiological conditions in humans.”<sup>440</sup> Finally, in the “Discussion” section, the draft poster noted that Vioxx was “not expected to result in bleeding, gastric toxicity, or renal toxicity” and raised the question of whether suppression of prostacyclin by Vioxx and other selective Cox-2 inhibitors might increase the risk of thrombotic events.<sup>441</sup> It also stated that the implications of prostacyclin suppression in vivo were unclear at the time but noted that “[i]nactivation of prostacyclin receptor gene in mice results in an increased susceptibility to thrombosis.”<sup>442</sup>

After MRL scientists reviewed the draft poster, Dr. Morrison asked Dr. Catella-Lawson\* to make several revisions to the “Conclusions” and “Discussion” sections of the poster.<sup>443</sup> First, Dr. Morrison asked that the poster state that Cox-2 “may be” (as opposed to “is”) the “predominant isozyme which accounts for biosynthesis of prostacyclin under physiological conditions in humans.”<sup>444</sup> Second, Dr. Morrison stated

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<sup>440</sup> Draft poster, MRK-NJ0002571, at 79-80

<sup>441</sup> Draft poster, MRK-NJ0002571, at 80-81 (“Inactivation of the prostacyclin receptor gene in mice results in an increased susceptibility to thrombosis in vivo. We have previously shown that urinary excretion of PGI-M is increased in syndromes of platelet activation, such as unstable angina, in vivo. It remains to be established whether chronic treatment with [Vioxx] and other selective Cox-2 inhibitors will suppress this response during ischemic events in humans.”) (citations omitted).

<sup>442</sup> Draft poster, MRK-NJ0002571, at 80-81.

<sup>443</sup> Undated (~3/99) letter from B. Morrison to F. Catella-Lawson\*, MRK-NJ0002569, at 69 (attached to undated (~3/99) memorandum from B. Morrison to B. Seidenberg, MRK-NJ0002566, at 66 (“You will see the letter I sent to Francesca.”)).

<sup>444</sup> Draft poster, MRK-NJ0002571, at 80.

that the “Discussion” section as a whole and the sentence raising the FitzGerald prostacyclin hypothesis specifically were “unnecessary.”<sup>445</sup> Dr. Morrison also stated that, if Dr. Catella-Lawson\* wanted to retain the discussion of the FitzGerald prostacyclin hypothesis, she should then “balance” that discussion by mentioning that “inhibition of prostacyclin [might] contribute to the analgesic and anti-inflammatory activity of Cox inhibitors.”<sup>446</sup>

Dr. Catella-Lawson\* did not agree to change the conclusion that Cox-2 “is” the predominant isozyme responsible for biosynthesis of prostacyclin but deleted the “Discussion” section from the poster.<sup>447</sup> It appears that, in the end, the abstract prepared in December 1997/January 1998 was included in the abstract book handed out at the Vascular Biology Meeting, but the poster prepared in March/April 1998 was not presented at the meeting. After Drs. Morrison and Catella-Lawson\* agreed upon a final version of the poster, Dr. Morrison submitted it to MRL’s publications clearance department.<sup>448</sup> This was, however, only five days before the Vascular Biology Meeting for which the poster was prepared. As mentioned above, under an MRL policy, “authors [were] required to provide at least two weeks for . . . clearance prior to the

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<sup>445</sup> Undated (~3/99) letter from B. Morrison to F. Catella-Lawson\*, MRK-NJ0002569, at 69.

<sup>446</sup> Undated (~3/99) letter from B. Morrison to F. Catella-Lawson\*, MRK-NJ0002569, at 69.

<sup>447</sup> Final draft of poster (as submitted for internal MRL publishing clearance), MRK-NJ0002795, at 799-800, 802 (attached to 4/9/98 memorandum from B. Morrison to W. Rozdilsky, MRK-NJ0002792).

<sup>448</sup> 4/9/98 memorandum from B. Morrison to W. Rozdilsky, MRK-NJ0002792, at 92.

presentation,”<sup>449</sup> and, as a result, the publications coordinator refused to put the poster through the clearance process.<sup>450</sup>

4. The Protocol 023 Manuscript.

A full article about Protocol 023 was published in the May 1999 issue of Journal of Pharmacology and Experimental Therapeutics under the following title: “Effects of Specific Inhibition of Cyclooxygenase-2 on Sodium Balance, Hemodynamics, and Vasoactive Eicosanoids.”<sup>451</sup> Like the McAdam article, it stated that the results of the study raised the issue of whether selective Cox-2 inhibitors might be prothrombotic.<sup>452</sup> The article’s lead author was Dr. Catella-Lawson\*, and co-authors included Dr. FitzGerald\* and MRL’s Drs. Gertz, Morrison and Hui Quan, an MRL statistician.

a. The initial draft.

In January 1998, Drs. FitzGerald\* and Catella-Lawson\* submitted a draft article to MRL for review.<sup>453</sup> Although the study had been designed to test the effect of Vioxx on

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<sup>449</sup> 4/14/98 memorandum from V. Aymer to B. Morrison, MRK-NJ0017792, at 92 (emphasis in original).

<sup>450</sup> 4/14/98 memorandum from V. Aymer to B. Morrison, MRK-NJ0017792, at 92 (“The manuscript is closed without release (emphasis in original)).

<sup>451</sup> Catella-Lawson\* F, McAdam\* B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289:735-41.

<sup>452</sup> Catella-Lawson\* F, McAdam\* B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289:735-41, at 740.

<sup>453</sup> 1/6/98 memorandum from F. Catella-Lawson\* to B. Morrison, MRK-NJ0017214 (attaching “a draft manuscript for the initial review”).

renal function,<sup>454</sup> the draft devoted significant attention to the urinary PGI-M finding, which was listed in the protocol under “secondary objectives,” not under “primary hypotheses” or “primary objectives.”<sup>455</sup>

MRL scientists reviewing the draft (specifically, Drs. Nies, Gertz, Seidenberg and Morrison) were dissatisfied with the way in which Drs. FitzGerald\* and Catella-Lawson\* were presenting the study results – particularly with the focus on the FitzGerald prostacyclin hypothesis, which was based on an observation outside the scope of the primary hypothesis – and sent a number of detailed memoranda to Dr. Catella-Lawson\* requesting specific changes to the manuscript, as discussed below.<sup>456</sup>

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<sup>454</sup> Protocol for Protocol 023, MRK-AGO0002456, at 2692 (stating that the “primary hypotheses” of the study were that (i) the effect of Vioxx on “net urinary sodium excretion during the first 72 hours of treatment with [Vioxx] [would] be similar to” that of indomethacin; and (ii) administration of Vioxx “will be sufficiently safe and well tolerated, based on assessment of clinical and laboratory adverse experiences, to permit continued clinical investigation of [the] drug”).

<sup>455</sup> Protocol for Protocol 023, MRK-AGO0002456, at 2692-93 (stating primary hypotheses as well as primary and secondary objectives).

The published article stated: “[W]e also wished to address the hypothesis that prostacyclin biosynthesis, as reflected by urinary excretion of [PGI-M], . . . also would be unaffected by inhibition of Cox-2.” Catella-Lawson\* F, McAdam\* B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289:735-41, at 736 (emphasis added). As discussed above, however, the PGI-M endpoint was not prespecified in the primary hypothesis of the protocol.

<sup>456</sup> 1/6/98 memorandum from F. Catella-Lawson\* to B. Morrison, MRK-NJ0017214, at 14 (attaching “a draft manuscript for the initial review”) (draft manuscript, MRK-NJ0017215-28); ~1/98 memorandum from B. Morrison to F. Catella-Lawson\*, MRK-NJ0017240, at 40 (attaching draft of the article with handwritten revisions, MRK-NJ0017242-55); 2/17/98 memorandum from F. Catella-Lawson\* to B. Morrison, MRK-NJ0017825, at 25 (attaching a revised draft of the manuscript “according to the comments of Hui Quan and Barry Gertz”); 3/3/98 facsimile from B. Morrison to F. Catella-Lawson\*, MRK-NJ0017863, at 63 (attaching comments/revisions by Drs. Gertz, Nies, and Seidenberg, MRK-NJ0017864-79); 3/11/98 facsimile from F. Catella-Lawson\* to B. Morrison, MRK-NJ0002689, at 89 (attaching “the most recent draft of the manuscript”); 4/9/98 memorandum from G. FitzGerald\* and F. Catella-Lawson\* to B. Gertz and B. Morrison, MRK-ABK0296749, at 49 (attaching “the final agreed draft” of the manuscript); 4/22/98 facsimile from B. Morrison to F. Catella-Lawson\* ,

First, the MRL team disagreed with the conclusion, which appeared on the first page of the draft, that Vioxx's inhibition of urinary excretion of PGI-M "impli[ed] a major role for Cox-2 in the vascular biosynthesis of prostacyclin in humans."<sup>457</sup>

Regarding this issue, Dr. Morrison wrote to Dr. Catella-Lawson<sup>\*</sup>: "The initial review . . . here at Merck is that the conclusions somewhat overstate the results. In particular, the final conclusion ('inhibition of PGI-M by [Vioxx] implies a major role for Cox-2 in biosynthesis of systemic prostacyclin') is not directly supported by the data."<sup>458</sup>

Drs. Gertz, Nies and Seidenberg thought that the article should mention the following alternative explanations for the PGI-M findings: (i) Vioxx could affect only renal biosynthesis of prostacyclin; and (ii) Vioxx could affect only metabolism or renal clearance of prostacyclin (as opposed to its biosynthesis).<sup>459</sup>

Second, Dr. Morrison asked Dr. Catella-Lawson<sup>\*</sup> "to minimize references to" a study that had shown that mice genetically engineered to have no prostacyclin gene were at increased risk of thrombosis (the "Murata Study").<sup>460</sup> Dr. Morrison stated:

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MRK-ABK0296719, at 19 (attaching letter and draft manuscript with handwritten revisions, including "mandatory changes that need to be changed," MRK-ABK0296720-45).

<sup>457</sup> See, e.g., Comments/revisions of B. Gertz, A. Nies, B. Seidenberg, MRK-NJ0017864, at 66 (attached to 3/3/98 facsimile from B. Morrison to F. Catella-Lawson<sup>\*</sup>, MRK-NJ0017863).

<sup>458</sup> Undated memorandum from B. Morrison to F. Catella-Lawson<sup>\*</sup>, MRK-NJ0017236, at 36.

<sup>459</sup> Undated memorandum from B. Morrison to F. Catella-Lawson<sup>\*</sup>, MRK-NJ0017236, at 36.

<sup>460</sup> ~1/98 memorandum from B. Morrison to F. Catella-Lawson<sup>\*</sup>, MRK-NJ0017240, at 40; see also 1/27/98 memorandum from B. Morrison to B. Seidenberg et al., MRK-NJ0017640, at 40 ("I had asked her [Dr. Catella-Lawson<sup>\*</sup>] to go easy on the references to knockout mice since that experimental model really is most useful for assessing developmental effects of gene products and is less relevant to a discussion of administration of an inhibitor to elderly – but she wants to keep some of it in.").

“[A]lthough very interesting, [the Murata Study] is not really relevant to a pharmacologic [experiment] in 60-80 year olds! I would discuss data from previous pharmacologic [experiments] that relate to the data in hand.”<sup>461</sup> Dr. Morrison has testified that the Murata Study did not address the question raised by Protocol 023 about the clinical implications (if any) of partial suppression of prostacyclin because the Murata Study involved mice with “complete suppression” of prostacyclin<sup>462</sup> and in vitro studies had shown that even a small fraction, perhaps as small as 10%, of the productive capacity for prostacyclin in normal blood vessels should produce enough prostacyclin to inhibit platelet function.<sup>463</sup> In Protocol 023, Vioxx resulted in only partial suppression of the urinary prostacyclin metabolite PGI-M, leading to the speculation that a potential reduction in vascular prostacyclin would be only partial.

Third, the MRL team asked for a number of other changes in the draft’s discussion of the FitzGerald prostacyclin hypothesis. For example, Dr. Gertz suggested that the article refer to an article about the Karolinska Institute Study, published in the Prostaglandins journal in 1989, which reported that a single dose of acetaminophen (Tylenol) 500 mg, like Vioxx in Protocol 023, “caused a marked reduction” of PGI-M and had “no obvious effect” on the thromboxane metabolite TX-M.<sup>464</sup> As discussed

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<sup>461</sup> 1/98 memorandum from B. Morrison to F. Catella-Lawson\*, MRK-NJ0017240, at 40.

<sup>462</sup> 12/18/03 deposition of B. Morrison at 138-40 (Younge v. Merck, S.D. Ala.).

<sup>463</sup> See text accompanying footnote 201.

<sup>464</sup> 2/17/98 memorandum from F. Catella-Lawson\* to B. Morrison, MRK-NJ0017825, at 26 (stating that Dr. Gertz requested a reference to the Vesterqvist article); Green\* K, Drvota\* V, Vesterqvist\* O.

above, acetaminophen had been on the market for 46 years and was believed to be a relatively safe drug with no effect on risk of cardiovascular events. As a result, Dr. Gertz thought that this article was relevant to the clinical implications (or lack thereof) of a potential prostacyclin/thromboxane imbalance as it suggested that a drug that reduced urinary excretion of PGI-M and had no effect on urinary excretion of TX-M – as Vioxx had done in Protocol 023 – did not have clinical implications for cardiovascular risk.<sup>465</sup>

Finally, Dr. Seidenberg disagreed with the order in which the article discussed the PGI-M findings in relation to the renal findings. Dr. Seidenberg asked that “the results” section of the article discuss the PGI-M results at the end because the PGI-M endpoint

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Pronounced reduction of *in vivo* prostacyclin synthesis in humans by acetaminophen (paracetamol). *Prostaglandins*. 1989;37:311-15, at 311. MRK-NJ0017635.

In the Karolinska Institute Study, PGI-M was measured in four healthy patients after single-dose treatment with acetaminophen 500 mg. In addition, TX-M was measured in two of the four patients. In the 1989 article about the study, its authors advanced their own “prostacyclin hypothesis” by stating: “acetaminophen may at least theoretically be disadvantageous for patients suffering from diseases where prostacyclin mediated vascular defense mechanisms are activated, like myocardial infarction, deep vein thrombosis and following surgery.” Green\* K, Drvota\* V, Vesterqvist\* O. Pronounced reduction of *in vivo* prostacyclin synthesis in humans by acetaminophen (paracetamol). *Prostaglandins*. 1989;37:311-15, at 311. MRK-NJ0017635.

<sup>465</sup> See 1/12/98 email from B. Gertz to A. Ford-Hutchinson, MRK-ADL0001533, at 33.

Dr. Gertz made a handwritten note on Dr. Morrison’s January 27, 1998 cover memorandum attaching a revised draft of the manuscript that read: “Perhaps we could hold them off until the APAP [acetaminophen] study is done.” MRK-NJ0017640, at 40. There is no evidence that anyone asked Drs. Catella-Lawson\* and FitzGerald\* not to publish the Protocol 023 manuscript until after the acetaminophen study was done. The acetaminophen study was completed around October 1999 – five months after Protocol 023 was published as an article.

At the time that these negotiations with Drs. FitzGerald\* and Catella-Lawson\* about the manuscript were taking place, Merck had not yet conducted its own acetaminophen study. See discussion in Section J.I.e of this Appendix.

was not prespecified in the primary hypothesis or objectives of the protocol.<sup>466</sup>

Dr. Seidenberg also asked that the “discussion” section of the article “focus on hypotheses [and] objectives of the study” and devote only one paragraph to the prostaglandin metabolite findings.<sup>467</sup>

b. Subsequent drafts and discussions.

Drs. FitzGerald\* and Catella-Lawson\* continued to submit drafts to MRL but did not agree to many of MRL’s proposed editorial changes.<sup>468</sup> Proposed changes they rejected (at least at first) included suggestions to:

- reference the possibility that Vioxx might alter the metabolism, as opposed to the synthesis, of prostacyclin;<sup>469</sup>
- remove a paragraph discussing the Murata Study in knockout mice;<sup>470</sup>

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<sup>466</sup> Comments/revisions of B. Gertz, A. Nies, and B. Seidenberg, MRK-NJ0017864, at 76 (Dr. Seidenberg’s comments indicate that she requested that the order of the results section of the article be based on primary hypotheses, secondary hypotheses/objectives, then “other + exploratory endpoints”) (attached to 3/3/98 facsimile from B. Morrison to F. Catella-Lawson\*, MRK-NJ0017863).

<sup>467</sup> Comments/revisions of B. Gertz, A. Nies, and B. Seidenberg, MRK-NJ0017864, at 79 (Dr. Seidenberg’s comments noting “too much emphasis [on the prostacyclin issue]. concluding [paragraph] should be renal effects”); *id.* at 878 (“focus on hypotheses and objectives of the study”; “one [paragraph] on PG metab. [prostaglandin metabolites]”).

<sup>468</sup> See 3/11/98 facsimile from F. Catella-Lawson\* to B. Morrison, MRK-NJ0002689, at 89 (attaching “the most recent draft of the manuscript”); 4/9/98 memorandum from G. FitzGerald\* and F. Catella-Lawson\* to B. Gertz and B. Morrison (attaching “the final agreed draft” of the manuscript), MRK-ABK0296749, at 49; 4/22/98 facsimile from B. Morrison to F. Catella-Lawson\*, MRK-ABK0296719, at 19 (attaching letter and draft manuscript with handwritten revisions, including “mandatory changes that need to be changed,” MRK-ABK0296720-45).

<sup>469</sup> 2/17/98 memorandum from F. Catella-Lawson\* to B. Morrison, MRK-NJ0017825, at 26 (“[W]e have not stated that a decrease in urinary PGI-M could reflect change in prostacyclin metabolism because our data do not support this statement. . . . There is no a priori reason to consider a shift in metabolism occurring”).

- include a reference to the Karolinska Institute Study of acetaminophen;<sup>471</sup> and
- remove the conclusion that the reduction in PGI-M suggested that Cox-2 was the predominant isozyme responsible for prostacyclin biosynthesis.<sup>472</sup>

On February 18, 1998, Dr. Morrison circulated the most recent draft of the manuscript to the MRL team reviewing the manuscript:<sup>473</sup>

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<sup>470</sup> 2/17/98 memorandum from F. Catella-Lawson\* to B. Morrison, MRK-NJ0017825, at 26 (“[W]e have not deleted the paragraph describing the prostacyclin receptor knock-out mice because we believe that, in absence of pharmacologic antagonists, this model provides the only published example of the potential consequences of prostacyclin inhibition.”).

<sup>471</sup> 2/17/98 letter from F. Catella-Lawson\* to B. Morrison, MRK-NJ0017825, at 26 (“[W]e have not added the reference to the effects of [acetaminophen] on prostacyclin because we have data that do not confirm [the Karolinska Institute Study] results. In our experience, [acetaminophen] is a weak, non-selective [Cox] inhibitor. Therefore, it decreases both prostacyclin (PGI-M) and thromboxane (T<sub>x</sub>-M) biosynthesis.”).

<sup>472</sup> 2/17/98 letter from F. Catella-Lawson\* to B. Morrison, MRK-NJ0017825, at 26.

Drs. FitzGerald\* and Catella-Lawson\* did agree to some of MRL’s proposed changes. For instance, the first draft stated that the renal effects of selective Cox-2 inhibition in patients with hypertension and/or impaired renal function remained to be established. It then stated that caution should be used during administration of Cox-2 inhibitors to individuals in clinical practice. Draft attached to the 1/27/98 memorandum from B. Morrison to B. Seidenberg *et al.*, MRK-NJ0017664, at 73. At Dr. Gertz’s suggestion, Drs. FitzGerald\* and Catella-Lawson\* deleted the suggestion to exercise caution in clinical practice. 2/17/98 letter from F. Catella-Lawson\* to B. Morrison, MRK-NJ0017825, at 25 (“the suggestion to use caution in clinical practice has been deleted”). Dr. Morrison explained the rationale for this deletion as follows: “Since the drug is not approved, we can not say anything about ‘clinical practice’ or mention warnings about prescribing the drugs.” ~1/1998 memorandum from B. Morrison to F. Catella-Lawson\*, MRK-NJ0017240, at 40 (attaching draft manuscript, MRK-NJ0017242, at 48).

<sup>473</sup> 2/18/98 memorandum from B. Morrison to A. Nies *et al.*, MRK-NJ0017824, 24. In the memorandum, Dr. Morrison was referring to the statement that “[i]nhibition of urinary PGI-M by [Vioxx] implie[d] a major role for Cox-2 in the vascular biosynthesis of prostacyclin in humans.” Draft manuscript attached to F. Catella-Lawson’s\* 2/17/98 letter, MRK-NJ0017825 at 28.



**MEMO**

**TO:** Alan Nies  
Barry Gertz  
Beth Seidenberg  
Hui Quan  
Jim Bolognese

**CC:**

**FROM:** Briggs

Handwritten initials 'DWM' inside a hand-drawn circle.

**SUBJECT:**

**DATE:** 2/18/98

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Attached is the latest version of manuscript for Protocol 023. The cover letter summarizes the changes made from last version. Please take a look and let me know what you think. I have also sent a copy to Ken Lasseter since he is an author as well.

You will see that some of the phrasing is not what we had suggested. The last sentence of the abstract, for example, was previously revised but has reverted. They also still use the wording "systemic biosynthesis of prostacyclin".

I would like to first receive comments from all. Depending on the intensity of "discomfort" with the present wording, we may need to have a teleconference with the folks at Penn to resolve any issues.

On March 11, 1998, when Drs. FitzGerald\* and Catella-Lawson\* sent another revised draft of the manuscript to MRL incorporating some proposed changes, their cover letter stated: "We assume that the multiple revisions of this manuscript has [sic] now resulted in a mutually acceptable paper."<sup>474</sup> On March 24, 1998, Dr. Catella-Lawson\* emailed Dr. Morrison asking about when the MRL team might respond to the March 11 draft.<sup>475</sup> In her email, Dr. Catella-Lawson\* stated that, under the funding contract, MRL had 60 days to review the manuscript and that the first draft had been submitted on

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<sup>474</sup> 3/11/98 letter from F. Catella-Lawson\* to B. Morrison, MRK-NJ0002689, at 89.

<sup>475</sup> 3/24/98 email from F. Catella-Lawson\* to B. Morrison, FITZG-002564, at 64.

January 6, 1998.<sup>476</sup> On the same day, Dr. Morrison responded that he would be meeting with Drs. Gertz and Nies about the manuscript the next day.<sup>477</sup> On March 25, 1999, Dr. FitzGerald\* sent an email to Dr. Nies (the head of MRL's pharmacology department), expressing a concern over the delays in finalizing the text of the manuscript:

I am getting very concerned about the delays with this manuscript. as you know, we have made multiple changes to accomodate [sic] the suggestions form [sic] merck. i have sincerely tried to phrase the manuscript in a way that is sensitive to your interests , but is still honest to the data.

however , i have the uncomfortable feeling . . . that this process is being strung out indefinitely for a variety of purposes.<sup>478</sup>

In the email to Dr. Nies, Dr. FitzGerald\* stated that his "concern" was further "emphasized by receiving a request from [the Journal of Clincial Investigation] last week to review a newly submitted manuscript on [Vioxx] from the merck group with briggs [Morrison] as first author !!"<sup>479</sup> Dr. FitzGerald\* went on to say:

We have dealt very openly and honestly with briggs and his colleagues about our manuscript. as they delay things, are they trying to scoop us at the journal which we had selected for manuscript submission? this is not the way i am used to doing business.<sup>480</sup>

Later that day, Dr. Nies responded to Dr. FitzGerald's\* email:

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<sup>476</sup> 3/24/98 email from F. Catella-Lawson\* to B. Morrison, FITZG-002564, at 64.

<sup>477</sup> 3/24/98 email from B. Morrison to F. Catella-Lawson\*, FITZG-002564, at 64.

<sup>478</sup> 3/25/98 email from G. FitzGerald\* to A. Nies, FITZG-002563, at 63.

<sup>479</sup> 3/25/98 email from G. FitzGerald\* to A. Nies, FITZG-002563.

<sup>480</sup> 3/25/98 email from G. FitzGerald\* to A. Nies, FITZG-002563, at 63.

I met with the Merck authors this afternoon. They are still not satisfied with the the [sic] manuscript, particularly the flow of discussion. I suggested they come up with something they are happy with and send it to you [over the next two days].<sup>481</sup>

Two days later, Dr. Gertz sent Dr. FitzGerald\* an email about “an apparent misunderstanding” about the other manuscript MRL scientists had submitted to the Journal of Clinical Investigation and the revision process concerning the Protocol 023 manuscript.<sup>482</sup> With respect to the former, Dr. Gertz explained that the “other paper” was not competing with the Protocol 023 manuscript because it was about the “cox-2 specific[ity]” of Vioxx and “[had] absolutely nothing to do with renal effects . . . or renal excretion of prostanoids [the subject of the Protocol 023 manuscript], and reflect[ed] work that was completed over 2 years prior to the completion of the UPenn study.”<sup>483</sup> With respect to the revisions concerning the Protocol 023 manuscript, Dr. Gertz wrote:

[T]he revised version of the manuscript you now have in hand does not take away any single point you were trying to make. It does put the paper into the perspective of the protocol in terms of primary endpoints and the principle [sic] hypothesis being tested. Equally important, I ask you to re-read the original discussion section and compare it to the revised version. I do not think any major point is missing but I do think the organization now adds clarity . . . .<sup>484</sup>

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<sup>481</sup> 3/25/98 email from A. Nies to G. FitzGerald\*, FITZG-002563, at 63.

<sup>482</sup> 3/27/98 email from B. Gertz to G. FitzGerald\*, FITZG-002559, at 59.

<sup>483</sup> 3/27/98 email from B. Gertz to G. FitzGerald\*, FITZG-002559, at 59.

<sup>484</sup> 3/27/98 email from B. Gertz to G. FitzGerald\*, FITZG-002559, at 59.

Some time between March 25, 1998, and April 9, 1998, Drs. Gertz and Morrison met with Drs. FitzGerald\* and Catella-Lawson\* at the University of Pennsylvania to discuss the manuscript.<sup>485</sup> On April 9, 1998, after the meeting had occurred, Drs. FitzGerald\* and Catella-Lawson\* sent Drs. Gertz and Morrison another draft of the manuscript with a cover letter that stated:

We are both most appreciative of your traveling to Penn for such a constructive meeting. We have revised the manuscript according to our joint decisions. We assume that this is the final agreed draft of the manuscript.

\* \* \*

Although the birth pangs have been evident, I think we are all agreed that this has been a well performed study which provides important insights into the human pharmacology of COX-2 inhibition.<sup>486</sup>

The April 9, 1998 draft of the manuscript, in the “Abstract” section, stated: “Although the precise mechanism remains to be established, the results of this study indicate a role for Cox-2 in the systemic biosynthesis of prostacyclin in humans.”<sup>487</sup> Nevertheless, the “Discussion” section of the draft stated: “Cox-2 is the predominant isozyme which accounts for biosynthesis of prostacyclin under physiological conditions in humans, at

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<sup>485</sup> 4/9/98 letter from G. FitzGerald\* and F. Catella-Lawson\* to B. Gertz and B. Morrison, MRK-ABK0296749, at 49.

<sup>486</sup> 4/9/98 letter from G. FitzGerald\* and F. Catella-Lawson\* to B. Gertz and B. Morrison, MRK-ABK0296749, at 49-50.

<sup>487</sup> 4/9/98 letter from G. FitzGerald\* and F. Catella-Lawson\* to B. Gertz and B. Morrison (attaching a revised draft), MRK-ABK0296749, at 53 (emphasis added).

least in healthy elderly subjects on controlled intake of sodium.”<sup>488</sup> In addition, as requested by Dr. Seidenberg, the last two sentences of the abstract and of the article focused on the renal results.

On April 17, 1998, Dr. Morrison forwarded the latest draft of the manuscript to Drs. Spector, Nies, and Seidenberg requesting only “mandatory comments”<sup>489</sup>:

We may be at an impass. [sic] . . . Barry and I went to Penn to discuss the manuscript with Garret and Francesca. The attached manuscript is as far as Penn is willing to accommodate our viewpoint. Please review the manuscript and provide only mandatory comments. If the style or tone of the writing is different than what you would write, but you feel the difference is one of style only, please try to restrain your editorial pen.

(Emphasis in original).<sup>490</sup>

On April 22, 1998, Dr. Morrison sent to Dr. Catella-Lawson\* another draft of the manuscript stating that it had been approved by everyone at Merck on the condition that

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<sup>488</sup> 4/9/98 letter from G. FitzGerald\* and F. Catella-Lawson\* to B. Gertz and B. Morrison, MRK-ABK0296749, at 60-61 (attaching a revised draft) (emphasis added).

<sup>489</sup> It was common MRL practice to distinguish between “mandatory” and “discretionary” comments in the context of reviewing and commenting on drafts of scientific papers. A “mandatory” comment meant that the reviewer’s approval of the draft was contingent on the author’s incorporating the comment. A “discretionary” comment, on the other hand, meant that the reviewer would approve the paper even if the author chose not to incorporate the comment. See, e.g., 4/1/02 email from “OSTIC Correspondence” to P. DiBattiste *et al.*, MRK-AAZ0009103 (listing three options for manuscript reviewers: (i) “No comments. Manuscript acceptable.”; (ii) “These comments are discretionary/editorial.”; (iii) “These comments are mandatory and must be resolved prior to release.”).

<sup>490</sup> 4/17/98 memorandum from B. Morrison to R. Spector, A. Nies and B. Seidenberg, MRK-ABK0297050, at 50.

certain changes be made.<sup>491</sup> These changes included: (i) stating that the PGI-M results suggested that Cox-2 played “a role,” rather than “the predominant” role in the biosynthesis of prostacyclin; and (ii) changing the sentence discussing the FitzGerald prostacyclin hypothesis, as follows:<sup>492</sup>

**Prostacyclin formation by the vasculature is of functional importance in limiting the response to a thrombotic insult in mice and we have previously shown that urinary excretion of PGI-M is increased in syndromes of platelet activation, such as unstable angina, *in vivo* (61). It remains to be established whether chronic treatment with specific Cox-2 inhibitors will suppress this response, during ischemic events in humans. —**

As discussed below, Drs. FitzGerald\* and Catella-Lawson\* agreed to these changes.

The manuscript was then submitted to the New England Journal of Medicine, which in June of 1998 declined to publish it.<sup>493</sup> The New England Journal of Medicine sent to Dr. Catella-Lawson\* comments of two peer reviewers, including comments regarding the PGI-M issue.<sup>494</sup> One reviewer commented that “[t]he reduction of the

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<sup>491</sup> 4/22/98 letter from B. Morrison to F. Catella-Lawson\* and accompanying draft manuscript, MRK-ABK0296720, at 20 (attached to 4/22/98 facsimile from B. Morrison to F. Catella-Lawson\*, MRK-ABK0296719).

<sup>492</sup> 4/22/98 letter from B. Morrison to F. Catella-Lawson\* and attached draft manuscript, MRK-ABK0296720, at 730-31.

<sup>493</sup> 6/24/98 letter from G. FitzGerald\*, F. Catella-Lawson\* to B. Gertz, B. Morrison, MRK-NJ0017381, at 81 (“Unfortunately, NEJM has rejected the manuscript.”).

<sup>494</sup> The New England Journal of Medicine, Suggestion for Transmittal to Authors 98-1247A, MRK-NJ0017382 (attached to 1/24/98 memorandum from F. Catella-Lawson\* to B. Gertz, B. Morrison, MRK-NJ0017381); The New England Journal of Medicine, Suggestion for Transmittal to Authors 98-1247B, MRK-NJ0017384 (attached to 1/24/98 memorandum from F. Catella-Lawson\* to B. Gertz, B. Morrison, MRK-NJ0017381).

urinary prostacyclin metabolites may be due to inhibition of either COX-1 or COX-2.”<sup>495</sup>  
That reviewer went on to say: “I suspect that before these data were obtained, the authors  
would have concluded that urinary prostacyclin metabolites were a measure of COX-1  
expression in the endothelial cells.”<sup>496</sup> The second reviewer noted that the manuscript did  
not discuss the possibility that the effect of Vioxx on the urinary prostacyclin metabolite  
may be explained in part by the “[i]nhibition of . . . COX2 in the renal . . . endothelial  
cells.”<sup>497</sup>

After the New England Journal of Medicine declined to publish the manuscript,  
Drs. FitzGerald\* and Catella-Lawson\* decided to submit the manuscript to the Journal of  
Pharmacology and Experimental Therapeutics. On September 21 and 30, 1998,  
Dr. Catella-Lawson\* emailed Dr. Morrison, asking when MRL co-authors might sign off  
on the manuscript so that she could submit it to the Journal of Pharmacology and  
Experimental Therapeutics.<sup>498</sup> (It appears that some time earlier Dr. Catella-Lawson\* had  
forwarded to Dr. Morrison the copy of the manuscript she intended to submit to the  
Journal of Pharmacology and Experimental Therapeutics.) Dr. Morrison “apologize[d]

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<sup>495</sup> The New England Journal of Medicine, Suggestion for Transmittal to Authors 98-1247A,  
MRK-NJ0017382, at 82 (attached to 1/24/98 memorandum from F. Catella-Lawson\* to B. Gertz,  
B. Morrison, MRK-NJ0017381).

<sup>496</sup> The New England Journal of Medicine, Suggestion for Transmittal to Authors 98-1247A,  
MRK-NJ0017382, at 82 (attached to 1/24/98 memorandum from F. Catella-Lawson\* to B. Gertz,  
B. Morrison, MRK-NJ0017381).

<sup>497</sup> The New England Journal of Medicine, Suggestion for Transmittal to Authors 98-1247A,  
MRK-NJ0017382, at 84 (attached to 1/24/98 memorandum from F. Catella-Lawson\* to B. Gertz,  
B. Morrison, MRK-NJ0017381).

<sup>498</sup> 9/21/98 email from F. Catella-Lawson\* to B. Morrison, FITZG-002545, at 45.

for the delay,” explaining that it was “quite busy around here . . . preparing our FDA submission for [Vioxx].”<sup>499</sup> In response, Dr. Catella-Lawson\* emailed that she had not changed anything in the text of the manuscript since the previous MRL-approved submission and that “Garret [FitzGerald\*] ha[d] given [her] an absolute deadline of [October 1, 1998] for submitting the manuscript.”<sup>500</sup> In response, Dr. Morrison wrote:

I must say I am perplexed by the sense of urgency here.  
You seemed perfectly content to take 6 months sending the  
paper to journals [the New England Journal of Medicine]  
that we all knew would reject the paper, so why do we now  
need to have it sent by [October 1, 1998]?

We are authors on the paper and must carefully review the  
paper before we sign that we agree with its contents.<sup>501</sup>

Upon seeing Dr. Morrison’s email, Dr. FitzGerald\* sent Dr. Morrison an email,  
stating:

I am a little taken aback by your tone.

since when did you know the nejm would reject the paper ?  
I dont recall that as part of our discussions.

you are more than familiar with this work and if it has been  
delayed , it is certainly not part of our doing.

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<sup>499</sup> 9/21/98 and 9/30/98 emails from B. Morrison to F. Catella-Lawson\*, FITZG-002544-45.

<sup>500</sup> 9/30/98 emails from F. Catella-Lawson\* to B. Morrison, FITZG-002544, at 44.

<sup>501</sup> 9/30/98 email from B. Morrison to F. Catella-Lawson\*, FITZG-002544, at 44

I expect to hear from you by [October 1, 1998] which is more than time enough [sic] given what has gone before.<sup>502</sup>

Later that same day, Dr. FitzGerald\* sent another email to Dr. Morrison, stating:

briggs, the rweality [sic] is here that we actually have grant deadlines currently. this paper has been held up in ways that are unprecedented in my experience and it is time for it to go. i would appreciate it if you would make it a priority, look at it tonight and send your signature tomorrow.<sup>503</sup>

To this, Dr. Morrison responded:

It will not be tonight – I have too many other priorities.  
Will try for the weekend. sorry.<sup>504</sup>

By October 19, 1998, MRL scientists had signed off on the manuscript, and, on that date, it was submitted to the Journal of Pharmacology and Experimental Therapeutics.<sup>505</sup> The Journal of Pharmacology and Experimental Therapeutics accepted the paper for publication on December 22, 1998<sup>506</sup> and published it in May 1999.<sup>507</sup>

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<sup>502</sup> 9/30/98 email from G. FitzGerald\* to B. Morrison, FITZG-002544, at 44.

<sup>503</sup> 9/30/98 email from G. FitzGerald\* to B. Morrison, FITZG-002533, at 33.

<sup>504</sup> 9/30/98 (Wednesday) email from B. Morrison to G. FitzGerald\*, FITZG-002533, at 33.

<sup>505</sup> Catella-Lawson\* F, McAdam\* B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289:735-41, at 735 (stating that the article was “[r]eceived for publication October 19, 1998”).

<sup>506</sup> Catella-Lawson\* F, McAdam\* B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289:735-41, at 735 (noting date on which paper was accepted for publication). The journal informed Dr. Catella-Lawson\* of the acceptance on January 7, 1998. 1/7/98 letter from S. Enna\* to F. Catella-Lawson\*, MRK-NJ0017318, at 18 (“I am pleased to inform you that your manuscript . . . has been accepted for publication.”).

<sup>507</sup> Catella-Lawson\* F, McAdam\* B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289:735-41.

c. The published manuscript.

The published article stated that: (i) “Cox-2 may play a role in the systemic biosynthesis of prostacyclin in healthy humans”;<sup>508</sup> (ii) PGI-M was “an index of total body biosynthesis of prostacyclin”;<sup>509</sup> (iii) it was “formally possible,” – i.e., not excluded as a possibility – that “the inhibition of urinary PGI-M by [Vioxx] reflect[ed] a property of [Vioxx] in addition to, but distinct from, its capacity to inhibit Cox-2”;<sup>510</sup> and (iv) it was possible that Vioxx altered the metabolism of prostacyclin or the renal clearance of its metabolite (i.e., PGI-M) (as opposed to its biosynthesis).<sup>511</sup> The discussion of renal

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<sup>508</sup> Catella-Lawson\* F, McAdam\* B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289:735-41, at 735 (“abstract” section) & 740 (“discussion” section) (emphasis added).

<sup>509</sup> Catella-Lawson\* F, McAdam\* B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289:735-41, at 736, 739.

<sup>510</sup> Catella-Lawson\* F, McAdam\* B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289:735-41, at 739.

<sup>511</sup> Catella-Lawson\* F, McAdam\* B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. J Pharmacol Exp Ther. 1999;289:735-41, at 739 (“The possibility that [Vioxx] might directly reduce the renal clearance of PGI-M also has not been excluded.”).

effects in the published article was more extensive than what Dr. Catella-Lawson\* had initially proposed, and the final article placed somewhat less emphasis on the FitzGerald prostacyclin hypothesis.

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