

APPENDIX O

COMMUNICATIONS WITH
THE FDA APART FROM LABEL NEGOTIATIONS.

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APPENDIX O

COMMUNICATIONS WITH THE FDA APART FROM LABEL NEGOTIATIONS.

Throughout the time that Merck marketed Vioxx, the Company provided information about the drug to the FDA pursuant to the FDA's regulatory authority. Other Appendices describe Merck's formal submissions to the FDA in connection with its applications for approval to market Vioxx and for changes to the label, clinical studies, and promotional materials. In addition to these submissions, Merck provided data about Vioxx via other types of communications both pursuant to regulatory requirements for safety updates and on its own initiative. This Appendix describes four such categories of information: (i) correspondence relating to mortality data from Merck's Alzheimer's trials; (ii) Merck's submissions of cardiovascular pooled analyses; (iii) Merck's submission every six months of Periodic Safety Update Reports; and (iv) Merck's withdrawal and resubmission of the Arcoxia New Drug Application.

A. Communications Relating to Mortality Data from Alzheimer's Studies.

As discussed in Appendix J, Merck submitted mortality data from its three studies of Vioxx in Alzheimer's disease patients – Protocols 078, 091, and 126 (collectively, the “Alzheimer's trials”)¹ – in a July 2001 Safety Update Report. Shortly after this

¹ The Alzheimer's trials all compared Vioxx 25 mg versus placebo. Protocols 091 and 126 were designed to determine whether Vioxx would slow the progression of Alzheimer's disease. Protocol 078 was designed to determine whether Vioxx could prevent the conversion of mild cognitive impairment into Alzheimer's disease.

submission, the FDA requested specific analyses of this data. As detailed below, Merck complied with all of the Agency's requests.

On September 26, 2001, Dr. Barbara Gould* of the FDA's Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products sent a facsimile to Dr. Robert Silverman, Senior Director of Regulatory Affairs, requesting "time to event plots for all deaths and for cardiovascular deaths in the Alzheimer's studies."² In his October 8 response, Dr. Silverman provided Kaplan-Meier survival plots by treatment group for all-cause mortality and cardiovascular mortality for each of the Alzheimer's trials.³ These charts are reproduced as Figures 1 and 2 at the end of this Appendix. The following table summarizes the all-cause mortality data from each of the three protocols as reported in Dr. Silverman's response as well as the p-values for the logrank comparisons of the survival times between the two treatment groups in each study, which indicate the probability of whether there is a true difference between survival times across the Kaplan-Meier survival curves:⁴

² 9/26/01 email from B. Gould* to R. Silverman, MRK-ACD0013906 (attaching facsimile, MRK-ACD0013907). Time-to-event plots, or Kaplan-Meier curves, chart cumulative probability of survival without any adjustment for other variables.

³ 10/8/01 letter from R. Silverman to J. Bull*, MRK-ACD0003846-47. Dr. Silverman addressed all of his replies to Dr. Gould's* requests to Dr. Jonca Bull*, who was the acting director of the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, the division in which Dr. Gould* worked.

⁴ For the underlying data, see Attachment I: Kaplan-Meier Survival Estimates for All-Cause Mortality, MRK-ACD0003850-53 (attached to 10/8/01 letter from R. Silverman to J. Bull*, MRK-ACD0003846-47).

Table 1

Mortality Data from the Alzheimer's Trials As of October 8, 2001

Protocol	Number of Deaths in Vioxx Arm	Number of Deaths in Placebo Arm	P-value from Logrank Comparison⁵
078	15	9	0.12
091	14	8	0.056
126	4	3	0.66

As indicated by the p-values, the between-group differences in the survival curves did not reach statistical significance in any of the three trials. Dr. Silverman's letter also reported that "[t]here were a total of 15 cardiovascular deaths from the three protocols."⁶ The following table summarizes the distribution of those 15 deaths as well as the p-value from the relevant logrank comparisons:⁷

Table 2

Cardiovascular Mortality Data from the Alzheimer's Trials As of October 8, 2001

Protocol	Number of Cardiovascular Deaths in Vioxx Arm	Number of Cardiovascular Deaths in Placebo Arm	P-value from Logrank Comparison
078	5	2	0.19
091	3	2	0.37
126	2	1	0.55

⁵ A between-group difference in survival times is statistically significant if the p-value from the logrank comparison is equal to or less than 0.05, indicating a 5% or lower probability that the difference observed is due to chance.

⁶ 10/8/01 letter from R. Silverman to J. Bull*, MRK-ACD0003846, at 46.

⁷ For the underlying data, see Attachment II: Kaplan-Meier Survival Estimates for Cardiovascular Mortality, MRK-ACD0003854-57 (attached to 10/8/01 letter from R. Silverman to J. Bull*, MRK-ACD0003846-47).

Although there were more cardiovascular deaths in the Vioxx arm of each trial, none of the between-group differences in the survival curves reached statistical significance.

In response to a follow-up request from Dr. Gould⁸, Dr. Silverman also provided the FDA with similar analyses of the all-cause and cardiovascular mortality across all three studies combined.⁸ The overall number of deaths in the three studies had not changed since Dr. Silverman's last letter, but one additional death on placebo had been determined to be a cardiovascular death in the intervening period.⁹ Thus, the number of cardiovascular deaths increased from 15 to 16 (10 on Vioxx and 6 on placebo). The combined analysis of the all-cause mortality data indicated that there was a statistically significant between-group difference in all-cause mortality ($p = 0.026$).¹⁰ There was, however, no statistically significant between-group difference with respect to cardiovascular mortality ($p = 0.21$).¹¹ In later correspondence on this subject, Dr. Silverman explained Merck's interpretation of these results to the FDA as follows:

Although there was a significant difference between rofecoxib and placebo groups in overall mortality based on the total number of deaths in all 3 protocols combined, there were no notable trends in the data . . . reflect[ing] any increases in particular types of events to suggest causality.¹² In a similar analysis of mortality in the

⁸ 11/5/01 letter from R. Silverman to B. Gould^{*}, MRK-AAF0004588-90.

⁹ 11/5/01 letter from R. Silverman to B. Gould^{*}, MRK-AAF0004588, at 89.

¹⁰ 11/5/01 letter from R. Silverman to B. Gould^{*}, MRK-AAF0004588, at 88.

¹¹ 11/5/01 letter from R. Silverman to B. Gould^{*}, MRK-AAF0004588, at 89.

¹² In addition to cardiovascular deaths, the most frequent causes of death included malignancies, infectious causes, and trauma. The distribution of these types of deaths between the Vioxx and placebo treatment groups did not reveal a trend against Vioxx with respect to any particular cause of death. 12/18/01 letter from R. Silverman to J. Bull^{*}, MRK-AAF0005014, at 14.

osteoarthritis program, there was statistically significant decreased mortality with rofecoxib compared to other NSAIDs combined. The small numeric differences between rofecoxib in overall mortality, although statistically significant in one program in favor of rofecoxib and in the other against rofecoxib, are most consistent with chance fluctuations.

Although there is a small imbalance in cardiovascular deaths between the 2 groups in the Alzheimer's disease studies, MRL does not agree with the Agency that there is a trend against rofecoxib for cardiovascular mortality The data presented in the July 2001 SUR [Safety Update Report] demonstrate that there is no excess of cardiovascular events in the Alzheimer's disease program.¹³ In fact, if there is any trend in the data on cardiovascular events, it is in favor of rofecoxib over placebo.¹⁴

After receiving this letter, the FDA did not formally request additional information from Merck. Nonetheless, on May 22, 2002, Dr. Ned Braunstein, Director of Regulatory Affairs, wrote to Dr. Lee Simon*, Director of the FDA's Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products, to update the FDA on mortality data from Protocol 078, which was still ongoing when the FDA originally requested information about the Alzheimer's trials.¹⁵ The letter reported that there had been an additional 13 deaths among patients enrolled in Protocol 078 since the last update, 8 on Vioxx and 5 on

¹³ The "July 2001 SUR" reported fewer cardiovascular events among the rofecoxib users than among the placebo users across all of the Alzheimer's trials. See 7/12/01 Rofecoxib Safety Update Report, MRK-01420145856, at 911 (reporting 77 cardiovascular adverse events on rofecoxib and 82 on placebo).

¹⁴ 12/18/01 letter from R. Silverman to J. Bull*, MRK-AAF0005014, at 14-15.

¹⁵ 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AAF0008651-53.

placebo.¹⁶ The letter explained that “[t]here is no specific pattern to the causes of death” and that “four of the deaths were confirmed by adjudication as cardiovascular: 1 in the rofecoxib group and 3 in the placebo group.”¹⁷ With the addition of these 4 cardiovascular deaths, the total numbers of cardiovascular deaths across all three Alzheimer’s trials was 11 and 9 for the Vioxx and placebo arms, respectively. Thus, the additional data further closed the initial gap between the two treatment groups.

B. Submission of Pooled Analyses of Vioxx Cardiovascular Data to the FDA.

Merck’s Cardiovascular Adjudication SOP specified that cardiovascular data from Vioxx studies would be pooled periodically.¹⁸ As discussed in Appendix I, Merck completed its first pooled analysis in January 2001 and then updated it by performing new pooled analyses in July 2001, May 2002, and August 2004 as additional clinical trial data became available.¹⁹ Merck’s first pooled analysis, which was submitted to the FDA in January 2001 and subsequently published in Circulation by outside consultant Dr. Marvin Konstam*, and its second pooled analysis, submitted to the FDA in July 2001 and reported in the medical literature by Dr. Matthew Weir*, are discussed in Appendix J.

¹⁶ 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AAF0008651, at 52.

¹⁷ 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AAF0008651, at 52.

¹⁸ Merck sometimes used the term “meta-analysis” interchangeably with “pooled analysis.” A meta-analysis combines the summary results of two or more studies, whereas a pooled analysis combines the actual underlying data from two or more studies. Technically, all of Merck’s analyses pursuant to the Cardiovascular Adjudication SOP were pooled analyses, which is how the Company characterized the final two analyses it sent to the FDA. Thus, this Appendix uses the term “pooled analysis” throughout.

¹⁹ 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140, at 40.

This Appendix discusses Merck's third and fourth pooled analyses, which were conducted in May 2002 and August 2004, respectively. Both of these analyses demonstrated no statistically significant increased rate of cardiovascular events on Vioxx versus non-naproxen NSAIDs or placebo. Each analysis, however, did show an increased rate of cardiovascular events on Vioxx versus naproxen.

1. The 2002 Pooled Analysis.

On May 22, 2002, Merck sent the FDA its third pooled analysis (the "2002 Pooled Analysis"), which included data from clinical trials completed and unblinded by January 31, 2001.²⁰ The 2002 Pooled Analysis included approximately 2400 additional patient-years on Vioxx or a comparator that had become available since the July 2001 analysis that Merck had previously provided.²¹

The 2002 Pooled Analysis included all Phase IIb through Phase V Vioxx clinical studies of at least four weeks' duration that included a comparator agent or placebo.²² Data from Phase I trials were excluded because those trials were relatively brief and involved a healthier patient population – *i.e.*, a population with fewer risk factors for cardiovascular events – than was representative of the typical Vioxx patient group.²³

²⁰ 5/22/02 letter from N. Braunstein to L. Simon* attaching 2002 Rofecoxib Pooled Analysis, MRK-AHN0022140.

²¹ 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, at 47 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

²² 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, at 49 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

²³ 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, at 77 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

Data from three six-week trials comparing Vioxx to Celebrex also were excluded because there were no placebo or non-selective NSAID comparators in those trials.²⁴

As in prior analyses, Merck separately pooled data from clinical trials using placebo, non-naproxen NSAIDs, and naproxen as comparator agents.²⁵ The primary analysis was based on the composite cardiovascular adverse event endpoint defined by the Antiplatelet Trialists' Collaboration ("APTC").²⁶ The secondary analysis used the endpoint of "thrombotic cardiovascular events" defined by the Cardiovascular Adjudication SOP.²⁷ As explained in Appendix F, the widely accepted Antiplatelet Trialists' Collaboration composite cardiovascular endpoint included non-thrombotic events, such as hemorrhagic strokes and deaths from unknown causes. The thrombotic cardiovascular events endpoint excluded all non-thrombotic events and included events that were not part of the Antiplatelet Trialists' Collaboration composite cardiovascular endpoint, including peripheral arterial thrombosis and peripheral venous thrombosis.²⁸

²⁴ 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, at 49 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

²⁵ 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, at 47 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

²⁶ As discussed in Appendix F, The Antiplatelet Trialists' Collaboration composite endpoint was used to ensure consistency of analysis of unadjudicated data (from clinical trials conducted prior to the Cardiovascular Adjudication SOP) and adjudicated, post-Cardiovascular Adjudication SOP data, both of which were included in the pooled analysis. 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, at 77-78 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

²⁷ 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, at 51 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

²⁸ 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, at 51-52 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

As reflected on Table 3 below, with respect to both the primary and secondary endpoints, the 2002 Pooled Analysis indicated that Vioxx was not associated with a statistically significant increased risk of an adverse cardiovascular event, except in comparison to naproxen:

Table 3

Relative Risk of Vioxx Versus Placebo, Non-Naproxen NSAIDs,
and Naproxen As Reported in Merck's 2002 Pooled Analysis

Endpoint	Relative Risk of Vioxx vs. Comparator (95% CI)		
	Placebo	Non-Naproxen NSAIDs	Naproxen
APTC Composite Cardiovascular Endpoint ²⁹	0.94 (0.62, 1.42)	0.87 (0.48, 1.58)	1.61 (1.04, 2.50)
Thrombotic Cardiovascular Events Endpoint ³⁰	1.04 (0.72, 1.52)	1.04 (0.65, 1.64)	1.59 (1.09, 2.31)

The 2002 Pooled Analysis also noted that the cumulative incidence of cardiovascular events among patients on Vioxx, placebo, and non-naproxen NSAIDs was similar over time, suggesting that Vioxx did not have a prothrombotic effect.³¹ The analysis concluded that the “totality of the data in this pooled analysis is most consistent

²⁹ 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, Figure 1 at 53 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

³⁰ 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, Figure 5 at 65 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

³¹ 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, at 78 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42). This similarity is illustrated in “Kaplan-Meier” time-to-event curves included in the pooled analysis. 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, Figure 2 at 56, Figure 3 at 60, Figure 6 at 68, Figure 7 at 72 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

with naproxen having provided a relative cardioprotective benefit in these studies and argue against a prothrombotic effect of rofecoxib.”³²

2. The 2004 Pooled Analysis.

On March 22, 2004 Merck sent to the FDA its fourth pooled analysis (the “2004 Pooled Analysis”),³³ which included data from Vioxx clinical trials completed and unblinded as of June 10, 2003.³⁴ The 2004 Pooled Analysis included approximately 750 additional patient-years of exposure to Vioxx or a Vioxx comparator that had become available since the 2002 Pooled Analysis.³⁵ The 2004 Pooled Analysis used a design similar to that used for the 2002 Pooled Analysis: the criteria for including or excluding clinical trials as well as both the primary Antiplatelet Trialists’ Collaboration composite cardiovascular endpoint and secondary thrombotic cardiovascular events endpoint were the same.³⁶

As shown on Table 4 below, with respect to both the primary APTC composite cardiovascular endpoint and the secondary thrombotic cardiovascular serious adverse experiences endpoint, the 2004 Pooled Analysis did not find a statistically significant

³² 2002 Rofecoxib Pooled Analysis, MRK-AHN0022143, at 78 (attached to 5/22/02 letter from N. Braunstein to L. Simon*, MRK-AHN0022140-42).

³³ 3/22/04 letter from D. Louie to B. Harvey*, MRK-AAF0015420.

³⁴ 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744-811.

³⁵ 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, at 45.

³⁶ 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744-811, at 50. Although the secondary endpoint was the same in both pooled analyses, the 2004 Pooled Analysis referred to the secondary endpoint as “Thrombotic Cardiovascular Serious Adverse Experiences.” Id.

association between Vioxx and increased risk of an adverse event, except in comparison to naproxen:

Table 4

Relative Risk of Vioxx Versus Placebo, Non-Naproxen NSAIDs,
and Naproxen As Reported in Merck's 2004 Pooled Analysis

Endpoint	Relative Risk of Vioxx vs. Comparator (95% CI)		
	Placebo	Non-Naproxen NSAIDs	Naproxen
APTC Composite Cardiovascular Endpoint ³⁷	1.14 (0.77, 1.68)	0.93 (0.51, 1.69)	1.61 (1.04, 2.50)
Thrombotic Cardiovascular Events Endpoint ³⁸	1.26 (0.89, 1.78)	1.09 (0.69, 1.73)	1.59 (1.09, 2.31)

The 2004 Pooled Analysis included several analyses of the impact of dose on Vioxx's cardiovascular effects. The first analysis compared the incidence of APTC endpoint events on the 12.5 mg dose and the 25 mg dose in trials that involved both doses and on the 25 mg and 50 mg doses in trials that involved both doses (there were no trials comparing all three doses or comparing the 12.5 mg and 50 mg doses). The results of this analysis are reported in the table below:³⁹

³⁷ 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, Figure 1 at 57.

³⁸ 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, Figure 5 at 71.

³⁹ For the underlying data see 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, Table 20 at 85.

Table 5

Relative Risk of Vioxx Doses for APTC Events
As Reported in Merck's 2004 Pooled Analysis

	Cases/Patient Years	Relative Risk (95% confidence interval)
Trials Comparing Vioxx 12.5 mg and 25 mg		
12.5 mg	12/993	
25 mg	13/1,411	0.76 (0.32, 1.83)
Trials Comparing Vioxx 25 mg and 50 mg		
25 mg	8/1,693	
50 mg	18/1,417	2.69 (1.11, 7.15)

While this first analysis demonstrated that there was no significant difference in the rate of APTC combined cardiovascular endpoint events between the 12.5 mg and 25 mg doses, it did show a statistically significant difference between the 25 mg and 50 mg doses. The second analysis examined the relative risk of each individual event in the APTC composite cardiovascular endpoint and found no significant difference between these doses with respect to the risk of myocardial infarction.⁴⁰ The final analysis demonstrated that the rate of these events was similar across all doses of Vioxx and all studies included in the pooled analysis.⁴¹

The 2004 Pooled Analysis also examined the risk of an Antiplatelet Trialists' Collaboration cardiovascular composite endpoint event in relation to duration of Vioxx

⁴⁰ 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, at 85.

⁴¹ See 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, Table 21 at 87. The rates of events on Vioxx 12.5, 25, and 50 mg were 1.44, 1.24, and 1.24 respectively. The confidence interval associated with the higher rate for the 12.5 mg dose encompassed the confidence intervals associated with the rates for the other two doses, indicating the rates of all three doses were statistically indistinguishable.

therapy by classifying clinical trial experience into three groups: (i) exposure for 3 months or less; (ii) exposure for between 3 and 12 months; and (iii) exposure for more than 12 months.⁴² The duration of therapy analysis showed that “[c]omparisons of relative risks over various duration periods were generally consistent.”⁴³ The following table summarizes the relative risks associated with each duration of therapy studied:⁴⁴

Table 6

Relative Risk of Vioxx Versus Comparators by Duration of Treatment
As Reported in Merck’s 2004 Pooled Analysis

Duration of Treatment	Relative Risk of Vioxx Versus Comparator (95% confidence interval)
Placebo Controlled Data	
≤ 3 months	1.28 (0.61, 2.67)
3 – 12 months	0.80 (0.40, 1.57)
> 12 months	1.37 (0.74, 2.55)
Non-naproxen NSAIDs Controlled Data	
≤ 3 months	1.16 (0.49, 2.75)
3 – 12 months	0.70 (0.25, 1.96)
> 12 months	0.92 (0.20, 5.69)
Naproxen Controlled Data	
≤ 3 months	1.33 (0.69, 2.54)
3 – 12 months	2.09 (1.08, 4.07)
> 12 months	1.07 (0.29, 3.90)

The 2004 Pooled Analysis also classified study participants into subgroups based upon aspirin use and baseline cardiovascular risk and found that the results for these

⁴² 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, at 53.

⁴³ 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, at 46.

⁴⁴ For the underlying data, see 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, at 89.

subgroups did not differ from those for all participants combined.⁴⁵ Participants who used low-dose aspirin for 50% or more of the study days and who also used naproxen suffered no events in 435 patient-years of experience, while others using low-dose aspirin concomitantly with non-naproxen NSAIDs or placebo suffered events at a rate of 4.37 and 2.20 per 100 patient years, respectively.⁴⁶

Because the only remaining sources of new clinical trial data following the 2004 Pooled Analysis were the APPROVe, VICTOR, and ViP Trials, all of which were ongoing when Vioxx was withdrawn from the market, Merck did not update its pooled cardiovascular safety analyses after the 2004 Pooled Analysis.⁴⁷

C. Periodic Safety Update Reports.

Merck submitted a formal Vioxx Periodic Safety Update Report to the FDA every six months while Vioxx was on the market. These reports were compiled in accordance with guidelines concerning periodic post-marketing safety reporting adopted by the International Conference on Harmonisation, a collaborative comprising regulatory agencies from all over the world, including the FDA. The Conference's guidelines recommend that drug manufacturers produce a standard post-marketing safety report

⁴⁵ 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, Table 24 at 91.

⁴⁶ 2004 Rofecoxib Pooled Analysis, MRK-AAB0100744, Table 26 at 94. The potential significance of these unadjusted findings must be considered in light of the potential for confounding.

⁴⁷ See 2004 Rofecoxib Pooled Analysis, MRK-AAB0100743, at 45.

every six months that would satisfy contemporary reporting requirements across multiple jurisdictions.⁴⁸

Merck's Vioxx Periodic Safety Update Reports included information from both clinical and market experience. This Appendix focuses on two categories of data routinely reported in the eleven Vioxx Periodic Safety Update Reports filed between August 13, 1999 and August 19, 2004: (i) usage data and (ii) spontaneously reported adverse experience data.

1. Usage Data.

Each Vioxx Periodic Safety Update Report contained data tracking the worldwide patient exposure to the drug in both clinical and real-world settings. The Company reported the clinical usage data by indicating the number of patients who had been enrolled in clinical trials of Vioxx during the preceding six months. With respect to the real-world usage data, the Company reported the periodic and cumulative patient exposure to Vioxx oral suspensions and tablets by dose in the worldwide marketplace, based on the amount of Vioxx it distributed.⁴⁹ Within six months of Vioxx's

⁴⁸ The FDA issued its own non-binding guidelines on periodic safety update reports for marketed drugs on May 19, 1997. International Conference on Harmonisation: Guideline on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs; Availability; Notice, 62 Fed. Reg. 27,470, 27,472 (May 19, 1997).

⁴⁹ See, e.g., 8/13/99 Periodic Safety Update Report #1, MRK-AIX0011566, at 575. Because Merck calculated the number of patient-years of exposure from how much Vioxx it distributed, the calculation may have overrepresented the actual number of patient-years of experience in the marketplace. See, e.g., *id.* (noting that some of the Vioxx distributed may reflect "distributor stocking of inventory because of marketing approvals received during this period").

introduction, there were 195,732 patient-years of total marketplace exposure.⁵⁰ By the time Merck withdrew Vioxx from the market, there were 23,619,552 patient-years of exposure.⁵¹

2. Spontaneously Reported Adverse Event Data.

Each Periodic Safety Update Report also contained analyses of adverse events that occurred in Vioxx users worldwide. Sources of information about these events included, among others, spontaneous notifications to Merck (e.g., from healthcare providers or consumers) stored in the Company's FDA-mandated adverse experience reporting system and scientific literature.⁵² The types of adverse events analyzed in a Periodic Safety Update Report depend upon the types of adverse events that have occurred during the six-month period covered by the report. At various times, the specific types of adverse events analyzed in the Vioxx reports included, among others, death, overdose, drug abuse, events during pregnancy, anxiety, seizures, and gastrointestinal perforations, ulcers, and bleeds.⁵³

⁵⁰ 8/13/99 Periodic Safety Update Report #1, MRK-AIX0011566, at 575.

⁵¹ 8/19/04 Periodic Safety Update Report #11, MRK-ACV0034321, at 331.

⁵² See International Conference on Harmonisation: Guideline on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs; Availability; Notice, 62 Fed. Reg. 27,470, 27,472 (May 19, 1997).

⁵³ See, e.g., 8/13/99 Periodic Safety Update Report #1, MRK-AIX0011566, at 566; 2/14/01 Periodic Safety Update Report #4, MRK-AIX0012503, at 505; 8/19/04 Periodic Safety Update Report #11, MRK-ACV0034321, at 322.

Beginning in February 2001 with Periodic Safety Update Report #4, the Company analyzed the reported incidence of ischemic heart disease and coronary artery disease.⁵⁴ The following table shows the cumulative incidence of these cases from Periodic Safety Update Reports #4 through #11 (the last one filed):⁵⁵

Table 7

Cumulative Number of Cases of Ischemic Heart Disease/Coronary Artery Disease as Reported in Merck's Fourth Through Eleventh Periodic Safety Update Reports

Report Number	Cumulative Cases of Ischemic Heart Disease/Coronary Artery Disease	Patient Years of Experience (approx. in thousands)
4	106	5,100
5	143	7,500
6	232	10,000
7	384	10,000
8	420	15,000
9	480	17,800
10	585	20,600
11	779	23,600

The most common adverse event falling into this category was myocardial infarction (i.e., heart attack). The following table reports the cumulative incidence of myocardial infarction:⁵⁶

⁵⁴ 2/14/01 Periodic Safety Update Report #4, MRK-AIX0012503, at 606-07.

⁵⁵ For the underlying data reflected in this table, see 2/14/01 Periodic Safety Update Report #4, MRK-AIX0012503, at 606; 8/14/01 Periodic Safety Update Report #5, MRK-AFV0006511, at 583; 2/20/02 Periodic Safety Update Report #6, MRK-AFV0026142, at 207; 8/21/02 Periodic Safety Update Report #7, MRK-AIX0052060, at 136; 2/25/03 Periodic Safety Update Report #8, MRK-ABS0456208, at 283; 8/15/03 Periodic Safety Update Report #9, MRK-ACV0030981, at 1048; 2/17/04 Periodic Safety Update Report #10, MRK-AEC0076205, at 316; 8/19/04 Periodic Safety Update Report #11, MRK-ACV003431, at 412.

⁵⁶ For the underlying data reflected in this table, see 2/14/01 Periodic Safety Update Report #4, MRK-AIX0012503, at 606; 8/14/01 Periodic Safety Update Report #5, MRK-AFV0006511, at 583; 2/20/02 Periodic Safety Update Report #6, MRK-AFV0026142, at 207; 8/21/02 Periodic Safety Update Report #7, MRK-AIX0052060, at 136; 2/25/03 Periodic Safety Update Report #8,

Table 8

Cumulative Number of Cases of Myocardial Infarction
as Reported in Merck's Fourth Through Eleventh Periodic Safety Update Reports

Report Number	Cumulative Incidence of Myocardial Infarction	Patient Years of Experience (approx. in thousands)
4	57	5,100
5	75	7,500
6	136	10,000
7	244	10,000
8	258	15,000
9	297	17,800
10	366	20,600
11	500	23,600

Each report analyzed the data quantitatively and qualitatively. Quantitatively, the reports compared the rate of ischemic heart disease and coronary artery disease among the population taking Vioxx with the rate of coronary artery disease among the general population as reported in a publication by the Centers for Disease Control. For example, Periodic Safety Report #11 stated:

In the United States, the age-adjusted incidence of CAD [coronary artery disease] ranges from 640 to 1,100 per 100,000 patient-years for women and men, respectively. Based on approximately 23.6 million patient-years of treatment worldwide . . . , the reporting rate of CAD/ischemic heart disease (IHD) in patients on therapy with rofecoxib is approximately 3.3 per 100,000 patient-years of exposure, which is far below the expected actual incidence.⁵⁷

MRK-ABS0456208, at 283; 8/15/03 Periodic Safety Update Report #9, MRK-ACV0030981, at 1048; 2/17/04 Periodic Safety Update Report #10, MRK-AEC0076205, at 316; 8/19/04 Periodic Safety Update Report #11, MRK-ACV003431, at 412.

⁵⁷ 8/19/04 Periodic Safety Update Report #11, MRK-ACV0034321, at 412.

The reports also examined the data qualitatively. The age, risk factor, and medical history characteristics of the Vioxx users experiencing these events revealed “no features or patterns distinguishing them from the same types of events occurring in the general population.”⁵⁸

D. Communications with the FDA About the Arcoxia New Drug Application.

While Vioxx was on the market, Merck also communicated with the FDA about its second-generation selective Cox-2 inhibitor, Arcoxia. Merck originally submitted a New Drug Application for Arcoxia in late 2001.⁵⁹ Subsequently, the Company withdrew its application and then resubmitted it. To date, the FDA has not approved Arcoxia for sale in the United States.

On March 15, 2002, Merck, pursuant to a decision by the Company’s Management Committee, withdrew the Company’s New Drug Application seeking FDA approval for Arcoxia.⁶⁰ The Company explained the reasons for the withdrawal in a press release:

Last month, Merck announced plans to submit an expanded New Drug Application (NDA) for ARCOXIA (etoricoxib) to the FDA to include new efficacy data for ankylosing spondylitis [a rare, but chronically painful disease of the

⁵⁸ 8/19/04 Periodic Safety Update Report #11, MRK-ACV0034321, at 412.

⁵⁹ See Timeline of IND/NDA Filings, in 2/16/05 slide presentation by J. Bull*, “Regulatory History: Joint Meeting of the [FDA] Arthritis and the Drug Safety and Risk Management Advisory Committee” http://www.fda.gov/OHRMS/DOCKETS/AC/05/slides/2005-4090S1_01_FDA-Bull_files/frame.htm#slide0047.htm (last visited Mar. 25, 2006).

⁶⁰ 6/11/02 Merck press release, “Merck Reconfirms 2002 Worldwide Coxib Sales Guidance and 2002 and 2003 EPS Guidance; Merck Plans to Refile U.S. New Drug Application for ARCOXIA™ in Second Half of 2003,” MRK-ADW0081756, at 56.

spine] that will better position the product to compete successfully in the coxib class, where there already are three entrants. Accordingly Merck announced the withdrawal of the original U.S. NDA for the investigational medicine. Merck believes the new data, along with the data previously submitted, will provide a fuller picture of the product's efficacy and safety and will position it more favorably for approval in the United States.⁶¹

Dr. Peter Kim, then an Executive Vice President of MRL, told industry analysts that ankylosing spondylitis “represent[ed] a very strong model for the treatment of chronic inflammatory pain.”⁶² At the time that Merck withdrew the application, British regulatory agencies had already approved Arcoxia for treatment of the signs and symptoms of “osteoarthritis, rheumatoid arthritis, acute gouty arthritis, acute pain associated with dental surgery, primary dysmenorrhea and chronic musculoskeletal pain, including chronic low back pain.”⁶³ Regulatory agencies in Mexico, Brazil, and Peru had also approved Arcoxia for similar indications.⁶⁴

Notwithstanding its withdrawal of the Arcoxia New Drug Application, Merck continued to meet with the FDA concerning Arcoxia. On June 11, 2002, the Company disclosed in a press release that, “In a meeting last week, the FDA requested additional

⁶¹ 4/18/02 Merck press release, “Merck Announces First-Quarter 2002 Earnings Per Share of 71 Cents,” MRK-PRL0000251, at 54.

⁶² 4/15/02 email from R. Roberts to C. Fanelle et al., including text of article, “Morgan Stanley Power Brunch with Peter Kim of Merck Research Labs,” MRK-ADN0079382, at 85.

⁶³ 4/18/02 Merck press release, “Merck Announces First-Quarter 2002 Earnings Per Share of 71 Cents,” MRK-PRL0000251, at 54.

⁶⁴ 4/18/02 Merck press release, “Merck Announces First-Quarter 2002 Earnings Per Share of 71 Cents,” MRK-PRL0000251, at 54.

data on the acute pain indications for ARCOXIA and additional cardiovascular safety data for ARCOXIA versus comparators other than naproxen.”⁶⁵

Merck resubmitted its New Drug Application on December 30, 2003, seeking indications for osteoarthritis, rheumatoid arthritis, chronic low back pain, acute pain, dysmenorrhea, acute gouty arthritis, and ankylosing spondylitis.⁶⁶ On October 29, 2004, the FDA issued an approvable letter to Merck, indicating that the Agency would approve the application upon the submission of additional efficacy and safety data.⁶⁷

According to a contemporaneous Merck press release, the Company planned to meet the FDA’s conditions in part by providing cardiovascular data from two clinical trials that were then ongoing: the MEDAL Trial (a cardiovascular outcomes trial comparing Arcoxia and diclofenac) and the EDGE II Trial (a gastrointestinal outcomes trial comparing Arcoxia and diclofenac).⁶⁸ The data from the two trials became available in 2006, and in each trial the rates of confirmed thrombotic events were similar between Arcoxia and diclofenac.⁶⁹ The Company has also pooled the cardiovascular data from

⁶⁵ 6/11/02 Merck press release, “Merck Reconfirms 2002 Worldwide Coxib Sales Guidance and 2002 and 2003 EPS Guidance; Merck Plans to Refile U.S. New Drug Application for ARCOXIA™ in Second Half of 2003,” MRK-ADW0081756, at 56.

⁶⁶ 1/27/04 Merck press release, “Merck Announces Full-Year 2003 Earnings Per Share (EPS) From Continuing Operations of \$2.92, Fourth-Quarter 2003 EPS of 62 Cents,” MRK-ABX0067968, at 72.

⁶⁷ 6/17/05 Merck press release, “Merck & Co., Inc. Provides Status Update on Ongoing ARCOXIA – etoricoxib – Trials,” MRK-AFV0415065.

⁶⁸ 6/17/05 Merck press release, “Merck & Co., Inc. Provides Status Update on Ongoing ARCOXIA – etoricoxib – Trials,” MRK-AFV0415065.

⁶⁹ In the MEDAL Trial, the relative risk for confirmed thrombotic events (Arcoxia versus diclofenac) was 0.96 (95% confidence interval, 0.81 to 1.15) and 1.08 (95% confidence interval, 0.94 to 1.25) for the prespecified per protocol and intention-to-treat analyses, respectively. 8/06 MEDAL Program

both of these trials together with that from an earlier trial using the same comparator, the original EDGE Trial, and released the preliminary results of the analyses on August 23, 2006. The combined data from these three trials, which comprised data from over 23,000 patients,⁷⁰ also demonstrated that the rate of cardiovascular events was similar in both treatment groups.⁷¹ Merck has announced that it intends to include these results, which have already been reported to the FDA, in its formal response to the October 2004 approvable letter.⁷²

* * *

Early Results, MRK-I4640003751, Table 22 at 791. See also 8/06 MEDAL Program Early Results, MRK-I4640003751, at 814 (“The thrombotic cardiovascular safety profile of etoricoxib is similar to that of diclofenac in [the EDGE II Trial].”).

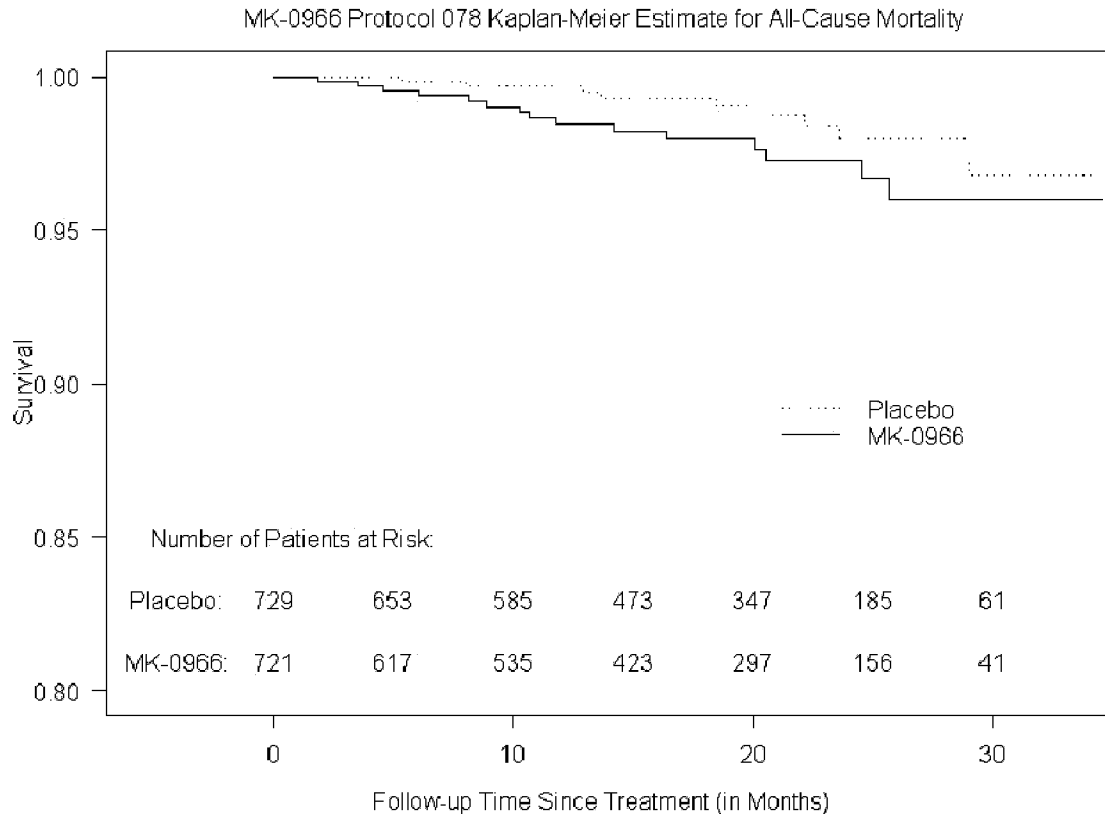
⁷⁰ 8/23/06 Merck press release, “Merck Provides Preliminary Analyses of the Completed MEDAL Program for Arcoxia,” MRK-I4640003746, at 47.

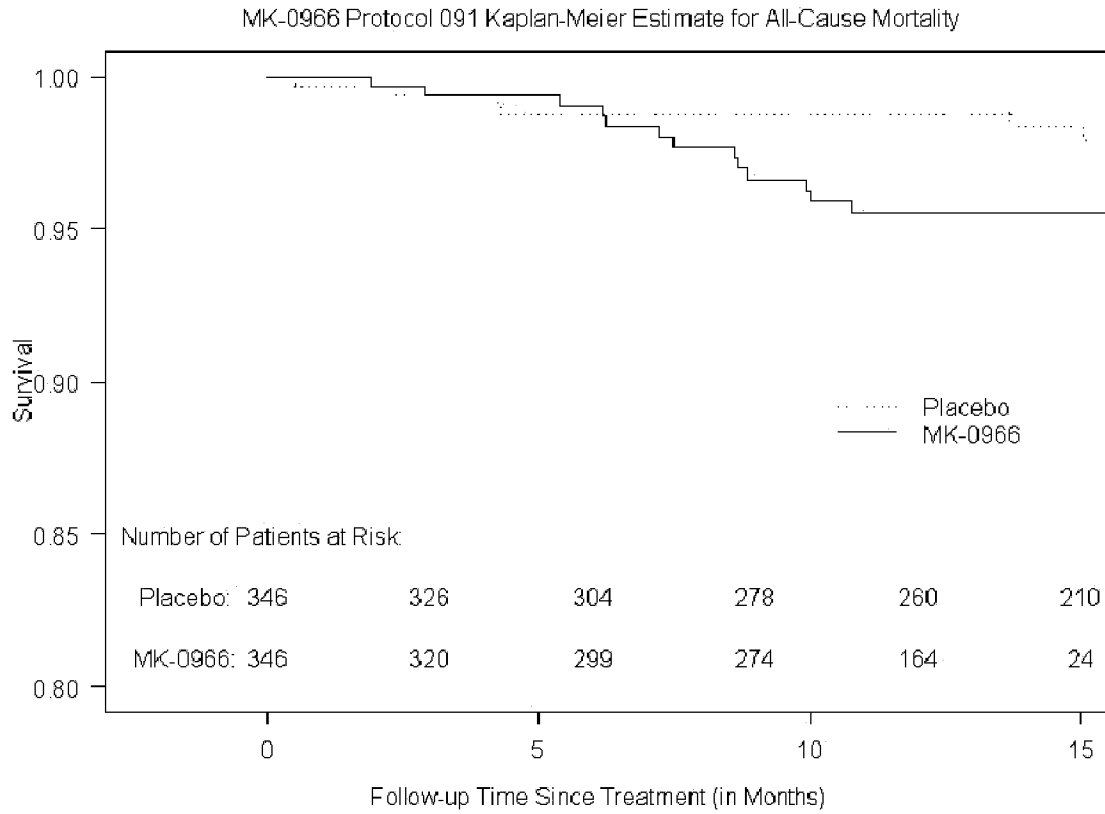
⁷¹ The relative risk for confirmed thrombotic events (Arcoxia versus diclofenac) was 0.95 (95% confidence interval, 0.81 to 1.11) and 1.05 (95% confidence interval, 0.93 to 1.19) for the prespecified per protocol and intention-to-treat analyses, respectively. 8/06 MEDAL Program Early Results, MRK-I4640003751, Table 6 at 765. The results for the APTC composite cardiovascular endpoint were similar. Id. Table 10 at 773.

⁷² 8/23/06 Merck press release, “Merck Provides Preliminary Analyses of the Completed MEDAL Program for Arcoxia,” MRK-I4640003746, at 47.

Figure 1

Kaplan-Meier Survival Plots for All-Cause Mortality
Provided to FDA by Dr. Silverman on October 8, 2001





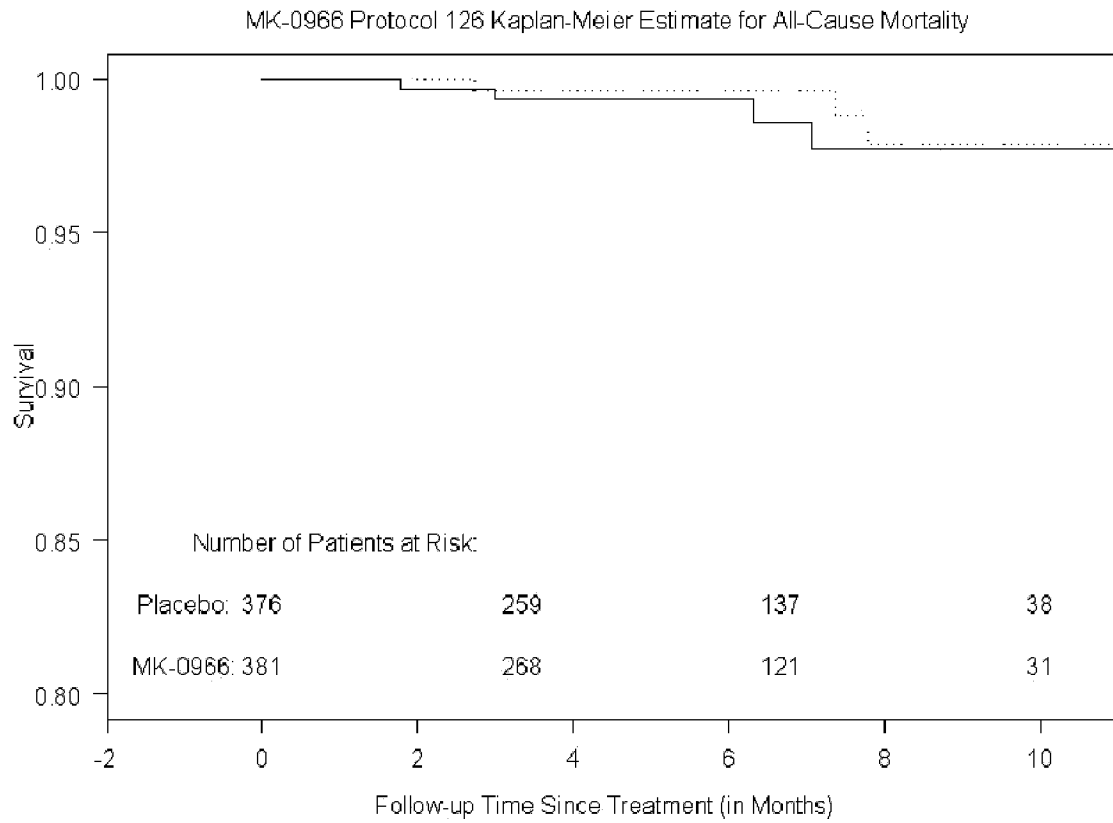


Figure 2

Kaplan-Meier Survival Plots for Cardiovascular Mortality
Provided to FDA by Dr. Silverman on October 8, 2001

