Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

March 29, 2002

Lee Simon, M.D., Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Simon:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a fax dated March 29, 2002 from Ms. Barbara Gould (FDA) to Dr. Ned Braunstein, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. requesting information.

By this submission, we are providing a response to the requested information.

FDA Request #1
Your analysis of CV thrombotic events in VIGOR uses the cutoff point of 500 patients per treatment group (approximately 10.5 months). Clarify whether there were additional cardiovascular thrombotic events that occurred after the cutoff point.

MRL Response #1
In the VIGOR study, there were no confirmed thrombotic CV serious adverse experiences in either treatment group that occurred after the cutoff time of 500 patients remaining per treatment group (10.8 months) and there were no confirmed PUBs in the VIOXX group after the cutoff. However, there were 2 confirmed PUBs, 1 of which was a confirmed complicated PUB, in the naproxen group that occurred after the cutoff. These 2 confirmed PUBs/1 confirmed complicated PUB are included in Table 1 of the draft label in the analysis of relative risk which, according to the DAP, is by Cox proportional hazard model, but are not included in the cumulative incidence of PUBs at end of study which, for Kaplan-Meier data, was defined in the DAP as the time when there were only 500 patients remaining in any treatment group.

All information is in electronic format as indicated in the Table of Contents for this amendment.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

March 21, 2002

Lee Simon, M.D., Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V

c/o
Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Simon:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

Amendment to Supplemental New Drug Application
(Revised Proposed Label)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 which provided for changes to the labeling as a result of the VIOXX™ Gastrointestinal Outcomes Research (VIGOR) study. Reference is also made to letters from the Agency to Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. containing the Agency's labeling proposals for the VIGOR sNDA dated October 15, 2001, December 21, 2001 and January 29, 2002; MRL's proposed labels submitted to the Agency via official submission on November 6, 2001, December 5, 2001, January 7, 2002, and February 19, 2002; MRL's proposed labels submitted to the Agency via e-mail on February 25, 2002, March 6, 2002 (PPI), and March 13, 2002; and labeling discussions held between the Agency and MRL on January 30, 2002, and February 8, 2002, February 20, 2002, March 7, 2002, and March 20, 2002; and several telephone conversations between FDA and MRL during which the VIGOR labeling was discussed.

By this letter, MRL is providing an updated draft label and Patient Product Information (PPI) for the VIOXX™ VIGOR sNDA based on discussions held on March 20, 2002. The draft label is provided in 2 columns with MRL's proposed label on the left and comments on the right. A brief rationale is provided in the mocked-up label for most of these changes.

In this draft label, MRL has attempted to accommodate all of the Agency's comments. With regard to changes to the text, we have provided wording that we believe incorporates all of the suggestions made by the Agency both in the label and the PPI. In particular, changes to the 2 bullets in the section on Possible Side Effects in the PPI have been changed consistent with your comments that this section should not include descriptions of the results of clinical studies. We have also included a new table of cardiovascular thrombotic events in VIGOR that we believe addresses the Agency's requests to show cumulative incidence rates over time for the confirmed thrombotic endpoint and made requested modifications to the current table to remove ——— information and to simply show the breakdown of events by type. We believe that this presentation complies with the Agency's request and highlights the time course but are willing to discuss other modifications to the tables if desired.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

March 21, 2002

Lee Simon, M.D., Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Simon:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

General Correspondence

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000, a submission dated June 19, 2001 from Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. based on an Arthritis Advisory Committee Meeting Request; and an email from the Agency on March 18, 2002 regarding an internal memo dated March 14, 2002 regarding VIOXX™ labeling comments.

MRL appreciates the Agency's sharing its statistical analysis of thrombotic cardiovascular event rates over time in VIGOR and would like to take this opportunity to respond to the Agency's statistical memo and point out that in the Agency's memo, there is a mixing of data from 2 different endpoints. Thus, the VIOXX™ analysis in Table 1 uses confirmed thrombotic event data whereas the naproxen analysis in this table represents a mixture of confirmed events (eg, for hazard rates) and investigator-reported data (eg, for number of events). Table 2 uses investigator-reported CV events for both VIOXX™ and naproxen analyses. As confirmed thrombotic events are the prespecified endpoints agreed to between MRL and the Agency, the analysis of confirmed events in Table 1 is the more relevant analysis. This analysis, in fact, is consistent with MRL's previous analyses sent to the Agency and supports MRL's conclusion that hazard in VIGOR was constant over time. Also provided in the current document are Kaplan-Meier plots of confirmed thrombotic events in the 2 long-term Alzheimer's Disease studies, Protocols 078 and 091. If VIOXX™ were associated with an increased risk of thrombotic events over time, one would have expected to see changes in the rates of events in the relatively high-risk patients in the AD studies. Instead, the K-M plots of the Alzheimer's Disease data corroborate that there is a generally constant hazard of confirmed thrombotic cardiovascular serious adverse events in patients taking VIOXX™. As there is no statistical evidence for a change in either relative risk or hazard over time, MRL continues to favor the representation of CV data using overall risks per 100 patient-years and using relative risk based on the Cox model.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

March 22, 2002

Lee Simon, M.D., Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Simon:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a fax dated March 18, 2002 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. requesting information on Protocol 078.

By this submission, we are providing a response to the requested information.

FDA Request #1
Please provide demographics and baseline characteristics (e.g. age, sex, prior medical condition, and prior medication) of patients in study 078.

MRL Response #1
Unlike the data on mortality and confirmed thrombotic events which are subject to a rigorous adjudication process, this preliminary summary describing the baseline characteristics of patients enrolled in MK-0966, Protocol 078 is based upon partially screened and cleaned data from an ongoing blinded study. As data review is ongoing and official data are being collected and reviewed by Merck Research Laboratories (MRL), these baseline characteristics data may differ from what is in the frozen database post study conclusion.

The summaries are for all patients enrolled, with treatments presented as Treatment A and Treatment B. Three tables are provided on the entire enrollment of the study in Attachment I. Table 1 presents the baseline patient characteristics. Table 2 presents the counts of patients with specific prior medications. Table 3 presents the counts of patients with specific secondary diagnoses.

Also included as Attachment II in this response are similar tables from the completed Protocol 091 which we realize the Agency has not yet seen. Although not yet audited, these tables are based on the frozen database of Protocol 091 and will be included in a CSR which is currently in review.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

March 5, 2002

MERCK

Lee Simon, M.D., Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Simon:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 which provided for changes to the labeling as a result of the VIOXX™ Gastrointestinal Outcomes Research Study (VIGOR) and a teleconference between representatives of FDA and Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on February 20, 2002 regarding MRL's proposed label.

During the teleconference, the Agency requested that Merck provide its justification for preferring the use of ———— rather than cumulative rates in the description in product labeling of the results from VIGOR. The attached report provides the requested response. As delineated in the attached report, MRL has accepted the Agency's preference for the use of cumulative rates in the current proposed product label for VIOXX™ but would like to retain the right to revisit this issue in the future for other product label situations where the differences between the 2 rates have a more significant impact on the analysis and interpretation of study results.

All information is in electronic format as indicated in the Table of Contents for this amendment.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the content of the CD are free of computer viruses (Norton AntiVirus® 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

February 25, 2002

MERCK

Lee Simon, M.D., Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Simon:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000, and a fax dated February 19, 2002 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. requesting additional information on the Alzheimer's studies.

By this submission, we are providing a response to the requested information.

FDA Request #1
For the Alzheimer's studies, please provide a listing of patients with adjudicated cardiovascular thrombotic events by category (cardiac (MI/sudden death; non-fatal MI; angina); cerebrovascular events (TIA, ischemic stroke) and peripheral events) and by treatment group (similar to your 2/5/02 submission for CV thrombotic events in VIGOR).

MRL Response #1
Attached please find the requested listings of confirmed thrombotic events by event category for — protocols combined (078, 091 ——— , Attachment I, and for two protocols combined (078 and 091) respectively, Attachment II. Also please find listings of cardiovascular mortality by protocol (Attachment III). Listings are based on data provided in the July 12, 2001 Safety Update Report.

All information is in electronic format as indicated in the Table of Contents for this amendment.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

February 19, 2002

MERCK

Lee Simon, M.D., Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Simon:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; three faxes dated February 14, 2002 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. requesting additional information on the Alzheimer's studies.

By this submission, we are providing a response to the requested information.

FDA Request #1
Please provide allocation treatment for Pt 078-021-00639 and 0126-023-0000-558 (sudden deaths) and median exposure from each of the Alzheimer's studies.

MRL Response #1
Patient 078-021-00639 was a 70 year-old male who was randomized to rofecoxib 25 mg in Protocol 078 on August 8, 1998. On ———————, blinded therapy was discontinued due to a non-compliance issue and the need for other non-steroidal anti-inflammatory drugs. On ——————— the patient died. The cause of death was reported as myocardial infarction; the adjudicated cause of death was sudden death. Because this patient died ~2 months after the last dose of study therapy (ie. more than the protocol specified 14 days after last dose) and because the death was not due to a serious adverse experience that began within 14 days of the last dose of therapy, the death is not considered an on-drug death and was not counted in the analyses.

Patient 126-023-0000 —— ID# 558) was an 82 year old patient who had been screened for entry in Protocol —— May 18, 2000, consent was obtained, and blood drawn. The patient was never randomized into the study and therefore was not allocated to study therapy. The patient died on ———————

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

February 19, 2002

MERCK

Lee Simon, M.D., Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V

c/o
Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Simon:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

Amendment to Supplemental New Drug Application
(Revised Proposed Label)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 which provided for changes to the labeling as a result of the VIOXX™ Gastrointestinal Outcomes Research (**VIGOR**) study. Reference is also made to letters from the Agency to Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. containing the Agency's labeling proposals for the VIGOR sNDA dated October 15, 2001, December 21, 2001 and January 29, 2002; MRL's proposed labels submitted to the Agency on November 6, 2001, December 5, 2001, and January 7, 2002; labeling discussions held between the Agency and MRL on January 30, 2002, and February 8, 2002; and a telephone conversation between Dr. Larry Goldkind (FDA) and other representatives from the Agency and Dr. Robert E. Silverman (MRL) on February 13, 2002 during which the VIGOR labeling was discussed.

By this letter, MRL is providing an updated labeling proposal for the VIOXX™ VIGOR sNDA to be discussed during label negotiations between FDA and MRL scheduled for February 20, 2002. The draft label is provided in 2 columns with MRL's proposed label on the left and comments on the right. Two versions of the text are provided: a clean-running copy and a mocked-up copy.

A brief rationale is provided in the mocked-up label for most of these changes. MRL will be prepared to discuss all of these changes in greater depth during the upcoming teleconference with the Agency.

All information is in an electronic format as indicated in the Table of Contents for this amendment. Attached on the CD are the following items:

Labeling – Item 2

I. Labeling Text
   a. Proposed labeling text
      1. Package Circular (Clean-running text)
      2. Package Circular (Mocked-up copy)

APPEARS THIS WAY
ON ORIGINAL

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

February 5, 2002

Lee Simon, M.D., Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V

c/o
Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Simon:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
NDA 21-052/S-004: VIOXX™ (Rofecoxib Oral Suspension)

Amendment to Supplemental New Drug Application
(Clarification of VIGOR Data in Proposed Label)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 which provided for changes to the labeling as a result of the VIOXX™ Gastrointestinal Outcomes Research (VIGOR) study. Reference is also made to the Agency's labeling proposals submitted on October 15, 2001, December 21, 2001 and January 29, 2002. Further reference is made to the following submissions from Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.: CSR for protocols 088 and 089 submitted with the original sNDA; a Safety Update Report (SUR) dated October 13, 2000; labeling proposals dated November 6, 2001, December 5, 2001 and January 7, 2002.

MRL has identified what it believes to be errors in the table of VIGOR Study Results contained in the Agency's proposed label submitted to MRL on January 29, 2002. By this letter, MRL is seeking to reach agreement with the Agency on the correct accounting of events for the table.

In VIGOR, 45 patients in the rofecoxib group and 19 in the naproxen group had a confirmed thrombotic cardiovascular event. A counts table and a listing of those events were provided in the October 13, 2000 Safety Update Report (Table 7 and Attachment 3 of the SUR); a table of events similar to the table in the SUR was also included by MRL in draft labeling dated January 7, 2002. The Agency, in its draft label dated January 29, 2002, proposed a slightly different grouping of cardiac events than in the previous MRL tables. However, in creating its table, it appears that the Agency has omitted some events. In order to expedite the current labeling negotiations and ensure that both the Agency and MRL agree on the underlying data, MRL is providing the Agency: 1) a corrected counts table that uses the same grouping of events as proposed by the Agency's in its draft label dated January 29, 2002 and 2) a listing to support MRL's accounting of events (ATTACHMENT I). Note that footnotes in the attached table are intended to help clarify the data. In addition, the number of deaths in VIGOR is incorrect in the Agency's draft label dated January 29, 2001. The correct values should be 22 patients in the rofecoxib group and 15 in the naproxen group (Table 45 of P088/089 [VIGOR] CSR).

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

January 21, 2002

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
NDA 21-052/S-004: VIOXX™ (Rofecoxib Oral Suspension)

General Correspondence
(Rofecoxib and Cardiovascular Events)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 which provided for changes to the labeling as a result of the VIOXX™ Gastrointestinal Outcomes Research (VIGOR) study; and a teleconference between FDA and Merck Research Laboratories (MRL), Merck & Co., Inc., scheduled for January 30, 2002 to discuss labeling.

In anticipation of upcoming discussions between MRL and the Agency on product labeling to be derived from the data provided in the above noted sNDA, MRL has assembled a summary of the available information concerning rofecoxib and cardiovascular effects. The attached report provides a coalescence of relevant pre-clinical, clinical pharmacology, epidemiologic and clinical trial data derived from MRL based research as well as the general scientific literature.

An understanding of the role of eicosanoids in the physiology and pathophysiology of the cardiovascular system and the impact of pharmacologic alteration of those physiologic processes is in a state of significant flux with new information being generated at a rapid rate. Not unexpectedly in a research area of great activity, the available data do not all suggest the same conclusions, and can, in fact, appear to be contradictory in some cases. Therefore, we believe it is particularly valuable to pull together the various data into a single report to facilitate the overall evaluation of the data.

In the attached document, MRL has attempted to bring together the important data that can help us understand the cardiovascular adverse event profile observed in the VIGOR trial. All of this data has been previously provided to the Agency or is in the public domain. In order to help frame the forthcoming product labeling discussions, and in response to the interest of Dr. Robert Temple (FDA) expressed in a prior conversation with Dr. Bonnie Goldmann, MRL has developed the attached summary.

[ ]

All information is in an electronic format as indicated in the Table of Contents for this amendment.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

January 17, 2002

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

NDA 21-052/S-004: VIOXX™ (Rofecoxib Oral Suspension)

Intent to Amend

Reference is made to the above cited supplemental New Drug Applications (sNDAs) submitted as an electronic archive on June 29, 2000 which provided for changes to the labeling as a result of the VIOXX™ Gastrointestinal Outcomes Research (**VIGOR**) study; the Agency's Approvable letter dated January 11, 2002; and ongoing telephone conversations between FDA and Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. during which MRL agreed to submit revised draft labeling.

With this letter and in accordance with 21 CFR 314.110, we are notifying you of our intent to amend this application. As stipulated by the Agency in the Approvable letter, MRL will submit revised draft labeling pending the completion of ongoing labeling negotiations.

All information is in an electronic format.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the content of the CD are free of computer viruses (Norton AntiVirus® 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

A list of Reviewers from the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products who should be provided access to this electronic submission from their desktops may be obtained from Ms. Barbara Gould, Project Manager.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

December 18, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000, a fax containing requests for information concerning the VIGOR database and the Alzheimer's studies dated December 5, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; and a partial response dated November 26, 2001 containing the Alzheimer's data.

By this submission, we are providing the remaining response to the requested information.

FDA Request #1

Please clarify whether the safety monitoring board and the IRB overseeing these studies are aware of the excess in total cause mortality in the Vioxx 25 mg group as compared to placebo (p=0.026) and the trend against Vioxx 25 mg on CV mortality compared to placebo.

MRL Response #1

Mortality in the Alzheimer's disease program was fully discussed in recent responses of October 8, 2001, November 5, 2001, and November 26, 2001 and in the July 12, 2001 Safety Update Report (SUR). In final data from Protocols 091 ——— 18 patients in the rofecoxib group and 11 in the placebo group died; in interim data from Protocol 078, additional 15 patients in the rofecoxib group and 9 in the placebo group died. Although there was a significant difference between rofecoxib and placebo groups in overall mortality based on the total number of deaths in all – protocols combined, there were no notable trends in the data. Examination of the most frequent causes of death reveals that 4 and 7 patients in the rofecoxib and placebo groups, respectively, died due to malignancies; 8 and 5 died from infectious causes (some associated with underlying malignancies); 4 and 1 died due to trauma; and 10 and 6 patients in the rofecoxib and placebo groups, respectively, died from a cardiovascular adverse experience. Based on these data, it was concluded that the difference between rofecoxib and placebo in overall mortality does not reflect any increases in particular types of events to suggest causality. In a similar analysis of mortality in the osteoarthritis program, there was statistically significant decreased mortality with rofecoxib compared to other NSAIDs combined. The small numeric differences between rofecoxib and comparators 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.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

December 5, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000, a fax containing requests for information concerning the VIGOR database and the Alzheimer's studies dated November 14, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; and a partial response dated November 26, 2001 containing the Alzheimer's data.

By this submission, we are providing the remaining response to the requested information.

FDA Request 1

For the Vigor database:

A. Please provide the following analyses by study drug group for all subjects and separately for those without a PUB or complicated PUB:

- Percent of patients with a replicated drop in Hgb (> 2gm/dl) during the study period
- Incidence of transfusion

B. Please provide listings (by patient) of sequential results for all patients with a replicated drop in Hgb of > 2gm/dl

Example of format:
Patient 1001: a. Baseline value b. Visit 1 (week X) c. Visit 2 (week Y) etc (for each result until final visit)

C. Please provide analyses of withdrawals due to adverse events and serious adverse events for subjects with a drop in Hgb (> 2gm/dl) that did not have a PUB or complicated PUB.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

December 5, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic,
and Ophthalmologic Drug Products
Office of Drug Evaluation V

c/o
Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

Amendment to Supplemental New Drug Application

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 which provided for changes to the labeling as a result of the VIOXX™ Gastrointestinal Outcomes Research (**VIGOR**) study. Reference is also made to an October 15, 2001 letter from the Agency to Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. containing the Agency's labeling proposal for the VIGOR sNDA; MRL's response to Agency's labeling proposal submitted on November 6, 2001; and a telephone conversation between Dr. Larry Goldkind (FDA) and Dr. Robert E. Silverman (MRL) on November 21, 2001 during which the VIGOR labeling was discussed.

By this letter, MRL is providing an updated labeling proposal for the VIOXX™ VIGOR sNDA in response to the telephone conversation between Dr. Goldkind and Dr. Silverman. The following sections of the label have been changed since the labeling revision submitted to FDA on November 6, 2001:

- DOSAGE AND ADMINISTRATION, *Management of Acute Pain and Treatment of Primary Dismenorrhea*
- PRECAUTIONS, *Laboratory Tests*
- PRECAUTIONS, *Geriatric Use*

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

November 26, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000, and a fax containing requests for information concerning the VIGOR database and the Alzheimer's studies dated November 14, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.

By this submission, we are providing a partial response to the requested information.

FDA Request 1

For the Vigor database:

A. Please provide the following analyses by study drug group for all subjects and separately for those without a PUB or complicated PUB:

- Percent of patients with a replicated drop in Hgb (> 2gm/dl) during the study period
- Incidence of transfusion

B. Please provide listings (by patient) of sequential results for all patients with a replicated drop in Hgb of > 2gm/dl

Example of format:
Patient 1001: a. Baseline value b. Visit 1 (week X) c. Visit 2 (week Y) etc (for each result until final visit)

C. Please provide analyses of withdrawals due to adverse events and serious adverse events for subjects with a drop in Hgb (> 2gm/dl) that did not have a PUB or complicated PUB.

MRL Response 1

The requested information is currently being assembled and will be sent to the Agency at a later date.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

November 9, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007, S-012: VIOXX™ (Rofecoxib Tablets)

Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Applications (sNDAs) submitted as electronic archives on June 29, 2000 (S-007) and February 28, 2001 (S-012); a fax containing requests for information received on September 7, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; and partial responses to this request dated September 20, 2001 and October 1, 2001. In the September 20, 2001 letter we promised to submit the requested CSR for protocol — by November 9, 2001.

By this letter, MRL is providing the remaining response to the above cited FDA fax request.

FDA Request #2
Please provide the status of study ———————. If study is completed, please submit report to the Agency. If not, provide estimated date of submission.

MRL Response #2
The requested report for Protocol — is attached.

All information is in an electronic format as indicated in the Table of Contents for this submission.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the content of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

November 6, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
NDA 21-052/S-004: VIOXX™ (Rofecoxib Oral Suspension)

Amendment to Supplemental New Drug Application

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 which provided for changes to the labeling as a result of the VIOXX™ Gastrointestinal Outcomes Research (**VIGOR**) study. Reference is also made to an October 15, 2001 letter from the Agency to Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. containing the Agency's labeling proposal for the VIGOR sNDA. Further reference is made to the following: Arthritis Advisory Committee Meeting held on February 8, 2001 and associated correspondence/submissions (i.e., background packages, transcripts, Meta-analyses); the original SUR dated October 13, 2000; three additional SURs in response to Agency requests dated July 12, July 30, and August 3, 2001; amendments to the label dated October 13, 2000, March 2, 2001, and May 21, 2001; submission of the ADVANTAGE CSR on March 30, 2001, followed by Items 11 and 12 on April 16, and April 30, 2001; the FDA Approvable letter dated April 6, 2001; and several responses to FDA requests for information.

By this letter, MRL is responding to the draft labeling for the VIOXX™ VIGOR sNDA proposed by the Agency on October 15, 2001.

MRL appreciates the efforts made by the Agency to digest the wealth of safety data provided in this supplement. However, MRL is disappointed both by the content and overall tone of the labeling proposal submitted by FDA to MRL on October 15, 2001. MRL strongly disagrees with FDA with respect to many of the labeling recommendations that seem inconsistent with previous conversations and understandings, inconsistent with the Advisory Committee Meeting, and, to our knowledge, unprecedented from a labeling and regulatory perspective. With this letter, MRL is providing new draft labeling in response to the Agency's proposal. The draft label is provided in 2 columns with MRL's proposed label on the left and comments on the right. Two versions of the text are provided: a clean-running copy and a marked-up copy.

In addition to the above general comments, MRL is providing more details on several issues pertinent to these labeling discussions.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

November 5, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000, and a fax containing a request for information dated October 19, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.

By this letter, MRL is responding to the Agency request.

FDA Request #1
Please provide the Kaplan Meier estimates for all cause mortality and cardiovascular mortality for the — Alzheimer's studies combined.

MRL Response #1
MRL is providing Kaplan-Meier survival curves for the Alzheimer's studies and also for the osteoarthritis Phase IIb/III studies.

Alzheimer's Studies

At the time of data cutoff for the recent SUR sent to the Agency on July 12, 2001, the overall exposure to rofecoxib 25 mg or placebo in – Alzheimer's studies (Protocols 078, 091, —— was 1461 patient-years in the rofecoxib group (N=1448) and 1634 patient-years in the placebo group (N=1451). There have been a total of 53 deaths in these – studies (24 from Protocol 078, 22 from Protocol 091, and 7 from Protocol — A listing of these deaths was provided in the SUR and is included with this response as Attachment 1. Kaplan-Meier survival curves of all-cause mortality in the Alzheimer's studies are provided as Attachment 2. The p-value for the logrank comparison between MK-0966 and placebo was 0.026.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

October 8, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 and a fax containing requests for information concerning the Alzheimer's studies dated September 26, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.

By this submission, we are providing the requested information concerning the Alzheimer's studies.

FDA Request 1
Please provide time to event plots for all deaths and for cardiovascular deaths in the Alzheimer's studies.

MRL Response 1
1. All-Cause Mortality

Kaplan-Meier survival curves for all-cause mortality by treatment groups (MK-0966 or Placebo) for each of the — protocols are provided as Attachment I. There were a total of 53 deaths from the — protocols (24 from Protocol 078, 22 from Protocol 091 and 7 from Protocol —. The list of all-cause deaths was provided in the July 2001 VIOXX™ VIGOR SUR. Data from Protocol 091 are complete. The cut-off date for data from protocols 078 —— was 03/16/2001.

2. Cardiovascular Mortality

Kaplan-Meier survival curves for cardiovascular mortality by treatment groups (MK-0966 or Placebo) for each of the —— protocols are provided as Attachment II. There were a total of 15 cardiovascular deaths from the ——protocols (7 from Protocol 078, 5 from Protocol 091 and 3 from Protocol —.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

October 5, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products.

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

Response to FDA Request For Information

Reference is made to the above-cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000. Reference is also made to two faxes from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc dated September 26, 2001 and October 1, 2001 and containing requests for information and to a telephone conversation held on October 1, 2001 to clarify the Agency's requests.

During the teleconference on October 1, 20001, it was clarified that the requests for tables of rates, relative risk and p-values for various endpoints in VIGOR were to use results already submitted to the Agency with the exception that MRL newly calculate and provide p-values for those estimates of relative risk where only 95% confidence intervals (CIs) had been previously supplied. For each set of endpoints, MRL is now providing 2 tables, one which presents rates, relative risk, and p-values for the estimates of relative risk and a second which provides rates, relative risk, and the 95% CIs for the estimates of relative risk.

By this submission, MRL is responding to the Agency requests.

SEPTEMBER 26, 2001 FAX REQUESTS

FDA Request 1
Summary table of GI safety events (table – of sponsor's proposed label) expressed in cumulative rates for PUBs and Complicated PUBs.

MRL Response 1
Please refer to Attachment 1.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

October 3, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

MERCK

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000. Reference is also made to a fax containing a request for information received on September 13, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.

By this letter, MRL is responding to the Agency request.

FDA Request #1
Please provide analysis of fractures presented by patients in the Alzheimer's studies for review for NDA 21-042/S-007.

MRL Response #1
"The Safety and Efficacy of MK-0966 in Slowing the Progression of the Symptoms of Alzheimer's Disease" - Protocol 091

VIOXX™ Protocol 091 0-12 Months On Drug Verbatim fracture terms	MK-0966 (n=346) number of fractures [number reported as serious]	Placebo (n=346) number of fractures [number reported as serious]
Arm fracture	0	1 [1]
Clavicular fracture	0	1
Femoral fracture	0	1 [1]
Forearm fracture	0	2
Hip fracture	1 [1]	2 [2]
Intertrochanteric fracture	0	1 [1]
Lumbar vertebral fracture L5	0	1
Patellar fracture	0	1
Pelvic fracture	3	0
Radial fracture	0	1

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

October 1, 2001

MERCK

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Applications (sNDA) submitted as electronic archives on June 29, 2000. Reference is also made to a fax containing requests for information received on September 7, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. and a partial response to that request submitted on September 20, 2001.

By this submission, we are providing the remaining response to the information requested on September 7, 2001.

FDA Request 3
Please provide analyses of HTN-related, edema related and CHF related events in the Alzheimer's studies.

MRL Response 3
The requested information is provided as follows:

- Attachment 1: HTN-Related Events – Protocol 091
- Attachment 2: HTN-Related Events – Protocol —
- Attachment 3: Edema-Related Events – Protocol 091
- Attachment 4: Edema-Related Events – Protocol —
- Attachment 5: CHF-Related Events – Protocol 091
- Attachment 6: CHF-Related Events – Protocol —

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

September 20, 2001

MERCK

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007, S-012: VIOXX™ (Rofecoxib Tablets)

Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Applications (sNDA) submitted as electronic archives on June 29, 2000 (S-007) and February 28, 2001 (S-012). Reference is also made to a fax containing requests for information received on September 7, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.

By way of this letter, a partial response to the above cited FDA fax is provided. A response to Request #3 will be sent to the Agency on or before September 28, 2001.

FDA Request #1
Please provide the location of the analyses of vital signs and ECG in the RA database.

MRL Response #1
Plots of means and mean changes from baseline in body weight, systolic and diastolic blood pressure, and pulse rate are found in appendices of the respective clinical study reports as follows:

- Protocol 068, Part I – Appendices 4.28 and 4.30
- Protocol 068, Part II – Appendices 4.18 and 4.28
- Protocol 068, Extension – No analyses of vital signs were done because the study was not completed at the time of reporting. These analyses are planned as part of the complete clinical study report (CSR) for Protocol 068 extensions after the entire set of extensions is completed.
- Protocol 096 – Appendix 4.27
- Protocol 097 – Appendix 4.28
- Protocols 098 and 103 – Appendix 4.12

Formal analyses of ECG data were not conducted within the scope of the RA supplemental application. Adverse experiences, based on abnormal ECG findings, were captured in the database and register on clinical adverse experience-counts tables (in individual study reports and in the integrated summary of safety). Of note, a proxy yes/no question on the ECG case report form asked whether or not findings from the ECG represented an adverse experience. If yes, investigators were to capture the finding in the adverse experience worksheet.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

September 7, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

MERCK

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)
Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a Safety Update Report submitted on July 12, 2001; and a fax containing requests for information concerning the Alzheimer's studies received on August 31, 2001 from Ms. Mary Jane Walling (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.

By this submission, we are providing the requested information concerning the Alzheimer's studies.

FDA Request 1
Clarify what was the cut off date for the reports.

MRL Response 1
The cutoff date for onset of serious adverse experiences was on March 16, 2001. The cutoff date for including a verdict from the Adjudication Committee was on May 15, 2001.

FDA Request 2
Provide exposure data to rofecoxib and placebo in patient years.

MRL Response 2
The requested data can be found in Table 37, page 79, of the Safety Update Report submitted on July 12, 2001. A copy of Table 37 is provided with this submission as Attachment I.

FDA Request 3
Provide a list with the allocation of patients referred for adjudication to the CV adjudication committee.

MRL Response 3
The requested list is provided as Attachment II.

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19486-0004
Tel 484 344 2944
Fax 484 344 2516

August 17, 2001

Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib)

Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a Safety Update Report submitted as an electronic archive on July 12, 2001, and a fax dated August 8, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting information regarding patient AN 915 in protocol 091.

FDA Request
Please provide the autopsy result of AN 915 in protocol 091 submitted 07-Jul-01 for NDA 21-042 S-007.

MRL Response
MRL has specifically queried the investigator with regard to the Agency request. Patient AN 915 did not undergo a post-mortem examination.

All information is in an electronic format as indicated in the Table of Contents for this submission.

We hope that responses provided in this submission have adequately addressed the Agency's comments and requests.

This response is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the response. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 4.0, Symantec Corp., 1991-1997) and we authorized the use of anti-virus software, as appropriate.