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February 6, 2001

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

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a fax received on November 27, 2000 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information; a submission dated January 19, 2001 responding to request number 4; and a fax from the Agency dated January 31, 2001 requesting clarification on the Table of Hospitalizations submitted in our response dated January 19, 2001.

By this submission, we are providing the requested information.

FDA Request 1:
Clarify how many of the patients with congestive heart failure, cardiogenic shock, presyncope and dissecting aortic aneurysm (included under the category "other") are also included under the "cardiovascular" category. Please provide the total number of patients hospitalized with events related to the cardiovascular system (including cerebrovascular events, congestive heart failure, cardiogenic shock presyncope and dissecting aortic aneurysm) in the VIGOR study.

MRL Response 1:
The total numbers of patients hospitalized with "cardiovascular-related" events per the Agency's definition (above) are 65 (1.6%) for Rofecoxib and 24 (0.6%) for Naproxen. A tabular breakdown by each diagnosis will be provided subsequently.

FDA Request 2:
Your category "other" includes several events already included under the GI category. It also includes events such as esophageal ulcer and gastritis that should probably have been included under the GI category. Please provide the total number of patients with hospitalizations related to the digestive system in the VIGOR study.

MRL Response 2:
The total numbers of patients hospitalized for "digestive system" events, per the Agency's request, are 29 (0.7%) for Rofecoxib and 49 (1.2%) for Naproxen. A tabular breakdown by each diagnosis will be provided subsequently.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

VIOXX™ Gastrointestinal Outcomes Research Study (VIGOR)

Response to FDA Request for Information

Reference is made to the supplemental New Drug Application (sNDA) cited above submitted on June 29, 2000 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; an Arthritis Advisory Committee meeting scheduled for February 8, 2001; the FDA Medical Reviewer's briefing document; and a Pre-Advisory Committee meeting on January 31, 2001.

During the meeting on January 31, 2001, the Agency requested copies of the protocols and amendments for MRL's Alzheimer's studies (Protocols 078 and 091).

By this letter, we are providing copies of the requested information.

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. This response application 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 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.

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. Sandra Folkendt, Project Manager.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

Response to FDA Request for Information

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It was noted in our response dated January 19, 2001 that it is not possible to provide the information on aspirin use in the meta-analysis requested by the Agency. However, we noted that this issue could be addressed by using information from the Alzheimer's Disease studies (Protocols 078 and 091), which we would provide at a later date. By copy of this letter, we are providing this analysis.

For this analysis of APTC endpoints in the Alzheimer's Disease studies, MRL defined aspirin users as those patients who took aspirin atleast 33% of the time. In light of aspirin's prolonged inhibition of platelet action, this definition was felt to be more conservative than requiring aspirin use for a greater percentage of the time. Attachment 1 contains a tabular presentation of the results. Due to the small number of events in the aspirin user group, this stratification does not disclose any significant changes from the unstratified analysis.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

VIOXX™ Gastrointestinal Outcomes Research Study (VIGOR)

Response to FDA Request for Information

Reference is made to the supplemental New Drug Application (sNDA) cited above submitted on June 29, 2000 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; an Arthritis Advisory Committee meeting scheduled for February 8, 2001; the FDA Medical Reviewer's briefing document; and a Pre-Advisory Committee meeting on January 31, 2001.

During the meeting on January 31, 2001, the Agency requested that MRL identify any additional mistakes in the medical reviewer's document concerning the description of Clinical GI event data.

By this letter, we are providing the following requested correction:

- On pages 8 and 21, the reviewer presents cumulative incidence data for PUBs and complicated PUBs that are, in fact, rates per 100 patient years. Table 5 (page 8) documents this.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

VIOXX™ Gastrointestinal Outcomes Research Study (VIGOR)

Response to FDA Request for Information

Reference is made to the supplemental New Drug Application (sNDA) cited above submitted on June 29, 2000 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; an Arthritis Advisory Committee meeting scheduled for February 8, 2001; and a Pre-Advisory Committee meeting on January 31, 2001, whereby Dr. Qain H. Li requested additional statistical information on CSR 069.

By copy of this letter, we are providing Dr. Li with the requested information.

FDA Request 1: Provide a copy of CSR 069.

MRL Response 1: A copy of CSR 069 is contained in Attachment I.

FDA Request 2: Provide the method used to calculate the cumulative incidence.

MRL Response 2: The method used to calculate the cumulative incidence is provided on page 26, Section 7.2.a of the attached CSR (Attachment I).

FDA Request 3: Provide the rates per 100 person years for the primary endpoint, confirmed Upper-GI PUBs.

MRL Response 3: The rates per 100 person years for the primary endpoint, confirmed Upper-GI PUBs, are provided in Table 12, page 46, of the attached CSR (Attachment I).

Also provided for your reference are the statistical appendices for CSR 069 (Attachment II).

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

VIOXX™ Gastrointestinal Outcomes Research Study (VIGOR)

ARTHRITIS ADVISORY COMMITTEE

MRL's Main Presentation Slides

Reference is made to the supplemental New Drug Application (sNDA) cited above submitted on June 29, 2000 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; an upcoming Arthritis Advisory Committee scheduled for February 8, 2001, during which this sNDA will be discussed; a letter to the Agency, dated January 17, 2001 requesting a Pre-Advisory Committee meeting; and telephone conversations between Ms. Sandra Folkendt (FDA) and Drs. Bonnie J. Goldmann and Robert E. Silverman (MRL), whereby Ms. Folkendt requested a copy of the slides we plan to use for the upcoming Arthritis Advisory Committee meeting.

By copy of this letter, we are providing *DRAFT* slides which will be presented by MRL at the upcoming Arthritis Advisory Committee meeting. These slides may be revised before the meeting on February 8, 2001, therefore, are not available for public dissemination by the Agency.

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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. Sandra Folkendt, Project Manager.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

Response to FDA Request for Information

Reference is made to the above supplemental New Drug Application (sNDA), and a teleconference between representatives of the Agency and Merck Research Laboratories (MRL), a Division of Merck & Co., on January 24, 2001, whereby the Agency and MRL revisited the issue of combining dose specific data across all trials.

By this letter and attachments, MRL is providing a response to the Agency's request for information.

Please note, a submission was emailed to Ms. Sandra Folkendt (FDA) on January 29, 2001, which contained tables with incorrect 95% confidence intervals. The enclosed submission supersedes the one sent today via email to Ms. Folkendt.

Although MRL continues to believe such combinations are inappropriate, we have performed the analysis as requested by the Agency. The attached table contains the individual study data, as will be evident upon review.

In the most inclusive of the combinations, rofecoxib versus any nonselective NSAID or placebo (Table 7), there are 60 APTC endpoints in the comparator group, representing an absolute risk of 1.18 events per 100 patient years. The rates for rofecoxib are 1.19, 0.97, and 1.30 for the 12.5, 25, and 50 mg doses, respectively. The risk of an event in each rofecoxib group relative to any nonselective NSAID or placebo is 0.99, 0.79, and 1.17 for 12.5, 25, and 50mg rofecoxib, respectively. These data do not suggest a dose-related effect of rofecoxib on the risk of an APTC event and, across all doses, the relative risk approximates 1.

The second most inclusive combination, rofecoxib versus ibuprofen, diclofenac, or placebo (Table 6), excludes naproxen data. For all three rofecoxib doses, the risk of an APTC endpoint was consistently less than for the comparator group (relative risks 0.58, 0.50 and 0.90, for 12.5, 25, and 50 mg rofecoxib, respectively).

Combining all studies for each dose and comparing this to individual comparators and combined comparators, as the FDA has requested, does not demonstrate a dose related effect of rofecoxib on the APTC combined endpoints.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

Response to FDA Request for Information

Reference is made to the above supplemental New Drug Application (sNDA); a fax received on January 22, 2001; and a teleconference between representatives of the Agency and Merck Research Laboratories (MRL), a Division of Merck & Co., on January 24, 2001. During the teleconference the Agency made several requests for additional information. By this letter and attachments MRL is providing responses to the Agency requests.

Attachment 1 contains an examination of heterogeneity among individual studies included in the cardiovascular meta-analysis.

Attachment 2 contains a series of APTC endpoint counts tables by protocol. The Agency requested tabulation of peripheral vascular events, as well. MRL is still in the process of extracting that data and will submit it subsequently.

Attachment 3 contains the overall dose by exposure tables requested by the Agency in a fax received on January 22, 2001, and discussed at the teleconference. These tables do not include columns for exposure $\geq$6 weeks as requested by the Agency. Extracting this data requires substantial additional programming and will be provided subsequently.

During the teleconference, the Agency also requested a listing table by individual studies of patient numbers per dose of rofecoxib or comparator with duration of exposure. MRL is still actively developing the requested data and a response will be forthcoming.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

VIOXX™ Gastrointestinal Outcomes Research Study (**VIGOR**)

ADVISORY COMMITTEE BACKGROUND PACKAGE

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Reference is made to the supplemental New Drug Application (sNDA) cited above submitted on June 29, 2000 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; a Background Package submitted on January 4, 2001 for the upcoming Arthritis Advisory Committee scheduled for February 8, 2001, during which this sNDA will be discussed; and a telephone conversation between Ms. Kathleen Reedy (FDA) and Dr. Robert Silverman (MRL) on January 24, 2001 whereby Ms. Reedy requested a copy of the Background Package be provided on compact disk (CD).

By copy of this letter, we are also providing the Division with MRL's Advisory Committee Background Package on compact disk (CD).

In accordance with the Federal Advisory Committee Act (FACA) and FDA's regulations governing disclosure of information concerning New Drug Applications in 21 CFR 314.430, MRL is submitting a copy of the Advisory Background Package **available for public disclosure without redaction** for distribution to the Advisory Committee and FDA staff members in preparation for the Arthritis Advisory Committee Meeting scheduled for February 8, 2001.

This Advisory Committee Background Package consists of materials **available for public disclosure without redaction.**

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

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 and to a fax received on January 11, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information.

By this submission, we are providing the following response to the Agency's request for information.

FDA Comment 1: Mean dose of MTX in each treatment group.

MRL Response 1: The mean dose of MTX at baseline in the VIGOR study was 13.3 mg per week in rofecoxib and 13.3 mg per week in naproxen. The median dose in both these treatment groups was 10 mg per week.

FDA Comment 2: Analysis of serious adverse experiences by body system in MTX users and non-MTX users in the VIGOR Study

MRL Response 2: An analysis of serious adverse experiences by body system in MTX and non-MTX users is provided in Attachment I of this submission.

There were two patients (AN 7058 and 7575) in the rofecoxib treatment group that had serious laboratory adverse experiences that appeared to be related to methotrexate. Narratives on these patients can be found in Section 9.6.4 of the 088C CSR.

FDA Comment 3: Table of laboratory AE's (similar to Table 62) in MTX and in non-MTX users in the VIGOR Study.

MRL Response 3: The table of laboratory adverse experiences in MTX users and non-MTX users can be found in Appendices 4.22.5 and 4.22.6 of the 088C CSR.

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

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a fax received on January 2, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information; and to a submission dated January 15, 2001 responding to request numbers 1 to 3.

By this submission, we are providing the final response to the Agency's request for information from January 2, 2001.

FDA Comment 4: Please submit the mean and median doses of prednisone for each treatment arm in VIGOR.

MRL Response 4: As noted in the preliminary report on the VIGOR trial, 56% of the patients were taking concomitant oral corticosteroids. Table 1 displays the mean mg dose for both prednisolone and prednisone used by patients prior to randomization into VIGOR. A total of 45.3% of patients used prednisone prior to randomization at a mean dose of 6.61 mg. A total of 4.8% of patients used prednisolone prior to randomization at a mean dose of 6.15 mg. These two medications are reported as they represent the vast majority (~90%) of pre-randomization glucocorticoid use in VIGOR. In addition, they are the typical forms used in the treatment of rheumatoid arthritis. Dosage forms that represent intraarticular and topical glucocorticoids (such as cm^3, ml and topical) are not included as these are unlikely to represent systemic treatment for rheumatoid arthritis.

Table 1. Summary of Pre-Study Glucocorticoid Use in VIGOR

Type of Steroids	Treatment Group	N	Pre-Study Use		Pre-Study Average Daily Dose (mg)			
			n	%	Mean	SD	Median	Range
Prednisolone	Rofecoxib	4047	195	4.8	6.34	3.00	5.00	
	Naproxen	4029	192	4.8	5.96	2.72	5.00	
	Total	8076	387	4.8	6.15	2.87	5.00	
Prednisone	Rofecoxib	4047	1831	45.2	6.46	3.58	5.00	
	Naproxen	4029	1830	45.4	6.76	12.31	5.00	
	Total	8076	3661	45.3	6.61	9.07	5.00	

[1]Following are not included in this summary

(1) dose frequencies = as needed are not included since daily dose cannot be ascertained

(2) dose units other than mg are not included due to conversion difficulties. Excluded units are [unit], cm^3, count, gm, gr, mL, tablet, topical form, topical lotion, etc.

(3) AN 908 prednisone use is not included due to missing start date on the medication

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January 19, 2001

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

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a FDA fax received on November 27, 2000; a partial response to this request submitted on December 21, 2000 containing information on our ADVANTAGE study; and a telephone conversation on December 29, 2000 between Ms. Sandra Folkendt (FDA) and Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., during which the Agency requested clinical narratives for patients in the ADVANTAGE study who had APTC events that were tabulated in the MRL response on December 21, 2000.

By this submission, we are providing the requested Clinical Narratives. Also provided are data packages used by the Adjudication Committee to evaluate investigator-reported cardiovascular serious adverse experiences in the ADVANTAGE study. The adjudication committee used these data, along with their expert clinical judgment, to determine whether these events met the categories pre-specified in the Adjudication SOP for confirmed thrombotic cardiovascular serious adverse experiences. The outcomes described in Table 1 represent the consensus opinion of this committee with regards to APTC endpoints.

Two additional events that were not adjudicated were also included in the analysis of events that met the Anti-platelet Trialist Collaboration definitions. These events were not adjudicated because the primary serious adverse experience terms were not part of the terms used to identify events that require adjudication. Narratives for these two patients are provided in Appendix 1. Both of these events were deaths. The first case was a death judged by the investigator to be "hypertensive heart disease"; however, the exact cause of death was not clear, as the patient had an unwitnessed death. Because a component of the APTC endpoint included "deaths due to unknown causes", this event was included in the APTC analysis for ADVANTAGE. The second case was a death that resulted from a ruptured abdominal aortic aneurysm. Because a component of the APTC endpoint is "death due to hemorrhagic causes", this event was also included in the APTC analysis for ADVANTAGE.

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

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By this submission, we are providing the following response to the Agency's request for information.

FDA Comment 1: Please provide the cause of protocol deviation for each patient and if the information is in the submission, to direct us to the appropriate section.

MRL Response 1: This information can be found in Reference P088C, Appendix 4.1, pgs 3146 to 3149. A copy is included as Attachment I of this response.

FDA Comment 2: Please submit the CRFs of all patients who withdrew consent.

MRL Response 2: Attached are 268 CRFs of patients who withdrew consent. These CRFs are provided in Item 12 of this submission.

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

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By this submission, we are providing the final response to the Agency's request for information from November 27, 2000.

FDA Comment 4: Similarly to the analysis submitted for serious gastrointestinal adverse events, provide an analysis of total number of hospitalizations and total days of hospitalization in study 088c for all causes and by body system, as follow:

*Renal
- Edema
- Hyperkalemia
- Hypokalemia
- Nephrotic syndrome
- Nephritis
- Renal calculus
- Renal insufficiency/failure (includes new onset or worsening of prior condition)

*Cardiovascular
- Cardiac
  - Arrhythmia
  - Angina (includes unstable angina, angina pectoris, coronary artery disease)
  - Myocardial infarction (includes myocardial infarction and acute myocardial infarction)
  - Hypertension (includes related terms: increase blood pressure, worsening hypertension, hypertension aggravated, malignant hypertension)
  - Peripheral vascular thrombosis, ischemia, vasculitis
  - Thrombophlebitis (includes phlebitis and thrombophlebitis related terms) and pulmonary embolism

*Biliary and pancreatic
*CNS
*Allergic
*Hematologic
*Others

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January 19, 2001

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)
Response to FDA Request for Information
Request for Teleconference

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 and to a fax received on December 29, 2000 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information.

By copy of this letter, we are providing the response. This request focuses on an additional analysis of cardiovascular events stratifying by dose of rofecoxib in studies of 6-months or longer duration. In order to do this, studies can be combined only if each study contains the two treatments that are being compared and/or if they have identical study designs and patients populations. Because the study designs and patients populations are different, to control for the differences between trials, this analysis was done combining only studies in which all doses to be compared are present. Thus, as will be apparent upon review, with the small number of events and the limited exposure per dose, the individual point estimates of risk associated with each of the doses vary widely among the comparisons in the new meta-analysis and do so in an inconsistent way.

It should be noted that it is not possible to provide the information on aspirin use in this meta-analysis as requested. However, we believe that this issue can be addressed by using information from the Alzheimer's Disease studies (Protocols 078 and 091). This analysis will be submitted shortly. Further, the request concerning cumulative incidence tables needs clarification so that we can provide the necessary response.

MRL would like the opportunity to discuss this meta-analysis and is requesting a teleconference which would include the FDA statistical reviewer.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)
Request for Agency Meeting

Reference is made to the supplemental New Drug Application (sNDA) cited above, submitted as an electronic archive on June 29, 2000 by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; a teleconference between the FDA and MRL on January 17, 2001; and a meeting of the Arthritis Advisory Committee scheduled for February 8, 2001, during which this sNDA will be discussed.

In response to the discussion with the Agency today, MRL requests a face-to-face Pre-Advisory Committee meeting with the Agency to be held, if possible, at least one week prior to the Febuary 8, 2001 meeting.

Attached is a proposed list of MRL participants and an agenda (Attachment I).

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. This supplemental application 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 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.

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. Sandra Folkendt, Project Manager. MRL will follow-up with Ms. Folkendt to ensure that the appropriate Reviewers have been given access to the electronic dossier.

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

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 and to a fax received on January 2, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information.

By this submission, we are providing a partial response to the Agency's request for information (Numbers 1 through 3). A response to the remaining request (Number 4) will be forthcoming under separate cover.

FDA Comment 1: Clarify if Table 62 of study 088c (abnormal laboratory values) refers to the acceptable range described in Table 1 and Table 2 of Appendix 3.4.3 of the study (eg. upper limit for creatinine of —and potassium of —

MRL Response 1: Table 62 of Study 088c is a summary table of laboratory adverse experiences reported at the discretion of the Investigator. Although each Investigator was provided with normal values from the laboratory performing the tests, we did not provide the Investigator with specific guidelines or laboratory parameters to determine whether a lab value should or should not be considered an adverse experience.

Table 1 and Table 2 of Appendix 3.8.3 are part of an internal Laboratory Standard Operating Procedure used by Merck in-house data reviewers as a general guide to ensure the consistent monitoring of lab value abnormalities. During the study, laboratory values were reviewed daily in conjunction with the Laboratory Standard Operating Procedure. Values outside the "acceptable" range were questioned further for additional information or, in many cases, a repeat test was requested and performed.

The Laboratory Standard Operating Procedure was never sent to the Investigator's for their use in reviewing the laboratory data. All laboratory adverse experiences reported in the study were done so at the discretion of the Investigator.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

Response to FDA Request for Information

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 and to a fax received on December 13, 2000 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting information.

By this submission, we are providing the following response to the Agency's request for information.

FDA Comment: Please provide an analysis of patients who had a change in creatinine of 25% above baseline in the VIGOR study.

MRL Response: A summary table is provided. This table includes an analysis of single "hits" on the requested parameter and an analysis of at least 2 consecutive "hits" or one "hit" plus associated discontinuation.

Number (%) of Patients With Serum Creatinine Increase $\geq$ 25% Above Baseline

	Rofecoxib (N=4047)		Naproxen (N=4029)	
Laboratory Test	n/m	(%)	n/m	(%)
Serum Creatinine				
In patients with increase of >= 25%	1082/3970	(27.3)	856/3979	(21.5)
In patients with consecutive values with Increase of >= 25% or one or more values with increase >= 25% associated with study drug discontinuation	294/3970	(7.4)	208/3979	(5.2)

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

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a fax received on November 27, 2000 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information/analyses; a submission dated December 20, 2000 responding to request numbers 1 to 3; and a submission dated December 21, 2000 responding to request number 6.

By this submission, we are providing an additional response to the Agency's request for information (Number 5). A response to the remaining request (Number 4) will be forthcoming under separate cover.

FDA Comment 5: Provide analyses of LFT's values exceeding the following limits of change from baseline:
AST: increase of 100% and ULN
ALT: increase of 100% and ULN

MRL Response 5: A summary table is provided. This table includes analyses of single "hits" on the requested parameters and analyses of at least 2 consecutive "hits" or one "hit" plus associated discontinuation.

Analysis of LFT Values Exceeding the Limits of Change

Laboratory Test	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n/N	(%)	n/N	(%)
ALT (U/L)				
In patients with one or more values >2 times baseline and >ULN	150/3971	(3.8)	101/3979	(2.5)
In patients with consecutive values >2 times baseline and >ULN or one or more values >2 times baseline and > ULN associated with study drug discontinuation	20/3971	(0.5)	10/3979	(0.25)
AST (U/L)				
In patients with one or more values >2 times baseline and >ULN	114/3972	(2.9)	87/3980	(2.2)
In patients with consecutive values >2 times baseline and >ULN or one or more values >2 times baseline and > ULN associated with study drug discontinuation	11/3972	(0.3)	8/3980	(0.2)

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

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; and a telephone conversation on January 9, 2001 between Ms. Sandra Folkendt (FDA) and Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., during which the Agency requested a copy of the Interim Cardiovascular Meta-Analysis that was submitted ——— —— on January 8, 2001, Serial No. 847.

By this submission, we are providing the requested documentation to NDA 21-042/S-007. Information from this report will be presented at the Arthritis Advisory Committee meeting on February 8, 2001.

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. This supplemental application 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 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.

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. Sandra Folkendt, Project Manager. MRL will follow-up with Ms. Folkendt to ensure that the appropriate Reviewers have been given access to the electronic dossier.

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

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 and to a fax received on November 27, 2000 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information.

By this submission, we are providing the following response to the Agency's request for information.

FDA Comment 1: In the patient Accounting table you provided, discontinuations due to death and GI events were counted as discontinuation due to clinical AEs or laboratory AEs.

Please provide the two sets of raw data, added in the patient accounting table under the discontinued category; one raw for death and one for GI confirmed and un-confirmed event. The new table shell is below.

Patient Accounting	Vioxx 50 mg N (%)	Naproxen 1000 mg N (%)	Total N (%)
Total	4047	4029	8076
Male	824 (20.4)	814 (20.2)	1638 (20.3)
Female	3223 (79.6)	3215 (79.8)	6438 (79.7)
Completed	2862 (70.7)	2880 (71.5)	5742 (71.1)
Discontinued	1185 (29.3)	1149 (28.5)	2334 (28.9)
Death	22 (0.5)	15 (0.3)	37 (0.5)
GI (confirmed & unconfirmed)			
Clinical AEs			
Laboratory AEs			
Lack of Efficacy			
Lost to follow-up			
Other reasons			
Patients moved			
Patient withdrew consent			
Protocol deviations			

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

Response to FDA Request for Information

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a fax received on November 27, 2000 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information/analyses; and a submission dated December 20, 2000 responding to request numbers 1 to 3.

By this submission, we are providing an additional response to the Agency's request for information (Number 6). A response to the remaining requests (Numbers 4 and 5) will be forthcoming under separate cover.

FDA Comment 6: Provide the final report for study 102 – Assessment of Differences between VIOXX and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness (ADVANTAGE). If the final report is not available, provide a preliminary report. In addition to your planned analyses, please provide analyses of serious gastrointestinal and cardiovascular thrombotic events similar to the ones performed in the VIGOR study. Please provide separate analyses by aspirin use.

MRL Response: A full report of Protocol 102 is still in preparation. In conformance with telephone conversations between myself and Dr. Goldkind, we have prepared a preliminary report of the serious upper gastrointestinal and cardiovascular events in this study that is provided in Attachment 1. As noted in the report, the number of events is quite small and, therefore, do not support meaningful analyses.

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. This supplemental application 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 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.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

Response to FDA Request for Information

Reference is made to the above supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000 and to a fax received on December 5, 2000 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information.

By this submission, we are providing a response to the Agency's request for information.

FDA Comment: Please provide the updated cardiovascular data sets (the whole CVD folder) to reflect the safety update information submitted on 10/13/00, which has 11 additional cardiovascular events adjudicated.

MRL Response: The requested data sets are provided in this submission.

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. This supplemental application 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.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

Amendment to Supplemental New Drug Application

VIOXX™ **G**astrointestinal **O**utcomes **R**esearch Study (**VIGOR**)

Reference is made to the supplemental New Drug Application (sNDA) cited above for VIOXX™ submitted as an electronic archive on June 29, 2000. Reference is also made to your letter of acknowledgment dated August 3, 2000.

The original sNDA for VIGOR included data from four new clinical studies, Protocols 085, 088, 089, and 090. Financial disclosure certification and disclosure information were presented for Protocols 088 and 089 only. MRL promised to submit financial information for Protocols 085 and 090 within 4 months of that submission. By this amendment, we are providing that data. Also included in this submission are additional financial information for Protocols 088 and 089 which was not included in the original submission because it was received from clinical investigators after the original cut-off date.

As indicated on the attached Form FDA 356h, this amendment provides for changes in Item 19, Financial Information, of the approved New Drug Application for VIOXX™. All information is in an electronic format as indicated in the Table of Contents for this amendment.

This amendment is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations. This supplemental application 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 amendment. All documents requiring signatures for certification are included as paper for archival purposes.

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)

SAFETY UPDATE REPORT

VIOXX™ Gastrointestinal Outcomes Research Study (**VIGOR**)

Reference is made to the supplemental New Drug Application (sNDA) cited above for VIOXX™ submitted as an electronic archive on June 29, 2000. Reference is also made to your letter of acknowledgment dated August 3, 2000.

With this submission, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing a Safety Update Report (SUR) for VIOXX™/S-007. This report provides updated cardiovascular safety information from the VIGOR study. The original report which was part of the VIGOR sNDA, included analyses of all adjudicated serious cardiovascular thrombotic events which were reported prior to February 10, 2000, the study cut-off date. This update to the original report includes data on 11 additional patients who experienced cardiovascular serious adverse experiences eligible for adjudication. These additional events were reported after the prespecified cut-off date, however, in an effort to ensure completeness in reporting and analyzing safety data, these events were referred for adjudication.

Five of the 11 patients experienced events that were confirmed by the cardiovascular endpoint adjudication committees to be thrombotic cardiovascular serious adverse experiences (3 confirmed myocardial infarctions on rofecoxib, 1 confirmed peripheral venous thrombosis on rofecoxib, and 1 confirmed ischemic cerebrovascular accident on naproxen). The data on cardiovascular events included in the proposed product circular submitted with the sNDA have been updated to reflect this additional information. Inclusion of these patients in the analysis did not meaningfully alter the findings or conclusions of the study.

As indicated on the attached Form FDA 356h, this submission provides for changes in the Labeling, Summary and Safety Update Report sections of the sNDA for VIGOR. All information is in an electronic format as indicated in the Table of Contents for this submission.