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August 3, 2001

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Dear Dr. Bull:

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

Response to FDA Request for Information
(SAFETY UPDATE REPORT No. 3)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a FDA Approvable letter dated April 6, 2001, requesting an additional safety update report (SUR); a submission dated July, 12, 2001, from Merck Research Laboratories (MRL), a Division of Merck and Co., Inc., containing the first SUR; a fax dated July 5, 2001 and telephone conversations between the FDA and MRL on July 6, 2001 and July 12, 2001 requesting a second SUR related to several short-term clinical studies not included in the first SUR; and submission of the second SUR dated July 30, 2001. Further reference is made to a telephone conversation between FDA and MRL on July 12, 2001 during which the Agency requested a third safety update.

By this letter we are submitting the third Safety Update Report in response to the FDA request dated July 12, 2001. This report contains counts tables for discontinuations due to non-serious adverse experiences for all studies included in the first SUR

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

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 amendment. All documents requiring signatures for certification are included as paper for archival purposes.

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July 30, 2001

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Dear Dr. Bull:

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

Response to FDA Request for Information
(SAFETY UPDATE REPORT No. 2)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a FDA Approvable letter dated April 6, 2001, requesting an additional safety update report (SUR); a submission dated July, 12, 2001, from Merck Research Laboratories (MRL), a Division of Merck and Co., Inc., containing the first SUR; a fax dated July 5, 2001 and telephone conversations between the FDA and MRL on July 6, 2001 and July 12, 2001 requesting a second SUR related to several short-term clinical studies not included in the first SUR. Further reference is made to a telephone conversation between FDA and MRL during which the Agency requested a third safety update.

By this letter we are submitting the second Safety Update Report in response to the FDA request dated July 5, 2001. This report contains information on serious adverse experiences and discontinuations due to adverse experiences in Protocols 112, 116, 905.

MRL will provide an additional safety report containing counts tables for discontinuations due to non-serious adverse experiences for all studies included in the first SUR. MRL plans submission of this report by August 6, 2001.

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

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 amendment. All documents requiring signatures for certification are included as paper for archival purposes.

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July 12, 2001

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Dear Dr. Bull:

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

Response to FDA Request for Information
(SAFETY UPDATE REPORT)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a FDA Approvable letter dated April 6, 2001, requesting an additional safety update report; a letter from Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., dated May, 16, 2001 containing our proposed safety update; a FDA fax dated May 18, 2001 containing comments on our proposed safety update; and a letter from MRL dated May 25, 2001 responding to the FDA fax dated May 18, 2001. Further reference is made to correspondence from FDA dated June 22, 2001 and July 5, 2001, and a telephone conversation between the FDA and MRL on July 6, 2001 concerning further details on the content needed in the safety update report to fulfill our response.

By this letter we are submitting the requested Safety Update Report in response to the FDA Approvable letter dated April 6, 2001.

In conformance with the study protocols and established procedures, all gastrointestinal and cardiovascular clinical events reported by investigators in studies 078, 091 ——— were adjudicated by independent committees. The documentation related to this process (Adjudication Packages) are provided in Item 20 of this submission.

MRL will provide a separate safety report concerning Protocols — 112, 116, 905 ——— as agreed between MRL and the Agency. MRL plans submission of this report by July 31, 2001.

In conformance with the Agency's telefax of June 22, 2001, MRL anticipates that the Agency will consider the current submission to represent the completion of the requested responses to the Approvable letter dated April 6, 2001.

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July 9, 2001

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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 telefax containing requests for information received on June 6, 2001 from Ms. Sandra Folkendt (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 June 22, 2001.

By this submission, we are providing the remaining response to the information requested on June 6, 2001.

FDA Request 1
Please provide a simple ASCII or TEXT table containing two fields: the first one is for the unique patient identifier (the same one used for the SAS transport files), and the second for the narratives of deaths, serious adverse events and discontinuations due to adverse events.

MRL Response 1
The following text tables are provided in this submission:

1. Deaths (10 Patients)
2. Discontinuations due to Serious Adverse Experiences (134 Patients)
3. Discontinuations due to Adverse Experiences (696 Patients)

The patient's Allocation Number is used as the unique patient identifier for the attached text files, which is the same identifier used in the SAS transport files.

A particular patient's information is included in 1 category only. If a patient qualifies for more than 1 of the above categories, the narrative will be included in the lowest numbered applicable category.

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

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June 29, 2001

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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, 2001, and a fax received June 22, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information.

By this submission, we are providing the requested information.

FDA Request 1
Please clarify why Table 9 of the CSR for ADVANTAGE shows 371 and 385 aspirin users in the rofecoxib and naproxen group, respectively, but Table 10 includes a total of 363 and 374 users respectively.

MRL Response 1
Table 9 is the Summary of Specific Concomitant Medications, and displays the number of patients who took *at least one dose of aspirin*: 371 and 385 patients for rofecoxib and naproxen, respectively. That is, patients were counted as an aspirin user for Table 9 if they took as little as only one aspirin tablet during the study.

Table 10 is the Summary of Patient Aspirin Use broken out by cardioprotective category (e.g. Low Dose Aspirin User vs. Other and Non-Aspirin User) and displays the following:

	Rofecoxib, 25 mg	Naproxen, 1000 mg
Low-Dose User	355	369
Non-Aspirin User	2422	2398
Other Aspirin User	8	5

All patients who took at least one dose of aspirin during the trial (per Table 9) were reviewed to see if their aspirin use was deemed to be cardioprotective. If their aspirin use averaged between 20 mg and 325 mg per day they were classified in Table 10 as "Low Dose". If their aspirin use averaged less than 20 mg per day or took aspirin only following a cardiovascular event they were classified as a "Non-User". Patients who took aspirin at an average dose greater than 325 mg per day are classified as "Other User".

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June 22, 2001

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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 telefax containing requests for information received on June 6, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; and a telephone conversation between Ms. Folkendt and Dr. Silverman on June 11, 2001, during which the Agency requested additional information.

By this submission, we are providing the requested information.

FDA Request 1 (Fax dated June 6, 2001)
Please provide a simple ASCII or TEXT table containing two fields: the first one is for the unique patient identifier (the same one used for the SAS transport files), and the second for the narratives of deaths, serious adverse events and discontinuations due to adverse events.

MRL Response 1
The requested text table is currently being assembled and is targeted for submission to the Agency within the next 2 weeks.

FDA Request 2 (Fax dated June 6, 2001)
Please clarify why [redacted] (Site No. [redacted] was disqualified as an investigator for the ADVANTAGE study and whether this investigator has participated in other VIOXX studies. Provide information regarding the treatment group to which his patients were randomized and whether any of these patients discontinued due to adverse events.

MRL Response 2
The only Merck study that Dr. [redacted] participated in was the ADVANTAGE study, Site No. 102-378. Correspondence was forwarded to the FDA, Office of Good Clinical Practices Branch I regarding this site's participation in the ADVANTAGE study by both the [redacted] which managed the trial [redacted] and MRL (Attachment I).

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June 19, 2001

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Dear Dr. Bull:

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

Response to Arthritis Advisory Board Question

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000, and the Arthritis Advisory Committee (AAC) Meeting held on February 8, 2001, during which VIGOR cardiovascular hazard rates were discussed.

During the AAC meeting, Dr. Harrell, a consultant to the committee, suggested an additional statistical approach to analyzing the "appearance" of an increased hazard ratio for cardiovascular events at later time periods, specifically after eight months, in the VIGOR trial. Prompted by Dr. Harrell's statement, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is, herein, providing the Agency with additional analyses of the relative risk over time for the cardiovascular event data from the VIGOR trial. This report summarizes various statistical techniques used to assess the consistency of the hazard ratio. All these analyses support the previous conclusion that, compared to naproxen, there is no statistical evidence of increasing risk over time for an event on rofecoxib in the VIGOR trial.

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 amendment. 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 contents 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.

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June 14, 2001

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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); an approvable letter from FDA for the above noted sNDA dated April 6, 2001; a letter from Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., sent May 11, 2001, that contained a proposed Table of Contents for the requested safety update report; the Agency's response received by telefax on May 18, 2001; a letter from MRL responding to the Agency's telefax on May 25, 2001; and a telephone conversation between Ms. Sandra Folkendt (FDA) and Robert E. Silverman (MRL) on June 11, 2001, during which the Agency requested additional information.

By this letter, we are providing a detailed list of studies that will not be included in the safety report as proposed in the letter dated May 25, 2001 (Attachment I). These studies are all of short duration (4-6 weeks). Their exclusion from the updated safety report represents less than a 3% reduction of the data base (as measured by patient-years of exposure) that is being used in the preparation of the report.

Also provided are Serious Adverse Experience narratives that were inadvertently missing from the ADVANTAGE CSR (Appendix 4.4) which was previously submitted to the Agency. (Attachment II)

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

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 amendment. All documents requiring signatures for certification are included as paper for archival purposes.

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June 12, 2001

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Dear Dr. Bull:

NDA 21-042 / S-007 VIOXX™ (Rofecoxib Tablets)
Minutes to April 11, 2001 FDA/MRL Meeting

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; and a meeting between representatives of Merck Research Laboratories (MRL), A Division of Merck & Co., Inc., and the Agency on April 11, 2001. During this meeting the use of Protocol 069, the combined clinical GI events analysis from the OA development program, in product labeling was discussed.

By this letter and attachments we are providing minutes from the meeting held on April 11, 2001.

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

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 amendment. 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 contents 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. Sandra Folkendt, Project Manager.

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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. Reference is also made to a February 27, 2001 letter from Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. to the Agency requesting a meeting to discuss issues that arose from the Advisory Committee Meeting on February 8, 2001; to the background package for that meeting submitted March 16, 2001; and to the subsequent meeting between MRL and FDA on April 11, 2001.

As indicated on the attached Form FDA 356h, this amendment provides for changes in the Labeling and Summary Sections of the approved New Drug Application for VIOXX™. The paragraphs discussing Protocol No. 069 in the CLINICAL STUDIES and WARNINGS sections of the labeling have been revised to reflect a briefer, less prominent, and less detailed description of the study results, as discussed on April 11, 2001. 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 history
II. Labeling Text
    a. Proposed labeling text
        1. Package Circular

Summary – Item 3
I. Annotated labeling text
    a. Annotated Package Circular

The Microsoft WORD version of the proposed labeling text is also provided on a separate diskette.

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May 16, 2001

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Dear Dr. Bull:

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

Reference is made to the above cited supplemental New Drug Application (sNDA); an approvable letter from FDA for the above noted sNDA dated April 6, 2001; and a meeting between representatives from Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., and the FDA on April 11, 2001, during which the Agency requests for additional information contained in the approvable letter were discussed.

MRL has provided, in previous submissions on March 30, 2001, April 16, 2001 and April 30, 2001, the requested material from the ADVANTAGE trial. As discussed on April 11, 2001, MRL is preparing a supplemental safety report.

Attached is the proposed Table of Contents for the supplemental safety update. The report will consist of 2 parts. The first will be an updated overview of thrombotic cardiovascular events. Data will be summarized by the protocol using the 3 classifications -Investigator-reported, Confirmed (Adjudication SOP), and APTC. The meta-analysis will also be updated using the APTC endpoint. The second part of the report will summarize SAEs and deaths in clinical trials from which there was new data added to the cardiovascular section or from completed studies not previously submitted to the FDA which were more than 6 weeks in duration. Listings of SAEs and narratives from the WAES database will be provided as references.

The proposed report will represent a comprehensive update of the safety profile of VIOXX since the filing of the above-noted sNDA. The assembly of this report will require the commitment of significant resources by MRL. Therefore, MRL is requesting the Agency's timely review and comment on the proposal. To that end, Dr. Silverman will contact Ms. Folkendt within the week to solicit the Agency's feedback.

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

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April 30, 2001

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Dear Dr. Bull:

NDA 21-042 / S-007 VIOXX™ (Rofecoxib Tablets)
Response to FDA Request for Information
(ADVANTAGE CSR – Item 12)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a fax dated February 14, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting the complete report for the ADVANTAGE study (Protocols 102 and 903); a FDA letter to MRL dated February 28, 2001 making an official request for the complete CSR for ADVANTAGE with the appropriate safety analysis similar to those ultimately performed for the VIGOR database; a letter from MRL to FDA dated March 15, 2001 containing our proposal for submission of the requested CSR; our submission dated March 30, 2001 containing the ADVANTAGE CSR without the associated elements of Items 11 and 12; an approvable letter dated April 6, 2001 which requested submission of Items 11 and 12; a letter from MRL dated April 13, 2001 documenting MRL's intent to amend the sNDA with submission of Items 11 and 12; and our submission dated April 16, 2001 containing the ADVANTAGE CSR with Item 11.

By this letter, we are submitting Item 12 of the ADVANTAGE study. Item 12 consists of the following categories:

- Deaths
- Discontinuations due to GI Adverse Experiences
- Discontinuations due to CV Adverse Experiences
- GI Endpoints
- CV Endpoints
- Discontinuations due to adverse Experiences other than CV and GI

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March 22, 2001

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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 dated February 1, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting information.

FDA Request 1: Provide the analyses of comparison of naproxen to placebo for the database used in the meta-analysis submitted on January 8, 2001.

MRL Response 1: The only placebo-controlled study periods in which one could directly compare patients taking naproxen (500 mg twice daily) to patients on placebo are the Part I, 12-week periods from protocols 096 and 097 (the Rheumatoid Arthritis [RA] Phase III efficacy studies) and the entire 12 weeks of protocols 098 and 103 (the RA surveillance endoscopy studies). Data on patient years at risk, numbers of patients studied, and number of APTC combined endpoint events are presented in the following table:

Protocol	# APTC Endpoint Events	Number of patients	Patients years at risk
Placebo			
096 + 097	0	600	120
098 + 103	1	221	56
Naproxen			
096 + 097	0	296	73
098 + 103	0	220	51

Given the small sample size and the fact that only a single event was detected, the data were not analyzed further.

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March 16, 2001

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Dear Dr. Bull:

NDA 21-042 / S-007 VIOXX™ (rofecoxib tablets)
Background Material for Meeting

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000; a meeting request from Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on February 27, 2001; and several telephone conversations between Dr. Robert E. Silverman (MRL) and Ms. Sandra Folkendt (FDA) related to the requested meeting. Per the Agency's request, MRL is providing, herein, background material for the meeting.

Attachment 1: Proposed Agenda

Attachment 2: Questions/Issues for Discussion

Attachment 3: Proposed Product Label (previously submitted 3/2/01)

Attachment 4: Request and rationale for meeting (previously submitted February 27, 2001)

Attachment 5: Excerpt from Integrated Summary of Safety NDA 21-042 (previously submitted November 23, 1998)

Attachment 6: Clinical Study Report: Protocol 069 (previously submitted NDA 21-042, November 23, 1998)

Since the emphasis of this meeting is the discussion of the use of Protocol 069 in product labeling, an issue that was discussed with senior CDER officials during the label negotiations for the original NDA 21-042, MRL believes participation in this meeting by CDER management would be most conducive to a timely and mutually satisfactory resolution of the issue. We look forward to confirmation of the time, date, and place of the meeting.

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March 13, 2001

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

VIOXX™ Gastrointestinal Outcomes Research Study (VIGOR)

ARTHRITIS ADVISORY COMMITTEE

Additional MRL Slides

Reference is made to a submission to this NDA on February 28, 2001, that provided additional slides that were presented by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. at the Arthritis Advisory Committee on February 8, 2001 that were not previously submitted to the Agency. Reference is also made to a telephone conversation between Dr. Silverman (MRL) and Ms. Reedy (FDA) on March 13, 2001.

The February 28, 2001 submission erroneously included a standard request from MRL to consider the contained information confidential. By this letter, MRL is withdrawing that confidentiality request. It is anticipated that the Agency will disseminate the additional slides, which were publically presented on February 8, via the Agency website in conjunction with other documents from the Advisory Committee Proceedings.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations. This submission 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.
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March 8, 2001

Central Document Room
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Attention: Jonca Bull, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products, HFD-550

MERCK
Research Laboratories

Dear Dr. Bull:

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

Reference is made to the above Supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000, and the meeting of the Arthritis Drug Advisory Committee on February 8, 2001. Merck Research Laboratories (MRL), a division of Merck & Co., Inc. would like to thank the Agency for their efforts in making the Advisory Committee proceedings a valuable exchange of information and perspectives. MRL is interested in continuing the dialogue with the Agency in a timely manner.

Reference is also made to a submission to this NDA on February 27, 2001 that included the same content as this submission. Per the Agency's request (multiple telephone conversations between Dr. Silverman (MRL) and Program Management representatives of the Agency on March 5, 2001 and March 6, 2001), this cover letter has been reformatted to document that the request included in this submission is directed to the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.

By this letter, MRL would like to raise two important issues that were discussed during the meeting on February 8, 2001, but were not specifically resolved. In furtherance of a timely resolution of these issues, MRL requests a meeting with FDA to discuss these issues in the context of the review of the above noted sNDA and within a timeframe consistent with the PDUFA target date for completion of the Agency's review of this sNDA.

First, MRL continues to be concerned with the Agency's perspective and interpretation of Rofecoxib Protocol 069, in the new light of the VIGOR study, that was only briefly discussed at the Advisory Committee meeting on February 8, 2001. Second, MRL is concerned with the Advisory Committee discussion related to the appropriateness of product labeling derived from a clinical study which did not meet predefined primary measures of success. Some remarks by Advisory Committee members appeared to challenge the Agency's established "standard of proof" for the assessment of important clinical outcome trials. These concerns are developed in more detail below.

Protocol 069: As discussed previously, Protocol 069 was a prospectively designed pooled analysis of clinically important GI events which occurred in the OA Phase IIb/III development program for VIOXX™ that was reported in the original NDA. The definition of clinical endpoints were predefined and rigorously adjudicated by an independent expert panel that was blinded to treatment assignment. Nonetheless, after extensive discussions prior to the initiation of VIGOR, during the original NDA review, and during the final product label negotiations for rofecoxib, the results of Protocol 069 were excluded from the initial approved product circular. At that time, the Agency justified the exclusion of Protocol 069 because the study design (e.g. pooling of data across numerous studies of varying duration and NSAID comparators) was insufficiently compelling to the Agency

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February 28,2001

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

VIOXX™ Gastrointestinal Outcomes Research Study (VIGOR)

ARTHRITIS ADVISORY COMMITTEE

Additional MRL 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., and an Arthritis Advisory Committee on February 8, 2001.

By copy of this letter, we are providing additional slides that were presented by MRL at the Arthritis Advisory Committee meeting that were not previously submitted to the Agency.

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

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations. This submission 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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February 27, 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 partial response to this request dated January 19, 2001; a fax from the Agency dated January 31, 2001 requesting clarification on the Table of Hospitalizations submitted in our response dated January 19, 2001; and a response to this request for clarification dated February 6, 2001.

The submission dated February 6, 2001 contained the total number of patients hospitalized with "cardiovascular-related" and "digestive system" events. In this letter we promised to submit a tabular breakdown of each diagnosis under separate cover.

By this submission, we are providing the remaining information. Attachment I contains "cardiovascular-related" events and Attachment II contains "digestive system" events.

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

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NDA 21-042/S-007 VIOXX™
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General Correspondence - Request for Meeting

Reference is made to the above Supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000, and the meeting of the Arthritis Drug Advisory Committee on February 8, 2001. Merck Research Laboratories (MRL), a division of Merck & Co., Inc. would like to thank the Agency for their efforts in making the Advisory Committee proceedings a valuable exchange of information and perspectives. MRL is interested in continuing the dialogue with the Agency in a timely manner.

By this letter, MRL would like to raise two important issues that were discussed during the meeting on February 8, 2001, but were not specifically resolved. In furtherance of a timely resolution of these issues, MRL requests a meeting with FDA to discuss these issues in the context of the review of the above noted sNDA and within a timeframe consistent with the PDUFA target date for completion of the Agency's review of this sNDA.

First, MRL continues to be concerned with the Agency's perspective and interpretation of Rofecoxib Protocol 069, in the new light of the VIGOR study, that was only briefly discussed at the Advisory Committee meeting on February 8, 2001. Second, MRL is concerned with the Advisory Committee discussion related to the appropriateness of product labeling derived from a clinical study which did not meet predefined primary measures of success. Some remarks by Advisory Committee members appeared to challenge the Agency's established "standard of proof" for the assessment of important clinical outcome trials. These concerns are developed in more detail below.

Protocol 069: As discussed previously, Protocol 069 was a prospectively designed pooled analysis of clinically important GI events which occurred in the OA Phase IIb/III development program for VIOXX™ that was reported in the original NDA. The definition of clinical endpoints were predefined and rigorously adjudicated by an independent expert panel that was blinded to treatment assignment. Nonetheless, after extensive discussions prior to the initiation of VIGOR, during the original NDA review, and during the final product label negotiations for rofecoxib, the results of Protocol 069 were excluded from the initial approved product circular. At that time, the Agency justified the exclusion of Protocol 069 because the study design (e.g. pooling of data across numerous studies of varying duration and NSAID comparators) was insufficiently compelling to the Agency [redacted]. The Agency's perspective was originally provided [redacted] and reiterated during the May 18, 1999 label negotiation teleconference with MRL which was documented in a letter from MRL to the NDA on June 4, 1999 (Attachment 2). At that time, the Agency did offer that [redacted] support inclusion of an appropriate description of Protocol 069 in product labeling.

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February 23, 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 February 14, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional information; and a partial response to this request submitted on February 16, 2001.

By this submission, we are providing an additional response to the Agency's request for information from February 14, 2001.

FDA Request 4: Provide patient narratives for discontinuations due to renal-related events in the VIGOR study.

MRL Response 4: The requested patient narratives are provided as Attachment I of 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 response 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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February 21, 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 teleconference between representatives of the Agency and Merck Research Laboratories (MRL), a Division of Merck & Co., on January 24, 2001 whereby the Agency requested APTC endpoint counts tables by protocol; and a response to this request submitted January 29, 2001. This response did not include a tabulation of peripheral vascular events which we promised the agency would be submitted subsequently.

By this letter and attachment MRL is providing the tabulations of peripheral vascular events as requested by the Agency. (Attachment I)

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

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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.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

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February 16, 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 and a fax received on February 14, 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 requested information.

FDA Request 1: Analysis of serious CV thrombotic events in the VIGOR study by age (<65 and >=65 years) with a separate analysis for MI's.

MRL Response 1: The requested analyses are provided as Attachment I of this submission.

FDA Request 2: Complete report of study 102 (Advantage).

MRL Response 2: MRL is still in the process of completing the CSR for ADVANTAGE (Protocol 102). We currently expect to submit the complete report within six to eight weeks. Efforts are being made to further expedite the completion of this report.

FDA Request 3: Resubmission of Study 061 (submitted with the original NDA) that evaluated the antiplatelet effect of naproxen as compared to other NSAIDs as presented at the AAC.

MRL Response 3: The requested CSR for Protocol 061 is provided as Attachment II of this submission.

FDA Request 4: Provide patient narratives for discontinuations due to renal-related events in the VIGOR study.

MRL Response 4: MRL is actively compiling this response which will be forthcoming under separate cover, and should be provided by February 23.

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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 fax received on February 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 the requested information.

FDA Request 1: Please provide the PUB rate for the sub-population of >65 years and prior PUB. Please provide cumulative and per 100 pt year rates.

MRL Response 1: The requested analysis is provided in Attachment I of this submission.

While the table provides rates, [redacted] was not provided because of the rules used in VIGOR for that calculation. For the entire cohort, [redacted] was provided at the time where there were at least 500 patients at risk in each treatment group. The rule was implemented to avoid undue influence of late events which occur when there are few patients at risk; such events can greatly skew [redacted] estimates. Since there were fewer than 500 patients at risk in the subgroups of interest at the beginning of follow-up, the rule could not be applied and the calculation was not made.

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February 15, 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 January 11, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting information; a response to this request dated January 25, 2001; and a FDA fax received on January 26, 2001 requesting additional clarification to the MRL response submitted on January 25, 2001.

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

Attachment I contains a listing table of Laboratory Adverse Experiences by Laboratory Test Category similar to the one presented for all patients in Table 62 of the 088C CSR.

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February 6, 2001

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NDA 21-042/S-007: VIOXX™ (rofecoxib tablets)
Arthritis Drug Advisory Committee Meeting
February 8, 2001

Reference is made to the above supplemental New Drug Application (sNDA) and an Arthritis Drug Advisory Committee Meeting (ACM) on February 8, 2001 that will discuss the above sNDA.

Attached is a preliminary report of an epidemiologic study derived from the [redacted] which is maintained by the [redacted] We just received permission, this morning, from [redacted] Chairman) for the database to cite this information during the ACM.

This data will not be presented by Merck in the initial formal presentations at the ACM. However, Merck will be prepared to present a summary of this data in response to relevant questions during the ACM discussions. If this information is introduced during ACM discussions, Merck will acknowledge that this report is preliminary and has not been reviewed by the Agency.

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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