Merck draft of 15 Feb 2002 with proposals resulting from 20 Feb 2002 FDA teleconference

FDA The Division has had internal discussions with statisticians from the Division and the Center regarding how safety data are most appropriately displayed in the context of cumulative exposure. The best way to display the data is the [redacted]. FDA is not comfortable with Merck's conclusion that the [redacted] The issue of potential change in hazard rate over time is not addressed in a crude rate or in event per 100 patient-years rate. Precedents for of including [redacted] in labels exist.

MERCK: The [redacted] has optical illusion and looks like something is happening that is not happening [redacted] Several statistical tests did not show statistically significant differences in hazard rates over time.

FDA: Failure to show a statistical significant difference does not prove absence of change in hazard rate over time. [redacted] statistics are standard to depict effects and outcome. [redacted] plot does portray rates over time information.

(Note: The time devoted to how to best display cardiovascular safety from VIGOR reflects how important the Agency considers the topic of clear labeling of safety information).

ACTION ITEMS:

1. The Division will arrange a meeting with Center statisticians to discuss statistical presentation of data for CV and GI events in the label.
2. Agreed to reconvene for further label discussions.
3. Minutes of the teleconference will be conveyed within 30 days.

Concurrence Chair:

Barbara Gould Date
Project Manager

Lawrence Goldkind, MD Date
Deputy Division Director

APPEARS THIS WAY
ON ORIGINAL

Initial by: LVillalba/
LStan/
RO'Neill/
LGoldkind/
JBull/

TELECON MINUTES

TELECON MINUTES

MEETING DATE: January 30, 2002 **TIME:** 08:30 a.m. **LOCATION:** Corp S300

NDA 21-042/S-007, 012
NDA 21-052/S-004, 007

Telecon Request Date: December 19, 2001
Telecon Cancelled by Sponsor: January 07, 2002
Telecon Rescheduled: January 17, 2002

DRUG: Vioxx (rofecoxib) Tablets 12.5 mg, 25 mg, 50 mg
Vioxx (rofecoxib) Suspension 12.5 mg/5 mL, 25mg/5 mL

SPONSOR/APPLICANT: Merck Research Laboratories

TYPE of TELECON: Labeling Negotiations

FDA PARTICIPANTS:	**Division of Anti-Inflammatory, Analgesics, & Ophthalmic Drug Product**
Jonca C. Bull, MD	Acting Director, Deputy Director, Office of Drug Evaluation V
Larry Goldkind, MD	Deputy Division Director
James Witter, MD, Ph.D.	Acting Medical Team Leader
Maria L. Villalba, MD	Medical Reviewer
Joel Schiffenbauer, MD	Medical Reviewer
Stan Lin, Ph.D.	Biostatistics Team Leader
Carmen DeBellas, R.Ph.	Chief, Project Management Staff
Barbara Gould	Project Manager
Robert Temple, MD	Director, Office of Medical Policy
Laura Governale	Project Manager, Office of Medical Policy, DDMAC

INDUSTRY PARTICIPANTS:	**Merck Research Laboratories**
Dr. Bonnie Goldmann	Regulatory Affairs
Dr. Robert Silverman	Regulatory Affairs
Dr. Ned Braunstein	Regulatory Affairs
Dr. Diane Benezra	Regulatory Affairs
Ms. Dawn Chitty	Regulatory Affairs
Dr. Alise Reicin	Clinical Research and Sciences
Dr. Kenneth Truitt	Clinical Research and Sciences
Dr. Thomas Simon	Clinical Research and Sciences
Dr. Barry Gertz	Clinical Research and Sciences
Dr. Deborah Shapiro	Clinical Biostatistics
Mr. James Bolognese	Clinical Biostatistics
Dr. Leonard Oppenheimer	Clinical Biostatistics
Dr. Douglas Watson	Epidemiology
Dr. Harry Guess	Epidemiology
Dr. Thomas Bold	Worldwide Product Safety and Epidemiology
Ms. Linda Hostelley	Worldwide Product Safety and Epidemiology
Dr. Douglas Greene	Clinical Scientific and Product Development

Dr. Peter Kim	Research & Development
Mr. Thomas Casola	Office of Medical/Legal

BACKGROUND INFORMATION:
Reference is made to the above cited supplemental New Drug Applications (sNDA) submitted as electronic archives 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; 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; a submission dated December 5, 2001 containing MRL's updated labeling proposal; and a FDA fax dated December 21, 2001 containing proposed labeling to be discussed at an upcoming teleconference scheduled for January 9, 2002.

At Merck's request the teleconference scheduled for January 09, 2002 was cancelled and rescheduled on January 17, 2002 for January 30, 2002, when Dr. Robert Temple would be available. On January 29, 2002 a list of FDA tentative participant, a revised label, and agenda was forwarded to MRL that would be basis for teleconference on January 30, 2002.

DISCUSSION:
The teleconference began with opening remarks by Dr. Jonca Bull. Dr. Bull acknowledged that the deletion of information regarding GI warning was an oversight. Both parties agreed that there is new safety information that needs to be communicated based findings in the VIGOR studies. Dr. Bull summarized by stating that the way to move forward in the interim clearly is by indicating what prescribers need to convey to their patients.

Dr. Goldmann stated that it would help Merck in understanding what key points the FDA felt needed to be communicated in the Vioxx label.

MERCK: VIGOR was primarily designed to evaluate GI outcomes. Other safety endpoints are always included in all Merck trials and should not be as prominent as the primary endpoint. The Agency is putting more weight on the non-GI findings than on the positive GI findings of the study. Edema and hypertension are known effects of the NSAID class.

FDA: The goal of the Division is not to detract from the GI endpoints. However, the Division views the overall safety data and CV data, particularly CV/thrombotic events in VIGOR as relevant and provide context for the GI results. We propose a single table ——— . More than one table in the clinical section of the label might also be acceptable.

MERCK: CV data in VIGOR is not supported in Alzheimer's studies. The Sponsor proposed including a paragraph about the Alzheimer's study and also requested putting back in dosage section: [redacted]

FDA: The Division has concerns over inclusion of prematurely completed studies and studies in progress. The complete report of these studies has not been submitted for review and one of the studies is still ongoing. We anticipate future dialogue regarding the Alzheimer's clinical studies.

MERCK: Would early termination of the ongoing study and submission of the Alzheimer's data suffice to be included in present label? Also could the meta-analysis of CV/thrombotic events in the VIOXX program, and/or analysis of phase IIbIII OA studies be included.

FDA: You may consider a labeling supplement when studies are completed. We do not advise you to stop the ongoing Alzheimer's study. Meta-analysis of studies of varying duration, dose, and indication are inherently difficult to interpret.

Meta-analysis has been discussed at the Arthritis Advisory Committee, at the center level and with biostatisticians in the Agency. The level of confidence with meta-analysis does not rise to the level of a prospectively designed, well-controlled, study of adequate duration, and size for a given dose.

MERCK: Merck proposed to send clarification of numbers where there seems to be misinterpretation of the data. The Sponsor requested clarification as to why information has been struck from label. Suggestion was make to the Agency to look again at the January 08, 2002 label proposal. Merck would like to go through the label to find why certain information has bee removed.

ACTION ITEMS:

1. FDA will re-review Merck's January 08, 2002 proposed label and future agendas will include further clarification of the Division's labeling concerns.
2. Agreed to reconvene in one week for further label discussions.
3. Minutes of the teleconference will be conveyed within 30 days.

Concurrence Chair:

Barbara Gould Date
Project Manager

Lawrence Goldkind, MD Date
Deputy Division Director

APPEARS THIS WAY
ON ORIGINAL

Initialed by:

TELECON MINUTES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lawrence Goldkind
4/17/02 05:11:11 PM

APPEARS THIS WAY
ON ORIGINAL

Memo to NDA 21,052 and 21,042
From: Lawrence Goldkind M.D.

Regarding: Teleconference with sponsor

Robert Silverman of regulatory affairs at Merck called on 7/11/01 with follow-up to an issue raised at a teleconference the week prior. The call was returned on 7/12/01 with Lawrence Goldkind and Lourdes Villalba present. Robert Silverman was the only participant from Merck.
The project manager for NDA 21,052 and 21,042 had recently moved and the acting project manager was not available.

Content of telecon:

The previous week the division had requested that the sponsor explore whether narratives and case report forms for patients withdrawn due to non-serious adverse events could be provided for ~ studies that have either not been completed or do not have completed study reports (CSR) prepared. These studies are of 6 weeks or less duration but may provide some additional meaningful information related to safety that cannot be obtained form the VIGOR or Advantage trials as the comparators for these studies were not anti-platelet drugs.

Dr. Silverman stated that **narratives** for such withdrawals are not typically provided in completed study reports (CSRs). Case report forms (CRFs) for all withdrawals due to non-serious as well as serious adverse events are ultimately included in CSRs. At this point in time however, **tables** of withdrawals due to non-serious adverse events for the — studies for which the division wishes to capture safety data can and will be supplied.

I informed Dr. Silverman that we will be sending a fax with multiple information requests within the next several days.

Lawrence Goldkind M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lawrence Goldkind
7/12/01 12:40:17 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

From: Mary jane Walling
Sent: Thursday, July 05, 2001

To: Dr. Robert Silverman/Merck
Fax'/484-344-2516

Subject: NDA 21-042/s007 Advantage.

Re: - NDA 21-042/s007 - April 6, 2001 FDA Approvable letter.
- Studies that Merck proposes to exclude from the Safety Update Report (June 14, 2001 letter).

As part of the Complete Response Safety Update Report, please submit the listing and narratives of serious adverse events and discontinuations from studies — 112, 116, 905 with a separate analysis of serious cardiovascular thrombotic events.

Thank you

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELE-CONS

DATE: April 5, 2001

PARTICIPANTS: Dr. Bull and Ms. Walling/FDA and Drs. Silverman and Simon/Merck

SUBJECT: NDA 21-042/21-052- VIOXX

We called Merck to let them know that at this time their supplemental applications were approvable and until a full and complete review of the ADVANTAGE (102) trial was conducted, a label could not be crafted. She stated that we needed ASAP, the case report tabulations. We will complete a review of the trail before we address the aspects of the label. We are prepared to discuss the meta-analysis on April 11.

DATE: April 6, 2001

PARTICIPANTS: Dr. DeLap and Ms. Walling/FDA and Dr. Silverman/Merck

SUBJECT: NDA 21-042 and 21-052

Dr. Silverman called to express concern about the AE action due to the need for submission and review of additional safety data. He was not surprised by the agency's position and understood that we had to be comfortable with the decision. He wanted assurance that their competitor would get the same language in their label and they would not derive a "halo" effect from the fact that Merck had conducted certain studies and they had not.

[ ]

Dr. DeLap assured him that we were interested in bringing this to closure and would not prolong the review of the additional data and that we were committed to getting a good label for his drug. He added that if Merck had evidence of misleading promotional activity, they should share that with us.

Dr. Silverman asked about an FDA web site with a list of all actions taken for all NDAs and supplements. We told him we were not aware of that web site and asked him for further clarification. Dr. DeLap said the April 11 meeting should be worthwhile and should take place.

Dr. Silverman stated that by April 16, we should have the SAS data set and by the end of April we should have the Adverse Event Reports (except for the ones that are considered by Merck to not be relevant- they will come a few days after).

/s/

Mary Jane Walling
4/16/01 08:09:13 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

TELECON MINUTES

Date: 1/17/01 **Time:** 9:30 am

NDA: 21-042/S-007, 21-052/S-004

Drug: Vioxx (rofecoxib tablets and suspension)

Applicant: Merck

FDA Participants:
Robert DeLap, M.D., Ph.D., Office Director
Jonca C. Bull, M.D., Acting Division Director
Deputy Office Director
Maria Lourdes Villalba, M.D., Medical Officer
Lawrence Goldkind, M.D., Medical Officer Team Leader
Sandra Folkendt, Project Manager

Merck Participants:

Dennis Erb, Ph.D.	Senior Director, Regulatory Affairs
Philip Huang	Director, Regulatory Affairs
Bonnie Goldman, M.D.	Regulatory Affairs
Briggs Morrison, M.D.	Senior Director, Clinical Research
Sean Curtis, M.D.	Director, Clinical Research
Barry Gertz, M.D.	Clinical Research
Alise Reicin, M.D.	Clinical Research
Ken Truitt	

Teleconference Objectives:

Merck requested a teleconference with the Office to discuss issues for NDA 21-042/S-007, IND —— , and IND ——

Rofecoxib Issues:
NDA 21-042/S-007, NDA 21-052/S-004, IND ——

A. Pending submission of ——————, studies

- **Concurrence with filing under existing acute pain indication**

[ ]

[

]

B. Pre meeting for VIGOR Advisory Committee (A.C.) Meeting

Merck inquired if a meeting before the A.C. meeting is possible. FDA agreed a meeting should be possible and asked Merck to submit a meeting request with an agenda. FDA indicated that the request for a meta-analysis was still outstanding and we are awaiting a response.

C. Status of Proposed Pediatric Request

- **Submitted by Merck on August 31, 2000**

Merck asked why there had not been a response to their request for a Pediatric Written request letter as it had been over 120 days since the submission of the request. FDA stated that the 120 days was an internal goal only and at this time hoped to have a letter issued by the end of April, 2001.

Concurrence:

Sandra N. Folkendt, Project Manager

Jonca C. Bull, M.D.
Acting Division Director

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandra Folkendt
5/11/01 10:01:15 AM
CSO

Jonca Bull
5/11/01 12:45:13 PM
MEDICAL OFFICER

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

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-012: 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 February 28, 2001; a fax dated November 28, 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 a response to the requested information.

FDA Request 1
For the sNDA 21-042 please provide an analysis pertaining to the number of subjects who are ACR 50 responders and responders and completers. Please do the same for the ACR70.

MRL Response 1
The results of the analyses are provided in Tables 1 through 4. In general, the active treatment groups had numerically more patients meeting ACR 50 and ACR 70 than the placebo group. In study 096, only naproxen was significantly better than placebo for ACR 50 responders and completers. In study 097, only rofecoxib 25 mg and 50 mg were significantly better than placebo for ACR 50 responders and for ACR 50 responders and completers.

It is important to note that these studies were not powered to detect significant differences in ACRxx. Therefore, since the results numerically favor active treatments, they are consistent with the results of ACR 20 and the primary endpoints, which indicated statistically significant differences between rofecoxib 25 mg and placebo.

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.

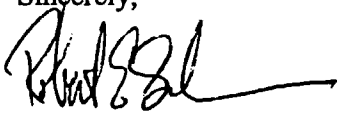
All the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the content of the CD are free of computer viruses (Norton AntiVirus® 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

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.

We consider the filing of this amendment 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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. 484-344-2944 or, in my absence, Bonnie J. Goldmann, M.D. 484-344-2383.

Sincerely,



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

Federal Express

Desk Copy: (cover letter only) Ms. Barbara Gould, Project Manager
HFD- 550, Room N353

Q:\howley\christa\21042\RFDA\015 (012).doc

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

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.

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.

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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (484) 344-2944 or, in my absence, Bonnie J. Goldmann, M.D. (484) 344-2383.

Sincerely,

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

Enclosure: CD

Federal Express

Desk Copy: Ms. Barbara Gould, Project Manager
(Cover letter only) HFD- 550, Room N353

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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

October 11, 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-012: 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 February 28, 2001. Reference is also made to a fax containing a request for information sent on September 28, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.

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

FDA Request #1
Please provide summary tables and analyses of mean and median changes in systolic and diastolic blood pressure at 6 and 12 weeks for each dataset in the RA database.

MRL Response #1
Please find attached tables of summary statistics for mean changes from baseline in systolic and diastolic blood pressure, by assigned treatment group at select study-time points.

Tables 1 and 2 show changes from baseline (for systolic and diastolic blood pressure, respectively) at 4, 8, and 12-week time points for the placebo-controlled data set. (Note: Protocols 068, 096, and 097 had 4 and 8-week visits but no 6-week visit; Protocol 098/103 had a 6-week visit but no 4 or 8-week visits; the last placebo-controlled visit in Protocol 068 was at 8 weeks; all other studies had a placebo-controlled 12-week visit [hence, 12-week data do not include patients from Protocol 068].) The 6-week data from Protocol 098/103 are included in these tables (Tables 1 and 2), combined with integrated 4 or 8 week data, based on postrandomization day of the scheduled 6-week visit. If the visit (scheduled, per-protocol, for 6 weeks) occurred on or before postrandomization day 42, and on or after postrandomization day 22, corresponding data were combined with 4-week data from Protocols 068, 096, and 097; if the visit occurred subsequent to day 42 and on or before day 70, data were combined with 8-week data from Protocols 068, 096, and 097.

For reference, 6 and 12-week data from Protocol 098/103 are shown separately in Tables 3 and 4 (changes from baseline for systolic and diastolic blood pressure, respectively). Again, of all protocols contributing to the placebo-controlled data set, only Protocol 098/103 had a scheduled visit at 6 weeks.

Tables 5 and 6 show changes from baseline (for systolic and diastolic blood pressure, respectively) at 4, 8, and 12-week time points for the long-term continuous therapy data set. (Note: this data set does not include patients from Protocol 098/103; hence, there are data at 4, 8, and 12 weeks, but not 6 weeks.)

Note that Tables 3 and 5 each represent different subsets of the data included in Table 1. Similarly, Tables 4 and 6 each represent different subsets of the data included in Table 2.

No tables are provided for the Part II continuation and extension data set. The first study visit on continuation/extension therapy for Protocol 068 occurred at 12 weeks, and the first study visit for Protocols 096/097 occurred at 14 weeks. (Protocol 098/103 had no continuation or extension period.) Hence, there are no integrated 6 and 12-week results for this particular data set.

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.

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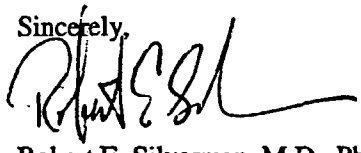
A list of Reviewers from the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products who should be provided access to this electronic submission from their desktops may be obtained from Ms. Barbara Gould, Project Manager.

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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. 484-344-2944 or, in my absence, Bonnie J. Goldmann, M.D. 484-344-2383.

Sincerely,



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

Enclosure: CD

Federal Express

Desk Copy (cover letter): Barbara Gould, Regulatory Project Manager
HFD-550, Room N353

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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 21, 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-012: 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 February 28, 2001; a fax containing requests for information received on July 18, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; a response to this request submitted July 27, 2001 which contained the cardiovascular Adjudication Packages for Rheumatoid Arthritis (RA); and a fax received on September 18, 2001 containing a subsequent request for these packages.

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

FDA Request 1
Please provide all adjudication packages of patients referred for evaluation to the CV adjudication committee for the RA efficacy supplement (012).

MRL Response 1
The requested cardiovascular adjudication packages for RA were submitted to the Agency on July 27, 2001.

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.

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Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. 484-344-2944 or, in my absence, Bonnie J. Goldmann, M.D. 484-344-2383.

Sincerely,

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

Federal Express

Desk Copy: Ms. Barbara Gould, Project Manager
(cover letter only) HFD- 550, Room N353

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APPEARS THIS WAY
ON ORIGINAL

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

Merck & Co., Inc.
BLA-20
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West Point PA 19486-0004
Tel 484 344 2944
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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.

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

MRL Response #2
The CSR for Protocol [redacted] is not yet complete. The full report will be submitted by November 9, 2001. If the Agency would like to designate particular elements of the study report of particular interest, MRL will endeavor to provide those specific elements prior to the full report.

FDA Request #4
21-042/012 – Please provide patient-years at risk in study 068.

MRL Response #4
The lists below indicate the patient years at risk by treatment and part of study 068.

Protocol 068, Part I (derived from CSR Table 36):
- Rofecoxib – mg – 22.5 patient years
- Rofecoxib 25 mg – 24.3 patient years
- Rofecoxib 50 mg – 22. 5 patient years
- Placebo - 22.8 patient years

Protocol 068, Part II (derived from CSR Table 14):
- Rofecoxib 25 mg – 161.7 patient years
- Rofecoxib 50 mg – 144.6 patient years
- Naproxen 1000 mg – 59.2 patient years

Protocol 068, Extension 10 and 20 (derived from CSR Table 6):
- Rofecoxib 25 mg – 115.9 patient years
- Rofecoxib 50 mg – 100.1 patient years
- Naproxen 1000 mg – 37.8 patient years

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.

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.

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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (484) 344-2944 or, in my absence, Bonnie J. Goldmann, M.D. (484) 344-2383.

Sincerely,

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

Enclosure: CD

Federal Express

Desk Copy: (Cover letter only) Ms. Barbara Gould, Project Manager
HFD- 550, Room N353

Q:\Lesher\Vioxx\NDA Subs\7Sep2001Response.doc

APPEARS THIS WAY
ON ORIGINAL

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August 13, 2001

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Dear Dr. Bull:

NDA 21-042/S-012: 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 February 28, 2001; a fax containing requests for information received July 13, 2001 from Ms. Mary Jane Walling (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; a partial response to this request submitted to FDA on July 26, 2001 containing information regarding the VIGOR sNDA (S-007). Further reference is made to a fax containing requests for information received on July 18, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, (MRL); and a partial response to this request submitted July 27, 2001 containing the cardiovascular adjudication packages for the rheumatoid arthritis sNDA.

By this submission, we are providing the requested information.

FDA Request 1 (FDA Fax dated July 13, 2001)
Regarding RA safety update (S012, submitted 6/27/01), please provide treatment allocation for those patients with serious cardiovascular events presented in table 66 of the RA SUR. That information is essential for a complete evaluation of the long-term cardiovascular safety of rofecoxib.

MRL Response 1
Attachment I contains a revised Table 66 which includes treatment allocation information for the patients. This information was not routinely provided in the submitted listing because this information was derived from data which had not completed the standard Merck review and audit process; that is, this portion of the database was not yet "frozen" and unblinded. In a review of the reyised table, it was noted that two patients (AN 2735 and AN 3618) were inadvertently omitted from the listing of patients with potential serious cardiovascular thromboembolic events (Table 64). This omission has been corrected in a revised Table 64 which is provided as part of the MRL response to another Agency comment (see below).

FDA Request 2 (FDA Fax dated July 18, 2001)
Table 65 of the RA SUR provides an analysis of confirmed adjudicated or APTC events combined. This analysis is inadequate. Please provide analyses of investigator reported, serious cardiovascular thrombotic adjudicated events and APTC events from RA studies 96, 97, 98 and 103. (Since study 068 did not use the adjudication process do not include study 068 in this analysis.)

MRL Response 2
Attachment II provides responses to the Agency's comments and requests. MRL acknowledges that the analysis of confirmed adjudicated or APTC events presented in Table 65 was inadequate. Therefore, Attachment II provides a revised section 4.2 (Adjudication of Potential Serious Thromboembolic Cardiovascular Events) that incorporates, in text and tables (64 and 65), a complete discussion of potential thromboembolic cardiovascular events. This revised section 4.2 includes modifications consistent with MRL's review of Table 66, discussed above.

FDA Request 3 (FDA Fax dated July 18, 2001)
Please clarify how the calculation of patient years at risk was made. Please provide the number of patients randomized to each treatment group (placebo, rofecoxib 12.5, 25, 50 mg and naproxen) regardless if exposure.

MRL Response 3
Patient years at risk were calculated for each treatment group by adding the days on which patients are recorded in the data base as having taken study medication, and dividing by 365 days/year.

Attachment III provides a table with the number of patients randomized to each treatment group. Protocols 068, 096 and 097 had multiple parts with some patients switching treatments between parts, by design. Therefore, this table includes patient numbers by treatment group for each part of each study. A patient may be counted in different treatment groups for different parts of a study.

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.

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.

We consider the filing of this amendment 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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. 484-344-2944 or, in my absence, Bonnie J. Goldmann, M.D. 484-344-2383.

Sincerely,

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

Federal Express

Desk Copy: (cover letter only) Ms. Barbara Gould, Project Manager
HFD- 550, Room N353

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APPEARS THIS WAY
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July 20, 2001

MERCK

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

REVISED SAFETY UPDATE REPORT

Rheumatoid Arthritis

Reference is made to the supplemental New Drug Application (sNDA) cited above for VIOXX™ submitted as an electronic archive on February 28, 2001, and a Safety Update Report submitted on June 27, 2001.

While evaluating FDA requests for additional information, MRL discovered that the Safety Update Report (SUR) submitted to the Agency on June 27, 2001 was not the final version intended for submission and contained several errors as listed below.

Page 19: Table 4, last column, Protocol 097 amended to include patient numbers separated for Parts I and II

Page 48: Table 10, Data source at the bottom of the table corrected from — to 47

Page 86: First sentence, Placebo numbers changed from ——— , to 24 (2.4%)

Page 145: Paragraph 2- Following AN5627, section referenced corrected from Section 2.3.1.3.5 to 2.3.1.2.5

Page 198: Second paragraph-final sentence changed from (Only one additional patient discontinued **therapy study**....) to read (Only one additional patient discontinued **study therapy**...)

Page 209: First paragraph, final sentence reference changed from — to [26]

Page 216: Final paragraph, third sentence, "rates of confirmed events, per 100 patient years at risk" for the 50 mg group corrected from —vents to 3 events.

Page 218: Table 61, AN5339 race corrected to Hispanic, AN5618 race corrected to white

Page 220: Second paragraph dose corrected for patient taking rofecoxib from — mg to 50 mg

Page 225-226: Table 64 -
Title corrected from "Listing of Potential Fatal and Nonfatal Serious Cardiovascular Thromboembolic Events Updated Cumulative Rheumatoid Arthritis Studies" to "Listing of Potential Fatal and Nonfatal Serious Cardiovascular Thromboembolic Events Updated Cumulative **Data for the** Rheumatoid Arthritis Studies"

Formatting change- Assigned therapy column changed so that the generic name precedes the dose.

Data sources at bottom of table updated from [48] to [48, 23, 27, 35, 41, 46]

Page 227: Table 65 -
The next to the last column was inappropriate and changed to what is now called "APTC Events (Utilizing Available Adjudication Diagnoses) (#) and appropriate data were inserted.

Data sources at bottom of table updated from [48] to [48, 23, 27, 35, 41, 46]

With this amendment, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing a Safety Update Report (SUR) for VIOXX™/S-012 which contains the intended version of the summary and its references and can replace the original SUR submitted on June 27, 2001..

As indicated on the attached Form FDA 356h, this submission provides for changes in the Safety Update Report section of the sNDA for rheumatoid arthritis. 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 Safety Update Report. 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 on their desktops may be obtained from Ms. Barbara Gould, Regulatory Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products.

We consider the filing of 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.

We apologize for any inconvenience this may cause in the Agency's review.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (484-344-2944) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely,

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

Attachment
Federal Express #1

Desk Copy: (Cover Letter)
Ms. Barbara Gould, Regulatory Project Manager
HFD-550, Room N353
Federal Express #2

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APPEARS THIS WAY
ON ORIGINAL

STATEMENT OF ORGANIZATION

NDA 21-042/S-012: VIOXX™ (Rofecoxib Tablets)
REVISED SAFETY UPDATE REPORT
Rheumatoid Arthritis

This Safety Update Report contains the following paper and/or electronic information:

ITEM(s)	DESCRIPTION	Contents on Archival CD	Review Aids	Paper Review Copies
1	Administrative Documentation containing Archival CD*	Yes	No	Blue Binder (1 volume)
9	Safety Update Report	Yes	No	Tan Binder (1 volume- Summary Only) Green Binder (1 volume- Summary Only)

TOTAL VOLUMES: 3

* The Archival CD is contained in Volume 1 (Blue Binder)

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

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June 27, 2001

MERCK
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Rockville, MD 20850

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

SAFETY UPDATE REPORT

Rheumatoid Arthritis

Reference is made to the supplemental New Drug Application (sNDA) cited above for VIOXX™ submitted as an electronic archive on February 28, 2001.

With this submission, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing a Safety Update Report (SUR) for VIOXX™/S-012. This report contains additional safety data for studies included in the sNDA for rheumatoid arthritis (RA). The data cutoff dates for protocols in the original application were: Protocol 068 and extensions on March 31, 2000; Protocol 096 on July 21, 2000; and Protocol 097 on June 06, 2000. The safety update reporting period extends from the day after data cutoff for protocols in the original RA application through November 21, 2000. The focus of this SUR is the newly accrued safety data from ongoing, large-scale clinical studies, and any corresponding extensions.

As indicated on the attached Form FDA 356h, this submission provides for changes in the Safety Update Report section of the sNDA for rheumatoid arthritis. All information is in an electronic format as indicated in the Table of Contents for this submission.

APPEARS THIS WAY
ON ORIGINAL

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 Safety Update Report. All documents requiring signatures for certification are included as paper for archival purposes.

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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 on their desktops may be obtained from Ms. Barbara Gould, Regulatory Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products.

We consider the filing of 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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (610-397-2944) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

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

Attachment
Federal Express #1

Desk Copy: (Cover Letter)
Ms. Barbara Gould, Regulatory Project Manager
HFD-550, Room N353
Federal Express #2

Q:Romanik/Christa.21042.6.25.01

STATEMENT OF ORGANIZATION

NDA 21-042/S-012: VIOXX™ (Rofecoxib Tablets)
SAFETY UPDATE REPORT
Rheumatoid Arthritis

This Safety Update Report contains the following paper and/or electronic information:

ITEM(s)	DESCRIPTION	Contents on Archival CD	Review Aids	Paper Review Copies
1	Administrative Documentation containing Archival CD*	Yes	No	Blue Binder (1 volume)
9	Safety Update Report	Yes	No	Tan Binder (1 volume- Summary Only) Green Binder (1 volume- Summary Only)

TOTAL VOLUMES: 3

* The Archival CD is contained in Volume 1 (Blue Binder)

Robert E. Silverman, M.D., Ph.D.
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June 27, 2001

Jonca Bull, M.D., Acting Director
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Rockville, MD 20852

Dear Dr. Bull:

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

AMENDMENT TO SUPPLEMENTAL NEW DRUG APPLICATION – PATENT INFORMATION (Rheumatoid Arthritis)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted in electronic format on February 28, 2001. Reference is also made to the Patent Information Update submitted on May 4, 2001.

As indicated on the attached Form 356h, this submission provides for changes in the Patent Section of the approved New Drug Application for VIOXX™.

Enclosed is an amendment to the Patent Information for VIOXX™ (rofecoxib tablets), 12.5, 25, and 50 mg tablets, under NDA 21-042 submitted in accordance with 21 CFR §314.53 on May 4, 2001. The expiration date of US 5,691,374 has been changed from November 11, 2017 to May 18, 2015 in accordance with data presented in the Orange Book. Similarly, the expiration date of US 6,063,811 has been changed from May 16, 2017 to May 6, 2017.

The patent information has been compiled by our patent attorney, Curtis C. Panzer using the FDA's suggested patent submission form.

For your convenience, enclosed please find a table listing the revised patent and expiration date corresponding to the noted patent.

All information is in an 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 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 Ophthalmologic Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Barbara J. Gould, Regulatory Project Manager, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products.

We consider the filing of this amendment 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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (610-397-2944) or, in my absence, to Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

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

Enclosure: CD

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Ms. Barbara J. Gould (cover letter only)
HFD-550, Room N353
Federal Express #3

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June 22, 2001

Jonca Bull, M.D., Acting Director
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Office of Drug Evaluation V

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Dear Dr. Bull:

NDA 21-042/S-012: 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 February 28, 2001, and a fax received June 19, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional statistical information.

By this submission, we are providing the requested information.

FDA Request 1
In regards to the supplemental New Drug Application NDA 21-042/S-012: VIOXX for Rheumatoid Arthritis, we request that Merck and Co., submit to the FDA an efficacy analysis of all randomized subjects and all randomized subjects who took at least one dose of the drug, for the ACR 20 efficacy endpoint (studies 096 and 097).

MRL Response 1
All randomized subjects took at least one dose of the drug in Protocols 096 and 097. The two populations referred to in the Agency's request, are in fact, one in the same. The requested analyses are provided in Attachment I.

All patients excluded from the primary analysis of the ACR 20 efficacy endpoint in the two pivotal trials (Protocols 096 and 097) were imputed to have no response and added to the analysis of all randomized subjects. In Protocol 096 there were 4, 2, 0, and 0 patients in the placebo, rofecoxib 12.5 mg, rofecoxib 25 mg, and naproxen groups, respectively, that were not included in the primary analysis of the ACR 20 endpoint reported in the CSR because they were missing either baseline or all on-treatment observations for some of the 7 ACR core endpoints. In Protocol 097 there were 4, 0, 2, and 1 patients in the placebo, rofecoxib 25 mg, rofecoxib 50 mg, and naproxen groups, respectively, there were not included in the primary analysis of the ACR 20 endpoint reported in the CSR for the same reasons. Imputing no response for these patients did not change the conclusions for any of the analyses, except the comparison of rofecoxib 25 mg versus rofecoxib 12.5 mg (Protocol 096) for which the p-value changed from 0.061 to 0.047. That is, for all other comparisons, all p-values which were > 0.05 as reported in the CSR's remained > 0.05 in these pure ITT analyses, and all which were < 0.05 remained <0.05.

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.

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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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director
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Enclosure: CD

Federal Express

Desk Copy (cover letter): Ms. Barbara Gould, Regulatory Project Manager
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Q:\Howley\Christa\21042\Response to FDA Request\006.doc

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May 16, 2001

Jonca Bull, M.D., Acting Director
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Dear Dr. Bull:

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

RESPONSE TO FDA REQUEST FOR INFORMATION
(Rheumatoid Arthritis)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on February 28, 2001 and a fax received May 11, 2001 from Ms. Sandra Folkendt (FDA) to Dr. Robert Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., requesting additional statistical information.

By this submission, we are providing the requested information.

FDA Request 1
Efficacy analyses on the following population: all randomized subjects, regardless of having any post-baseline data.

MRL Response 1
The results of the requested analysis are attached. All patients left out of the primary analysis of the primary endpoints in the two pivotal trials (Protocol Nos. 096 and 097) as submitted in the original SNDA were imputed to have zero change from baseline and added to the analysis. In Protocol No. 096, 11, 5, 4, and 0 patients in the placebo, rofecoxib 12.5 mg, rofecoxib 25 mg, and naproxen groups, respectively, were not included in the primary analysis reported in the clinical study report included in the original SNDA because they were missing either baseline or all on-treatment observations for at least one of the primary endpoints. In Protocol No. 097, 10, 2, 6, and 2 patients in the placebo, rofecoxib 25 mg, rofecoxib 50 mg, and naproxen groups, respectively, were not included in the primary analysis reported in the clinical study report included in the original SNDA for the same reasons. Imputing zero for these patients did not change the conclusions for any of the analyses. That is, all p-values which were > 0.05 as reported in the clinical study report remained > 0.05 in these pure ITT analyses, and all which were < 0.05 remained < 0.05.

FDA Request 2
Efficacy analyses on the following population: all randomized subjects who took at least one dose of drug, regardless of having any post-baseline.

MRL Response 2

In both Protocol Nos. 096 and 097, all randomized patients took at least one dose. The populations presented in FDA Request 1 and FDA Request 2 are the same; therefore, the attached analysis applies to FDA Request 2 as well.

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 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 Ophthalmologic Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Sandra Folkendt, Regulatory Project Manager, Division of Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products.

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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

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

Enclosure: CD

Federal Express

Desk Copy (cover letter): Ms. Sandra Folkendt, Regulatory Project Manager
HFD-550, Room N322

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Robert E. Silverman, M.D., Ph.D.
Senior Director
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May 4, 2001

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

MERCK
Research Laboratories

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: VIOXX™ (Rofecoxib Tablets)

Amendment to Supplemental New Drug Application – Patent Information
(Rheumatoid Arthritis)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on February 28, 2001, and a telephone conversation between Ms. Sandra Folkendt (FDA) and Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on April 25, 2001 regarding the Debarment Certification submitted on February 28, 2001.

As indicated on the attached Form FDA 356h, this amendment provides for updated Patent Information.

All information is in 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 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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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 filing of this amendment 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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

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

Federal Express

Desk Copy: Ms. Sandra Folkendt, Project Manager
HFD- 550, Room N322

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APPEARS THIS WAY
ON ORIGINAL

Robert E. Silverman, M.D., Ph.D.
Senior Director
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MERCK
Research Laboratories

March 23, 2001

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

Submitted through

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: VIOXX™ (rofecoxib tablets)

Amendment to Supplemental New Drug Application
(Rheumatoid Arthritis)

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on February 28, 2001, and a telephone conversation between Dr. Bart Ho (FDA) and Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on March 19, 2001 regarding the Environmental Assessment submitted on February 28, 2001.

As indicated on the attached Form FDA 356h, this amendment provides for changes to the administrative documentation of the approved New Drug Application for VIOXX™. The original cover letter inadvertently contained the incorrect environmental assessment exclusion criteria. The following is the revised language:

> Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b). The supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(b) because the estimated concentration of the substance at the point of entry into the environment will be below 1 part per billion. To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

All information is in 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 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.

We consider the filing of this amendment 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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

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

Federal Express

Desk Copy: Ms. Sandra Folkendt, Project Manager
HFD- 550, Room N322

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APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF CONSULTATION

DATE: March 14, 2002

FROM: M. F. Huque, Ph.D.
Division of Biometrics III/OB/OPSS/CDER/
HFD-725

TO: Lawrence Goldkind, M.D.
Division of Anti-inflammatory, Analgesic and Ophthalmologic Drug Products/
HFD-550

SUBJECT: NDA 21-042/ Rofecoxib Labeling Comments

Documents Reviewed: 1) Merck draft of 15 Feb 2002
2) Merck "VIGOR Cardiovascular Hazard Rates Analysis"

I have done a few analyses of the VIGOR cardiovascular events data. The results are summarized in Tables 1 and 2, and in Figures 1 and 2. The Rofecoxib group tends to show different hazard rate pattern than the ——— group. This difference appears during the 8-12 month interval. The data cast doubt on the constant hazard rate assumption for the Rofecoxib group.

The above 2 tables and figures along with this memorandum document may be shared with the sponsor for them to consider the following:

1. Crude rates will not be appropriate because effective sample size decreases over time.
2. Incidence rate (per patient-years) calculations on assuming constant hazard rate for the Rofecoxib group for this data is hard to justify.

I suggest that the sponsor consider including following information regarding CV events in the revision of their draft-labeling document.

3. Twelve-month cumulative incidence rates, by treatment groups, for example, by the Kaplan-Meier or Life-Table method, along with the total number of events.
4. Graphical displays with respect to time, e.g., cumulative hazard rate plots, to convey total risk picture over time conveyed by the data, along with the log-rank test p-value for the between treatment comparison.
5. Relative risk estimate and confidence interval using Cox-regression, if convinced that the proportional hazard assumption is at least approximately valid. Otherwise, actuarial relative risk estimates and confidence intervals for appropriate time intervals, e.g., 4-month intervals.
6. Table 1 (p. 8) and Table 2 (p. 10) need to be similar in including the type of information.

Attachments:

Table 1 gives hazard rate estimates for every 4-month intervals and confidence intervals for the cardiovascular events only

Table 2 gives hazard rate estimates for every 4-month intervals and confidence intervals for all events (data extracted from the sponsor's Table 1 of the document "VIGOR Cardiovascular Hazard Rates Analysis."

Figure 1 gives cumulative hazard rate plot (also known as -log (S) plot) for the cardiovascular events only

Figure 2 gives hazard rate plot (unit is month). Multiply by 12 when reading this plot for hazard rate/year

cc:
HFD-550
HFD-550/Ms. Gould
HFD-550/Dr. Goldkind
HFD-725/Dr. Stan Lin
HFD-725/Dr. Qian Li
HFD-725/Dr. Huque
HFD-700/Dr. O'Neill
HFD-700/Dr. Anello

***Table 1 :* Hazard Rate Estimates**
Cardiovascular Events Only (Rofecoxib 45 versus ~~~ 19)
(Data extracted from the sponsor's electronic data file)

Rofecoxib Group

By Every 4 Months	d= number of Events	Number censored	Effective Sample Size (n-w/2)	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
0-4	17	625	3734.5	1245	1.36%	0.3324	(0.69, 2.02)
4-8	12	587	3111.5	1037	1.16	0.3348	(0.49, 1.83)
8-12	16	2733	1439.5	480	3.35	0.8388	(1.67, 5.03)

~~~ Group

By Every 4 Months	d= number of Events	Number censored	Effective Sample Size (n-w/2)	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
1-4	~~~	625	3716.5	1239	0.73%	0.2424	(0.25, 1.21)
4-8	~~~	591	1033.2	1033	0.58	0.2376	(0.10, 1.06)
8-12	~~~	2734	1431.0	477	0.84	0.4200	(0.00, 1.68)

***Table 2 :* Hazard Rate Estimates**
Total events Rofecoxib 64 versus ~~~ 32
(Data extracted from the sponsor's Table 1)

Rofecoxib Group

Months	d= number of Events	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
1-4	26	1232	2.13%	0.418	(1.30, 2.97)
4-8	17	1056	1.62	0.394	(0.84, 2.41)
> 8	21	407	5.30	1.156	(2.98, 7.61)*

*Non-overlapping interval with previous 2 intervals

~~~ Group

Months	d= number of Events	Patient-years at risk	h=hazard rate	SE(h)	h ± 2*SE
1-4	14	1231	1.144%	0.306	(0.53, 1.76)
4-8	12	1055	1.144	0.330	(0.48, 1.80)
> 8	6	410	1.474	0.602	(0.27, 2.68)**

** Overlapping interval with previous 2 intervals

References for Computing Formulas: