If you have any questions, call Sandra N. Folkendt, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Lawrence Goldkind, M.D.
Medical Officer Team Leader
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/s/

Jonca Bull
2/28/01 01:59:39 PM

APPEARS THIS WAY
ON ORIGINAL

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

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Tel 610 397 2944
215 652 5000
Fax 610 397 2516

February 5, 2001

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

MERCK
Research Laboratories

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

Reference is made to the above supplemental New Drug Application (sNDA) a fax received on January 22, 2001; and a teleconference between representatives of the Agency and Merck Research Laboratories (MRL), a Division of Merck & Co., on January 24, 2001. During the teleconference, the Agency requested a listing table by individual studies of patient numbers per dose of rofecoxib or comparator with duration of exposure.

By this letter and attachments MRL is providing responses to the Agency requests.

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.

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.

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

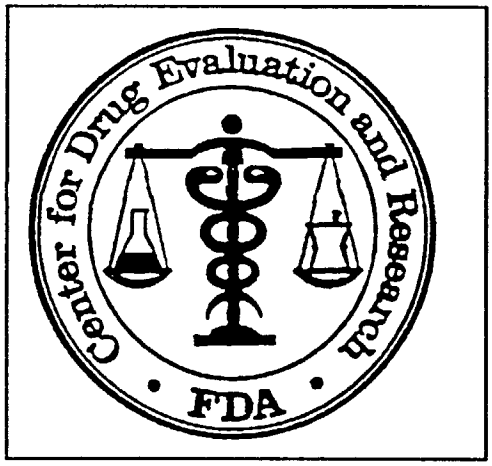
Federal Express #1

Attachment

Desk Copy (cover letter only): Sandra Folkendt, HFD-550, N322
Federal Express #2

Q:\howley\christa\21042\response10.doc

FACSIMILE TRANSMISSION
RECORD



From: Sandra Folkendt

Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 1/11/01

To:

Name: Robert Silverman, M.D.
Company: Merck
City: State:
Phone #: (610) 397-2944

FAX #: (610) 397-2516

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

Hi Bob,

Please provide the following for NDA 21-042/S-007:

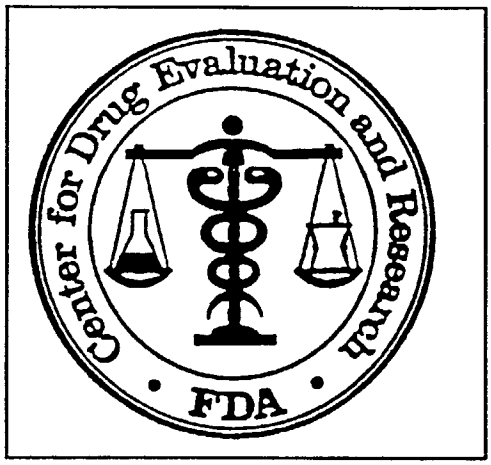
1. Mean dose of MTX in each treatment group.
2. Analysis of serious adverse experiences by body system in MTX users and non-MTX users in the VIGOR study.
3. Table of laboratory AE's (similar to Table 62) in MTX and non-MTX users in the VIGOR study.

Please call me if you have any questions.

Thanks,

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE TRANSMISSION
RECORD



From: Sandra Folkendt

Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date:

To:

Name: Robert Silverman, M.D.
Company: Merck
City: State:
Phone #: (610) 397-2944

FAX #: (610) 397-2516

Number of Pages (INCLUDING COVER PAGE): 1

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

Hi Bob,

I have a couple of more requests for the reviewers for NDA 21-042/S-007:

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

- Please submit the CRF's of all patients who withdrew consent.

Thanks,

Sandy

APPEARS THIS WAY
ON ORIGINAL

Sandy, please also ask the sponsor to provide the cause of protocol deviation for each patient and if the information is in the submission, to direct me to to the appropriate section.

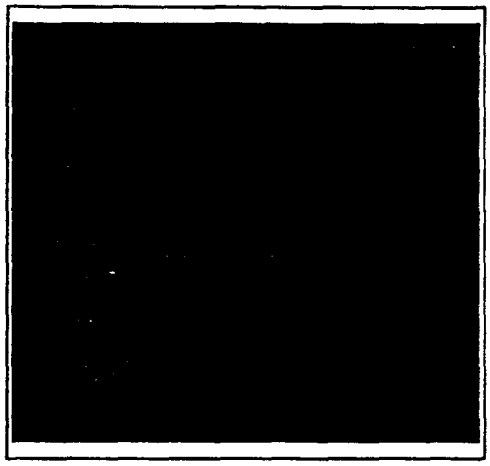
thank you

Lourdes

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE TRANSMISSION RECORD

APPEARS THIS WAY ON ORIGINAL



From: Sandra Folkendt

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date:

To: Name: Robert Silverman, M.D.
Company: Merck
City: State:
Phone #: (610) 397-2944

FAX #: (610) 397-2516

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

Bob,

The attached request is from the statistical reviewer for NDA 21-042/S-007. Please call me if you have any questions.

Thanks,

Sandy

APPEARS THIS WAY ON ORIGINAL

In the Patient Accounting table you provided, discontinuations due to

death and GI events were counted as discontinuation due to clinical AEs or laboratory AEs.

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

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

Electronic Mail Message

Date: 12/29/00 3:59:45 PM
From: Maria Villalba (VILLALBAM)
To: Sandra Folkendt (FOLKENDTS)
Subject: question to MERCK

Please forward the following question to the sponsor:

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

Thank you

Lourdes

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 12/14/00 10:56:32 AM
From: Maria Villalba (VILLALBAM)
To: Sandra Cook (COOKS)
Cc: Lawrence Goldkind (GOLDKINDL)
Subject: vigor

Please ask the sponsor to submit the CRF's of all patients who withdrew consent.

Thank you

Lourdes

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

Date: 12/11/00 11:52:10 AM
From: Maria Villalba (VILLALBAM)
To: Sandra Cook (COOKS)
Cc: Lawrence Goldkind (GOLDKINDL)
Cc: Shari Targum (TARGUMS)
Subject: VIGOR-request to Merck

Sandy, please ask the sponsor to provide an analysis of patients who had a change in creatinine of 25% above baseline in the VIGOR study.

Thank you

Lourdes.

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ned Braunstein, MD	**From:** Barbara Gould
Fax: 732 594-1030	**Fax:** 301 827-2531
Phone: 732 594-2886	**Phone:** 301 827-2504
Pages: 1(including cover)	**Date:** 29-March-02
Re: NDA 21-042/S-007	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

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

Please call if you have any question(s).

BJ Gould

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ned Braunstein, MD	**From:** Barbara Gould
Fax: 732 594-1030	**Fax:** 301 827-2531
Phone: 732 594-2886	**Phone:** 301 827-2504
Pages: 6 (including cover)	**Date:** 18-March-02
Re: NDA 21-042/S-007 Study 078	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

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

Please call if you have any question(s).

BJ Gould

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products

Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ned Braunstein, MD	**From:** Barbara Gould
Fax: 732 594-1030	**Fax:** 301 827-2531
Phone: 732 594-2886	**Phone:** 301 827-2504
Pages: 6 (including cover)	**Date:** 18-March-02
Re: NDA 21-042/S-007, 012 Statistical Analysis for Label	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Please call if you have any question(s).

BJ Gould

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2504
Pages: 1 (including cover)	**Date:** 19-February-02
Re: NDA 21-042 Alzheimer's Study	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

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

Thanks,

BJ Gould

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 14-December-01

Re: NDA 21-042/S-012 Clinical Information Request

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Please provide the individual study reports for Studies # 098 and #103 for review for NDA 21-042/S-012 for rheumatoid arthritis indication.

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 05-December-01
Re: NDA 21-042/S-007	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Please provide the location of the following information for review for NDA 21042/S-007 VIGOR:

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

Have these oversight groups commented on the ethics of continuing study 078 in light of the mortality data and the fact that [redacted] because of lack of efficacy in study 091?

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 2 (including cover)	**Date:** 14-Nov-01
Re: NDA 21-042/S-007 Clinical Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

For the Vigor database:

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

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

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

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

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 19-October-01

Re: NDA 21-042/S-007 Clinical Information Request

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

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

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 22 (including cover)	**Date:** 15-October-01

Re: NDA 21-042/S-007 and NDA 21-052/S-004 Draft Label Proposal

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 02-October-01
Re: NDA 21-042/S-008	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Please provide the location of the following information for review for NDA 21042/S-008:

For all biopharm studies please provide the location of the raw data in the electronic submission. If the raw data was not included please provide as an electronic document.

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 01-October-01
Re: NDA 21-042/S-007	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Please provide the location of the following information for review for NDA 21042/S-007 VIGOR (study 088/089:

- Cumulative rates of confirmed (adjudicated) serious cardiovascular thrombotic events for all randomized patients and by subgroup of patients who may have been potential candidates for cardiovascular prophylaxis.

- Cumulative rates of Hypertension, edema and CHF -related discontinuations.

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 26-September-01
Re: NDA 21-042/S-007 Clinical Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

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

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 26-September-01

Re: NDA 21-042 Vigor Study Information Request

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Please provide the following information for review:

1. Summary table of GI safety events (table 3 of sponsor's proposed label) expressed in cumulative rates for PUBs and Complicated PUBs.

2. Table of cumulative incidence and relative risk of complicated and uncomplicated ulcers by age (<65 and ☐65 years) and by history of prior symptomatic upper GI ulcers.

3. Calculation of relative risk of developing serious CV/thrombotic events for VIOXX compared to naproxen based on cumulative rates.

4. Calculation of relative risk of discontinuations due to HTN- and edema-related events as well as CHF related events for VIOXX compared to naproxen based on cumulative rates.

Please call if you have any questions.

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 12-September-01

Re: NDA 21-042/S007 Clinical Information Request

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

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

Please call if you have any questions.

Thanks,

BJ

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 07-September-01
Re: NDA 21-042 Clinical Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

As per our conversation on 06-Sep-01, please provide the following clinical information for review for NDA 21-042 S-007/012 along with the two additional requests (3&4):

1. Please provide the location of the analyses of vital signs and ECG in the RA database.
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.
3. 21-042/s007---Please provide analyses of HTN-related, edema related and CHF related events in the Alzheimer's studies.
4. 21-042/s012---Please provide patient-years at risk in study 068.

Please call if you have any questions.

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products

Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** 08-August-01
Re: NDA 21-042 Clinical Information Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

- Comments:

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

Please call if you have any questions.

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products

Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 484 344-2516	**Fax:** 301 827-2531
Phone: 484 344-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** July 18, 2001

Re: NDA 21-042 S-012 Clinical Information Request

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Please provide the following clinical information for review for NDA 21-042 S-012:

1. Please provide where in the RA submission the cardiovascular adjudication packages are located?

2. 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.)

3. 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 of exposure.

Please call if you have any questions.

Thanks,

BJ Gould

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert E. Silverman, MD	**From:** Barbara Gould
Fax: 610 397-2516	**Fax:** 301 827-2531
Phone: 610 397-2944	**Phone:** 301 827-2019
Pages: 2 (including cover)	**Date:** July 2, 2001
Re: NDA 21-042 S-007	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

1. Please provide the correct table for serious investigator reported CV events by aspirin/non aspirin use.

2. Several of the narratives submitted on 6/14/01 are not clear about what was the assigned therapy at the time of unblinding. Attached is one example. Please provide a list of correct treatment allocation for all narratives submitted on that date.

Please call if you have any questions.

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert Silverman	**From:** Barbara Gould
Fax: 610 397-2516	**Fax:** 301 827-2531
Phone: 610 397-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** June 22, 2001

Re: NDA 21-042 S-007 Exclusion from Safety Update Report

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Reference is made to the Approvable letter issued to NDA 21-042-s007 in April 6, 2001. Once the Safety Update Report (SUR) is provided to the Agency, we will consider that a complete response has been submitted.

In order to expedite the submission of the SUR, we accept your proposal not to include studies —, 112, 116, 905 —— in the forthcoming SUR. However, you should submit all available data from these studies as part of the Four-month Safety Update.

Please call if you have any questions.

BJ Gould

APPEARS THIS WAY
ON ORIGINAL

Fax

Division of Anti-Inflammatory, Analgesic, Ophthalmic Drug Products
Center for Drug Evaluation and Research, HFD-550
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Robert Silverman	**From:** Barbara Gould
Fax: 610 397-2516	**Fax:** 301 827-2531
Phone: 610 397-2944	**Phone:** 301 827-2019
Pages: 1 (including cover)	**Date:** June 22, 2001
Re: NDA 21-042 S-007 Request for Information	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐**Please Reply** ☐ **Please Recycle**

● Comments:

Please provide the following request for information for NDA 21-042 S-007:

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.

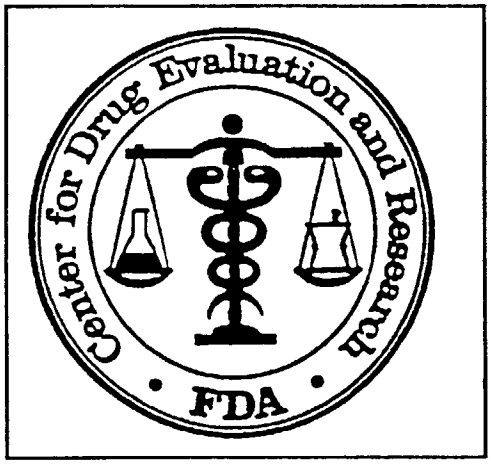
2. Why the number of low dose ASA users in Table 39 (352 and 367 in rofecoxib and naproxen respectively) is different from the numbers given in table 10 of the CSR (355 and 369 for rofecoxib and naproxen respectively).

Please call if you have any questions.

BJ Gould

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE TRANSMISSION
RECORD



From: Sandra Folkendt

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 2/14/01

To:

Name: Robert Silverman, M.D.
Company: Merck
City: State:
Phone #: (610) 397-2944

FAX #: (610) 397-2516

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

Hi Bob,

See the following requests for NDA 21-042/S-007:

This is what I would like to ask Merck

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

2. Complete report of study 102 (Advantage)

Electronic Mail Message

Date: 2/13/01 2:49:07 PM
From: Maria Villalba (VILLALBAM)
Subject: Request for additional data

This is what I would like to ask Merck

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

2) Complete report of study 102 (Advantage)

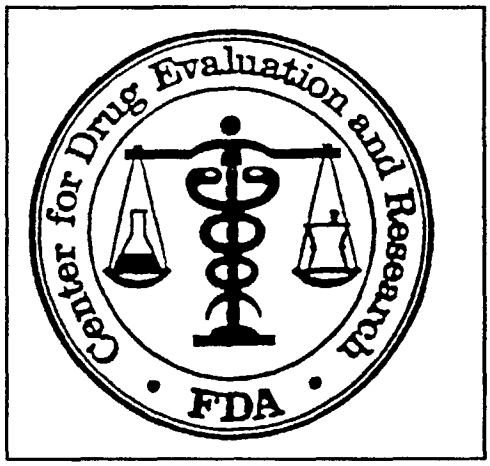
[ ]

Please see if you agree. Thank you

Lourdes

APPEARS THIS WAY
ON ORIGINAL

FACSIMILE TRANSMISSION
RECORD



From: Sandra Folkendt

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 2/2/01

To:

Name: Robert Silverman, M.D.
Company: Merck
City: State:
Phone #: (610) 397-2944

FAX #: (610) 397-2516

Number of Pages (INCLUDING COVER PAGE): 1

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

Hi Bob,

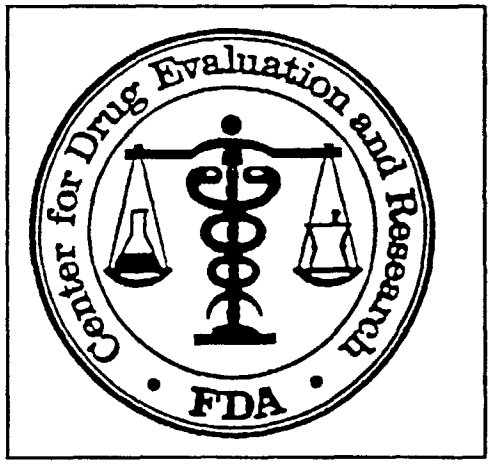
See the following request for NDA 21-042/S-007:

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

Also, provide a list as to when the previous requests will be forwarded.

Please call me if you have any questions.

FACSIMILE TRANSMISSION RECORD



From: Sandra Folkendt

Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 1/31/01

To:

Name: Robert Silverman, M.D.
Company: Merck
City: State:
Phone #: (610) 397-2944

FAX #: (610) 397-2516

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

Hi Bob,

Please see the attached request for NDA 21-042/S-007:

Please call me if you have any questions.

Thanks,

Sandy

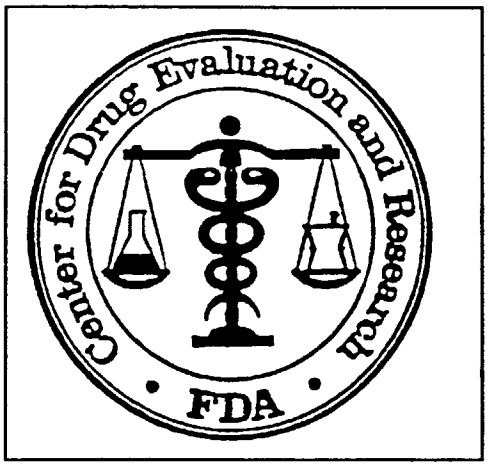
APPEARS THIS WAY
ON ORIGINAL

Please clarify the Table of Hospitalizations submitted on January 19, 2001.

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

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

FACSIMILE TRANSMISSION
RECORD



From: Sandra Folkendt

Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

Phone 301-827-2090
Fax 301-827-2531

Date: 1/22/01

To:

Name: Robert Silverman, M.D.
Company: Merck
City: State:
Phone #: (610) 397-2944

FAX #: (610) 397-2516

Number of Pages (INCLUDING COVER PAGE): 2

Please telephone (301) 827-2090 IMMEDIATELY if re-transmission is necessary.

Hi Bob,

Please see the attached request for NDA 21-042/S-007:

Please call me if you have any questions.

Thanks,

Sandy

Table1 . Exposure to rofecoxib in all studies included in the meta-analysis of CV events.

	≥ 6 weeks	≥ 6 months	≥ 9 months	≥12 months
Any dose < 12.5 mg				
12.5 mg				
25 mg				
50 mg				
> 50 mg				

Table 2. Exposure to placebo and nonselective NSAIDs in studies included in the meta-analysis

	≥ 6 weeks	≥ 6 months	≥9 months	≥ 12 months
Placebo				
Ibuprofen				
Naproxen				
Nabumetone				
Diclofenac				

Table 3 – Same as table 1 but without VIGOR.

Table 4 – Same as table 2 but without VIGOR.

TELECON MINUTES

TELECON DATE: March 20, 2002 **TIME:** 10:00 a.m. **LOCATION:** Corp S314

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

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
Maria L. Villalba, MD	Medical Reviewer
Stan Lin, Ph.D.	Biostatistics Team Leader
Lisa Hubbard, RPh	Labeling Reviewer
Barbara Gould	Project Manager
Robert O'Neill, Ph.D.	Director, Office of Biostatistics

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

DISCUSSION:

The Division position is that the best way to display cardiovascular data from VIGOR in the label is to include a representation of the event rates over time of study as in the [redacted] of adjudicated cardiovascular thrombotic events, and an additional table that summarizes important information on relative risk estimates, events and numbers of persons in trial.

The Division does not agree with the display of the CV data as events per 100 patient years because relative risk is presented as a single number which, by its very definition, assumes that the hazard rate is constant over the 12 months of the study (an average over the 11 month period that does not reflect different risk over time). Our analyses strongly suggest that the data does not support this assumption and that, in contrast, there is considerable evidence to suggest that the hazard rate is not constant and that therefor no single incidence rate metric adequately summarizes the incidence rate over time.

Merck does not want the [redacted] of cardiovascular thrombotic events because the [redacted] of cumulative risk makes it look as if the hazard rate changed over time, when in fact, their multiple analyses demonstrate that it is not the case.

FDA does not agree with Merck's conclusions. Failure to demonstrate a statistically significant difference does not prove that there is no difference in hazard rates over time. Since VIGOR was not specifically designed and adequately powered to show statistically significant differences in hazard rates of CV events, the number of observed events, though pictorially consistent with an increasing hazard rate, does not allow for demonstrating statistically significant evidence for an increasing hazard rate for the adjudicated CV events using available methodology that is recognized as having low power to do so. This does not mean that the lack of evidence for an increasing hazard rate is adequately better supported by the data to conclude that the hazard rate is constant.

Statistical analyses of cardiovascular thrombotic events done by Dr. Huque (March 14, 2002) suggest that the relative risk of developing cardiovascular thrombotic events for VIOXX relative to naproxen is not constant over time, and that it is higher after 8 months. In particular, the estimated hazard rate of adjudicated cardiovascular thrombotic events over the 0-4, 4-8 and 8-12 month periods were 1.36 %, 1.16% and 3.35% for VIOXX and 0.73%, 058% and 0.84% for naproxen, respectively. Table 2. of Dr. Huque's review shows all investigator reported serious cardiovascular thrombotic events. Analyses of this dataset are entirely consistent with the analyses of adjudicated events, and because of the larger number of numerator events, does illustrate non-overlapping confidence intervals for Vioxx when comparing the 0-4 month interval with the 8-12 month interval.

(Of note, the memo submitted by Dr. Huque had typographical errors in Table 1. (number of adjudicated cardiovascular thrombotic events for naproxen). The table lists [redacted] instead of 9, 6 and 4 (for the number of events) for the 1-4, 4-8 and 8-12 month periods. However, the statistical analyses and calculations of hazard rates and relative risks were done with the correct numbers.and the results in table 1 are correct). Merck is aware that this was a typographical error in the materials sent to them prior to the telephone conference call.

Merck's proposal to display a table of cumulative incidence rate for all adjudicated CV thrombotic events (along with relative risk, 95% CI and p value) and number of events (without cumulative rates but with p values for all cardiac events and MI), is better than their proposal for the display of rates per 100 patient years but still is not the optimal way to present the data.

Of note, the cumulative incidence rate of adjudicated CV thrombotic events is 1.8 % and 0.6 % for the VIOXX and naproxen groups respectively. Taking the ratio of these two cumulative incidence rates provides a 3 fold increase in risk, ie relative risk. However, the estimated relative risk based on the COX proportional hazard rate analysis is 2.37. The reason for this discrepancy is that the Cox models is an average hazard rate over the 12 months and since the rate is very suggestive of increasing in the latter part of 12 months, these two estimates do not agree. That is the motivation for presenting the ——— over 12 month time period.

Merck strongly disagrees with ——— Merck was encouraged to provide different ways of presenting these cardiovascular data for agency review. The Division expressed an understanding that the transient decrease in event rate at the 6-7 month point gives an exaggerated visual appearance to the ——— However, changes in rate over time must be addressed in labeling.

ACTION ITEMS:

1. The Division will consider a predecisional meeting to discuss statistical presentation of data in the label.
2. Merck will submit updated draft label and Patient Product Information (PPI) for the VIOXX™ VIGOR sNDA based on discussions held on March 20, 2002.
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

Attachments:

1. March 14, 2002 Memorandum of Consultation from Dr. Huque
2. Addendum to the Memorandum of Consultation of March 14, 2002

Initialed by: ONeillR/*22-Mar-02*

TELECON MINUTES

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

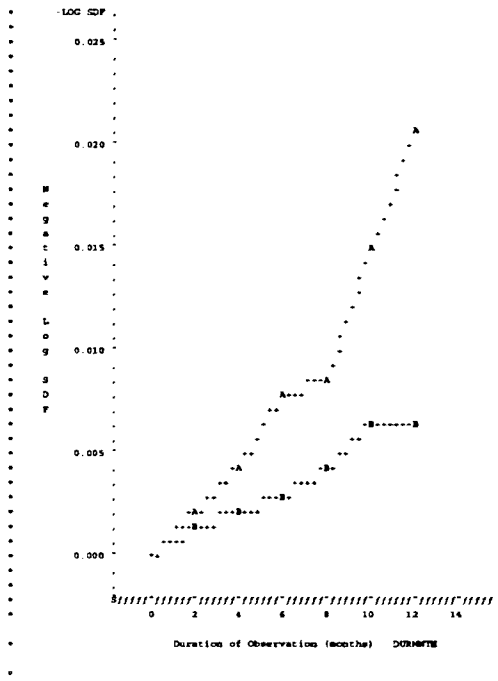
Figure 2 gives hazard rate plot (unit is month). Multiply by 12 when reading this plot for hazard rate/year

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

1. Gehan's Large-sample Formula *1969 J. Chron. Dis. 21, 629-644*
2. SAS: PROC LIFETEST Program

Figures 1 and 2 are also included as power point documents

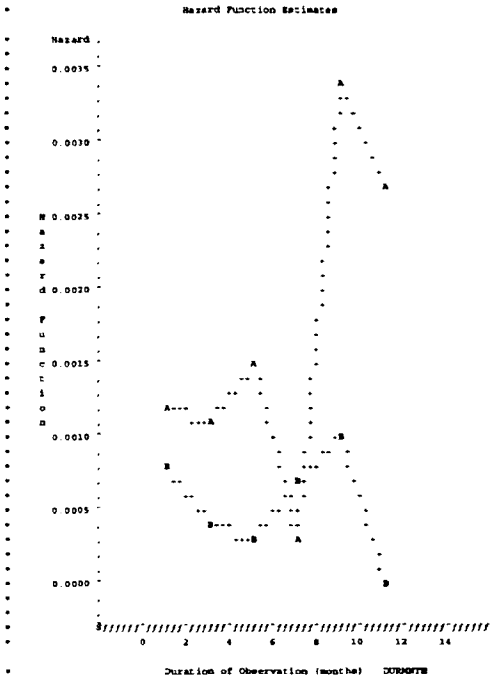
Figure 1: Plot of the Cumulative Hazard Function
-Log(Survival Function) Estimates
Cardiovascular Events Only (A, 45 events; B, 19 events)
(A=Vioxx 50 mg/day; B= ——— 1000 mg/day)



APPEARS THIS WAY
ON ORIGINAL

Figure 2:
Hazard Function Estimates

Cardiovascular Events Only (A 45 events; B, 19 events)
(A=Vioxx 50 mg/day; B= 1000 mg/day)
(Note: The hazard rate in the figure needs to be multiplied by 12 for the rate per year)



APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF CONSULTATION (Addendum to the Memorandum of March 14, 2002)

DATE: March 20, 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: Memorandum of March 14, 2002/
NDA 21-042/ Rofecoxib Labeling Comments

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

This memorandum corrects a few typographical errors that were found in column (2) and (4) of Table 1 of the Naproxen group. This table was sent to you as an attachment of the memorandum of March 14, 2002. The new revised table is labeled as "Table 1 (Revised)" to distinguish it from the old table "Table 1". The old table however had correct hazard rate estimates, standard error of the estimates and confidence intervals for drawing statistical conclusions.

All my earlier comments and suggestions included in the March 14 memorandum hold and do not change.

Attachment:
Table 1 (Revised) gives hazard rate estimates for every 4-month intervals and confidence intervals for the cardiovascular events only, total 45 CV events for the Rofecoxib group and total 19 CV events for the Naproxen group.

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 (REVISED) :* Hazard Rate Estimates**
Cardiovascular Events Only (Rofecoxib 45 versus Naproxen 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)

Total 45 Events

Naproxen 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	9	625	3716.5	1239	0.73%	0.2424	(0.25, 1.21)
4-8	6	591	3099.5	1033	0.58	0.2376	(0.10, 1.06)
8-12	4	2734	1431.0	477	0.84	0.4200	(0.00, 1.68)

Total 19 Events

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
4/18/02 09:52:01 AM

APPEARS THIS WAY
ON ORIGINAL

TELECON MINUTES

MEETING DATE: March 07, 2002 **TIME:** 2:00 P.M. **LOCATION:** Corp N351

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

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
Maria L. Villalba, MD	Medical Reviewer
Stan Lin, Ph.D.	Biostatistics Team Leader
Lisa Hubbard, RPh.	Labeling Reviewer
Barbara Gould	Project Manager
Robert O'Neill, Ph.D	Director, Office of Biostatistics (Joined the teleconference at 3:40 P.M.)

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

DISCUSSION: