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

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

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February 5, 1999

Robert DeLap, M.D. Ph.D., Acting Director
Division of Anti-inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550, Room N322
Office of Drug Evaluation V (CDER)
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

BL

ORIG AMENDMENT

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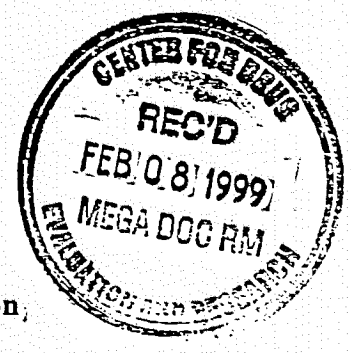
Research Laboratories



Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets
NDA 21-052: VIOXX™ (Rofecoxib) Oral Suspension

GENERAL CORRESPONDENCE

Reference is made to the above New Drug Applications (NDAs) submitted on November 23, 1998. Merck Research Laboratories (MRL) has become aware of several minor errors in the NDA documentation of proposed product labeling (bottles and cartons) and a few of the annotations to the proposed product circular (Item 2, NDA volume 1.2). By this letter and attachments MRL is providing the following:

- Correction to the storage statement for bottle labels and cartons.
- Corrections to annotations #17, 20, and 255 in the proposed Package Circular.

Attached for submission are the following revised draft bottle labels and cartons for VIOXX. Please note that, on each component, the submitted storage statement, "Store at 25° (77°C), excursions permitted to 15-30°C (59-86°F)," was corrected to read as follows:

"Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F)."

Tablets VIOXX 12.5 mg and 25 mg

unit dose packages of 100 [front, bottom, and back panel labels only]
NOTE: The 12.5 mg and 25 mg unit dose packages of 100 blister mats do not contain storage information.
bottles of 100 (bulk package)
bottles of 1000 (bulk package)
bottles of 8000 (bulk package)

DUPLICATE

Please note that the submitted storage statement on the following components is correct:

Tablets VIOXX 12.5 mg and 25 mg

unit of use bottles of 30
unit of use bottles of 90

Oral Suspension VIOXX 12.5 mg/5mL and 25 mg/5mL

unit of use bottles containing 150 mL - bottle label
unit of use bottles containing 150 mL - carton label

Also, the inactive ingredients listed on the bottle labels and cartons for Oral Suspension VIOXX each began with a capital letter. These were changed to lower case letters throughout.

Lastly, a recent review of the annotations associated with the proposed package circular disclosed that certain parts of annotations #17, 20, and 255 were incorrect. The corrections for each are listed below.

Annotation Number	Correction
17	[Biopharm Ref. P012: p. 37] This annotation is the correct page in the NDA, but it is hyperlinked incorrectly in the electronic submission for both NDA #21-042 and NDA #21-052.
20	[Biopharm Ref. P002: p. 63-64, 69] Pages 63-64 are incorrect. These should be pages 48-56. Page 69 is correct.
255	[Clinical Ref. P061: p. 108, 745] should read [Clinical Ref. P069: p. 112, 745].

Please direct any questions or need for additional information 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

Federal Express #1

Desk copy: Sandra Cook, Project Manager, HFD-550, Room N322, Federal Express #1

Q\Michener\DeFusco\NDA21-042B

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

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DUPLICATE

NDA ORIG AMENDMENT

February 9, 1999

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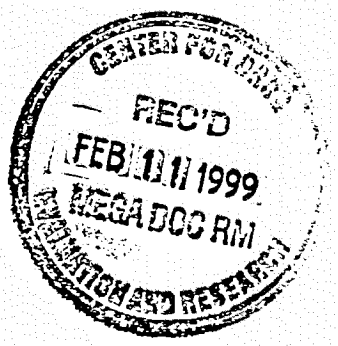

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets
Response to FDA Request

Reference is made to the above New Drug Application (NDA) and to an e-mail sent to Dr. R. Silverman (Merck Research Laboratories [MRL]) from Ms. Sandra Cook (FDA) on February 9, 1999 containing a request for information from the medical reviewer. By this letter, MRL is providing a response to the Agency's request.

FDA Comment: Please send the detailed statistical methodology including model and covariates used for the integrated analysis that generated the best fit dose response curves (studies 010 and 029). We did find the paragraph mentioning that a pooled analysis might be performed, but there was no description as to how the analysis would be performed.

MRL Response: The following non-linear (three-parameter logistic) model was fit for each set of Least Squares means plotted as data points on each of Figures D-4, D-5, and D-6 in Section D of the Clinical Documentation Volume (Vol.1.94):

$$y = (a)/(1+(x/c)^b)$$

where y=response variable (LSmean difference from placebo)
x=log(dose)
a, b, c = model parameters to be fitted by maximum likelihood
(No covariates were included)

This is a standard model for an s-shaped (sigmoidal) dose-response curve. It derives from the standard four-parameter logistic model

$$y = (a-d)/(1+(x/c)^b)$$

with the "d" parameter set to zero to force the fitted curve through the origin, since zero response is assumed for zero dose (i.e., since the response variable is difference from placebo). SAS PROC NLIN was used for the computations.

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.

If you have any questions or need additional information please contact Robert 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

q/mcs/ltr/594

Federal Express

Desk Copy: Ms. Sandra Cook, HFD-550 CRP2 N317, Federal Express #1

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

DUPLICATE

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February 9, 1999

NDA ORIG AMENDMENT
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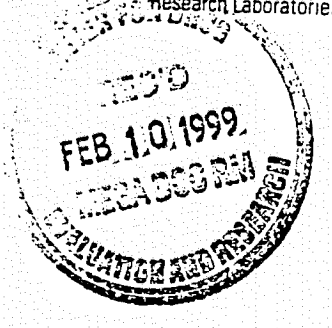

Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20857

NDA 21-042: VIOXX™ (Rofecoxib) Tablets

Dear Dr. DeLap

Reference is made to the above New Drug Application (NDA) submitted November 23, 1998 and to a telephone conversation between Dr. J. Carreras (FDA) and Dr. R. Silverman (MRL) on January 27, 1999, and a follow up telefax from Dr. Carreras on the same day requesting documentation to aid the Agency in clinical site inspections.

By copy of this letter, we are providing Dr. Carreras with a single copy of the documentation designated in his telefax. Information is provided for the following clinics:

Primary Investigator	Study No.	Volume No.
James McKay	033-041	1
Peter Holt	035-018	2
Maria Jurado	058-015	3
Steven Christensen	066-001	4
Stephen Daniels	056-001	5
Maurice Jove	072-008	6
Howard I. Schwartz	044-032	7

Please direct questions or need for additional information 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

Attachments:

Federal Express # 1 (cover letter only)

cc: (cover letter only) Federal Express #1
Ms. Sandra Cook, Project Manager, HFD-550

cc: (cover letter with attachments) Federal Express #2
Dr. Jose Carreras
Office of Compliance
HFD-344
7520 Standish Place
Rockville, MD 20855

Q/YELO/NDA21-042

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

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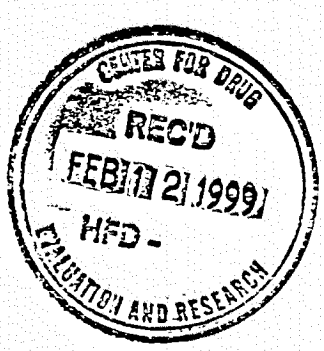
DUPLICATE

NDA ORIG AMENDMENT

February 11, 1999

BZ

MERCK
Research Laboratories



Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets
Response to FDA Request

Reference is made to the above New Drug Application (NDA) and to an e-mail sent to Dr. R. Silverman (Merck Research Laboratories [MRL]) from Ms. Sandra Cook (FDA) on February 8, 1999 containing a request for information from the medical and statistical reviewer. By this letter, MRL is providing a response to the Agency's request.

FDA Comment: Please provide the efficacy data and analyses of studies 034 and 035 up to 12 months SEPARATELY. (FDA does not accept pooled data for efficacy claims; this is documented in the meeting minutes of 5/26/96).

MRL Response: As discussed with the Agency during the May, 1996 meeting and documented in the Protocols for 034 and 035, the primary analysis of efficacy for each study was based on the assessment of the predefined primary efficacy endpoints after 12 weeks of treatment. It is the 12 week results which were replicated in 034 and 035 that are the bases for MRL's claim of efficacy in the treatment of OA comparable to diclofenac. Replicative secondary assessments of efficacy, made after 26 weeks of treatment for each study, separately, corroborated the primary efficacy seen at 12 weeks in each study and are reported in the respective clinical study reports.

The prespecified combined analysis of Protocols 034 and 035 for treatment durations beyond 6 months was designed to determine longer term safety and to support the maintenance of efficacy established primarily at 12 weeks. In addition, analyses of the primary efficacy parameters during the second six months for each of the Protocols (034 and 035, separately) have been provided in Appendices 4.6.11, 4.6.12 and part of 4.6.13 (the first page of 4.6.12 was erroneously placed as the first page of 4.6.13) and are attached to the Clinical Study Report of the combined studies (designated as "Protocol 034C") in the original NDA.

These analyses demonstrate the continued efficacy of rofecoxib through 12 months of treatment, in each study separately. It should be noted that these analyses encompassed two of the primary efficacy endpoints (PainWalking on a Flat Surface and Investigator Global Assessment of Disease Status) used in efficacy analyses at earlier timepoints. The third efficacy endpoint (Patient Global Assessment of Response to Therapy) was not ascertained after 26 weeks since patients were permitted concomitant medication for the treatment of OA during the second 6 months of these studies.

The efficacy data for the second six months of these studies was included in the SAS datasets provided to the Agency on CD as part of a submission to the NDA on January 13, 1999.

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.

If you have any questions or need additional information please contact Robert 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

q/mcs/ltr/593

Federal Express

Desk Copy: Ms. Sandra Cook, HFD-550 CRP2 N317, Federal Express #1

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

Merck & Co., Inc.
P.O. Box 4
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215 652 5000

DESK COPY

February 16, 1999

MERCK
Research Laboratories

Dr. Larry Goldkind, Medical Reviewer
HFD-180
Food and Drug Administration
5600 Fishers Lane, Room 6B-24
Rockville, MD 20857

Dear Dr. Goldkind:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets

Reference is made to the above New Drug Application (NDA); a telefax from the Agency on January 7, 1999 containing requests for additional information; a submission on January 18, 1999 containing MRL's response; and a telefax on February 16, 1999 from Ms. Sandra Cook (FDA) with a follow-up telephone conversation with Dr. Silverman (MRL), asking for an additional copy of the January 18, 1999 submission to be sent to you, directly.

By copy of this letter we are providing the requested additional copy of the January 18, 1999 submission.

Please direct questions or need for additional information 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

Attachments
Federal Express

Desk copy: (cover letter only), Ms. Sandra Cook, HFD-550

Q\robinson\defusco\request

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

DUPLICATE

Merck & Co., Inc.
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West Point PA 19486
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215 652 5000

February 18, 1999

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Robert DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic & Ophthalmic
Drug Products, HFD-550, Room 2063
Office of Drug Evaluation V (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20850

MERCK
Research Laboratories

NEW CORRESP
NC

NDA 21-042: VIOXX™ (Rofecoxib) Tablets

Dear Dr. DeLap:

Reference is made to the above New Drug Application (NDA) submitted on November 23, 1998 and to a telephone conversation on February 12, 1999 between Dr. Averbuch (FDA) and Dr. Silverman (MRL) whereby the Agency requested additional SAS transport files that included age and gender information on participants involved in the following studies: 055, 056, 066, 071, and 072.

Per your request, MRL is providing one (1) Compact Disk (CD) [redacted] which contains additional Demographic SAS Transport Files.

We have taken precautions to ensure that any software on this CD is free of computer viruses and we authorize the use of anti-virus software, as appropriate.

There are two attachments of support documentation:

Attachment 1: Instructions for CD-ROM copy.
Attachment 2: Complete Listing of File Names

Under separate cover this information is also been submitted to the Central Document Room for installation on the MRL-dedicated server.

If you have any questions or need additional information, please contact 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

Q:CAT\CDF\21042\CDSAS

Federal Express #:
Attachments:

Desk Copy/Attachments: Ms. Sandra Cook, Proj. Mgr., HFD-550, N322
(CD Number ML8BP0842274)

Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

ORIGINAL

Merck & Co., Inc.
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215 652 5000
Email larry_bell@merck.com

February 18, 1999

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Central Document Control Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, Maryland 20850

NEW CORRESP
NC

MERCK
Research Laboratories

NDA 21-042: VIOXX™ (Rofecoxib) Tablets

By copy of this letter, Merck Research Laboratories (MRL), a division of Merck & Co. Inc., is providing one (1) Compact Disk (CD) which contains a Response to an FDA Request for SAS Transport files with specific age and gender information on participants involved in studies 055, 056, 066, 071 and 072.

The information on the CD is to be copied to the currently installed on the MRL-dedicated network server in use at the Agency for the VIOXX New Drug Application.

Under separate cover this information is also being submitted directly to the Division for the Reviewer. Ms. Sandra Cook should be contacted for a list of reviewers from the Division of Dermatology and Dental Drug Products who will require access to this submission.

We have taken precautions to ensure that any software on this CD is free of computer viruses and we authorize the use of anti-virus software, as appropriate.

There are two attachments to this letter:

Attachment 1: Instructions for CD-ROM copy.

Attachment 2: A complete list of file names.

During the time that the electronic review aid is actively being used, MRL will provide technical support. Any questions relating to this electronic submission should be addressed to me (610/397-2310) or, in my absence, Margo Herron (301/881-9000).

Sincerely,

Larry Bell, M.D.
Senior Director
Regulatory Affairs

Q:CAT\CDF\21042\CDCR

CENTER FOR DRUG
REC'D
FEB 19 1999
MEGA DOC RM

Attachments
Enclosures: Compact Disk
Federal Express #1

cc (cover letter only):
K. Edmunds, Division of Technology Support Services Staff, HFD-70
Federal Express #2

cc (cover letter with attachments):
NDA 21-042, HFD-550 (2 copies), Federal Express #3

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

Merck & Co., Inc.
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West Point PA 19486
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Tel 610 397 2944
215 652 5000

DESK COPY

February 18, 1999

MERCK
Research Laboratories

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets
Response to FDA Requests

Reference is made to the above New Drug Application (NDA) and to E-mails sent to Dr. R. Silverman (Merck Research Laboratories [MRL]) on February 11 and 16, 1999 from Ms. S. Cook (FDA) with several requests for information from the GI reviewer.

By this letter, we are responding to these requests.

From the E-mail of February 11

FDA Comment 1: Please clarify whether the final Protocol analysis in 044 and 045 blinding was present until after all violations that resulted in exclusion were decided before or after unblinding. The original study protocol states that the criteria for "major violations" which resulted in exclusion were done before unblinding. In the report of the protocol statistics section there is no mention as to whether this was done before or after unblinding.

MRL Response: All violations that resulted in exclusion were decided before unblinding. The data excluded from per protocol analysis are identified in Attachment 1 (for Protocol 044) and Attachment 2 (for Protocol 045).

FDA Comment 2: Please provide a list of endoscopy results for all excluded patients in the per-protocol analysis.

MRL Response: Complete endoscopy results for patients excluded from per protocol analysis appear in Attachments 3 and 3A (Protocol 044), and Attachments 4 and 4A (Protocol 045). Only endoscopic data collected after the date of major violation were

excluded from the per protocol analysis. Endoscopic data that were excluded from per protocol analyses are marked by the symbol " †".

FDA Comment 3: Why were patients discontinued due to the presence of erosions as noted in table 14 of protocol 044 report?

MRL Response: In a small number of cases, investigators decided to discontinue patients from study medication, because of potential safety concern. The presence of erosions was not a prespecified reason for discontinuation.

FDA Comment 4: Please provide the list and treatment assignment of all patients withdrawn due to gastroduodenal erosions from studies 044 and 045.

MRL Response: Patients withdrawn due to erosions and their treatment assignment are listed in Attachment 5.

From the E-mail of February 16

FDA Comment 1: Please provide the 12 week placebo ulcer rate for the conservative sensitivity analysis. Also provide whether patients with erosions but not ulcers at the time of study endoscopies were withdrawn from the study. There is an allusion to this on page 69 of the report on protocol 044 under the section on discontinuations, but I don't see this point explicitly stated anywhere.

MRL Response: The placebo rates for the conservative sensitivity analysis were 9.91% and 5.10% in Protocols 044 and 045, respectively. The 12 week placebo rate for the conservative sensitivity analysis of these two studies may be found in Attachments 6 and 7. [These data are taken from Appendix 4.1.10 in Protocol 044 and Appendix 4.1.10 in Protocol 045].

The presence of erosions was not a prespecified reason for discontinuation. However, in a small number of cases, investigators decided to discontinue patients from study medication, because of potential safety concern.

Patients withdrawn due to erosions and their treatment assignment are listed in Attachment 5.

FDA Comment 2: I still don't have the primary case report forms for the patients with ulcers from the studies 044 and 045. I have only received volumes 2 and 4 of 4 volumes dated 1/18/99 from Merck that had the data on patiens from study 069. Were all the volumes sent directly to Dr. Goldkind?

MRL Response: All four volumes originally submitted on January 18 were re-submitted, under separate cover, directly to Dr. Goldkind on February 16.

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.

If you have any questions or need additional information please contact Robert 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

Attachment

Federal Express #1

q/mcs/ltr/595

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317 (w/o attachments)
Federal Express #1
Dr. Lawrence Goldkind, HFD-180, PKLN 6B-24 (w/attachments)
Federal Express #2