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

Merck & Co., Inc.
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DESK COPY

MERCK
Research Laboratories

May 19, 1999

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

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 a teleconference between representatives of Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. on May 18, 1999, and the FDA reviewers. During this teleconference, Dr. Villalba requested that MRL provide documentation on patients who were mistakenly recorded as having an adverse event reported as "hypertensive crisis".

By this letter, we are responding to the Agency's request.

In the OA safety database, 3 patients had an adverse experience reported as hypertensive crisis. All three patients were in the same study, Protocol 045, and at the same site, Dr. Quevedo of Peru. Allocation numbers and treatment assignments were: AN 556 (rofecoxib 25 mg), AN 557 (rofecoxib 50 mg) and AN 559 (placebo). In all three cases the verbatim term (term recorded on the case report forms) was arterial hypertension increased. This term was incorrectly encoded into the OA safety database, by the monitor in Peru, as hypertensive crisis. This is based on a review of these cases. None of the patients were hospitalized or treated in an emergency room for their blood pressure. In addition there was no clinical manifestation of neurological, cardiac or renal changes.

Narratives for the two rofecoxib patients are provided. These narratives illustrate that the hypertension adverse experiences do not support a diagnosis of hypertensive crisis. Thus a consistent misencoding of the term arterial hypertension increased occurred at this one site. Based on this conclusion, there are no cases of hypertensive crisis in the OA safety database.

AN 556 (rofecoxib 25mg) is a 71 year old woman with an active medical history of hypertension and osteoarthritis. Patient was on no anti-hypertensive treatment at the start of the study. Baseline blood pressure was 130/90 mm Hg. On study day 64, the patient's blood pressure was 180/110 mm Hg. This is the maximum recorded value during the study. The chart below lists all blood pressures during the study. Patient was not hospitalized or seen in an emergency room for her blood pressure. On study day 141, patient began treatment with enalapril, 5 mg, At the completion of study therapy, study day 169, the patient's blood pressure was 130/90 mm Hg. During the study there were no cardiac or neurological complaints. The patient's creatinine was 0.8 mg/dL at baseline and ranged between [redacted] during the study. The investigator considered the event of arterial hypertension increased (verbatim term on the case report form) as possible related to study therapy.

Visit	Study Day	BP
1.0A	-14	
2.0A	1	
4.0	22	
5.0	43	
6.0	64	
7.0	85	
8.0A	113	
10.0	141	
11.0A	169	
12.0	183	

AN 557 (rofecoxib 50 mg) is a 65 year old woman with an active medical history of hypertension, osteoarthritis and neck pain. Patient was on no anti-hypertensive treatment at the start of the study. Baseline blood pressure was 140/90 mm Hg. On study day 64, the patient's blood pressure was 170/90 mm Hg. This is the maximum recorded value during the study. The chart below lists all blood pressures during the study. Patient was not hospitalized or seen in an emergency room for her blood pressure. No treatment was instituted. Patient remained on study therapy and blood pressure returned to normal for the duration of the study. During the study there were no cardiac or neurological complaints. The patient's creatinine was 0.9 mg/dL at baseline and ranged between [redacted] during the study. The investigator considered the event of arterial hypertension increased (verbatim term on the case report form) as probable not related to study therapy.

Visit	Study Day	BP
1.0A	-14	
2.0A	1	
4.0	22	
5.0	43	
6.0	64	
7.0	85	
8.0A	113	
10.0	141	
11.0A	169	
12.0	183	

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/shilling/ltr/

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. M. Villalba, HFD-550, CORP N334, Federal Express #2

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

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MERCK
Research Laboratories

May 17, 1999

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA), a previous submission to the Agency by Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. related to a list of chemistry deficiencies provided to MRL by E-Mail on May 6, 1999; MRL's response to those deficiencies on May 12, 1999; the Agency's FAX of May 14, 1999 containing an amended list of chemistry deficiencies (added comment #6); and a teleconference between representatives of MRL and the Agency on May 14, 1999.

By this letter, we are providing a response to the Agency's May 14 comment #6 and revising our response to comment #12 based on the May 14 discussion.

Drug Product

FDA Comment #6

The dissolution specification for the 12.5 mg tablet is not based on the observed values. Please revise it to Q= in

MRL Response #6

In NDA 21-042, both an automated and manual method for dissolution testing was provided. The automated method was used for the market container stability studies (MCSS) and release of all clinical lots during development. Consequently, data from the automated dissolution testing were used to establish the specification proposed for this

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2 pages

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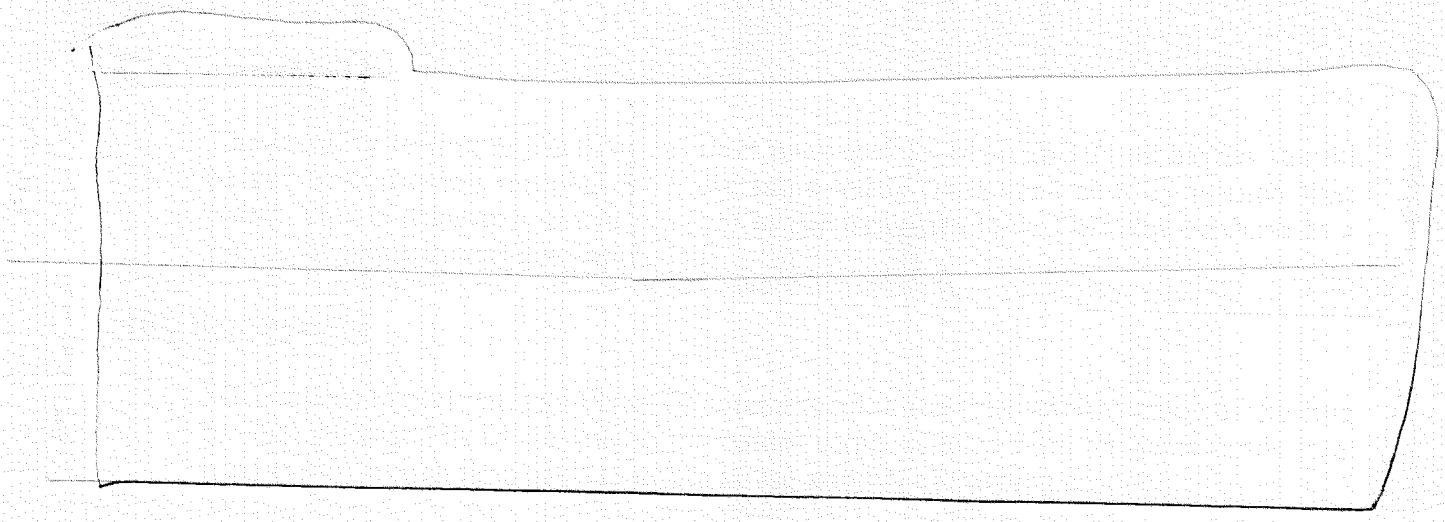
Commercial



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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/shilling/ltr/663

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Bartholome Ho, HFD-550, CRP2 N348, Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
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BM

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April 13, 1999

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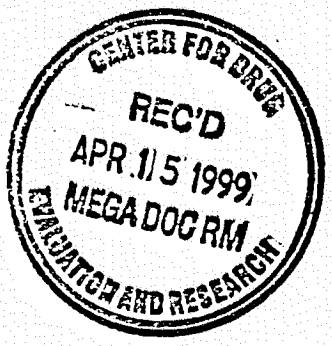

Robert J. DeLap, M.D., Ph.D. Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application, the forthcoming Arthritis Advisory Committee Meeting (AACM) on April 20, 1998, and a pre-AACM meeting held between the FDA and representatives of Merck Research Laboratories (MRL), a division of Merck & Company, Inc. on April 8, 1999. During the meeting, MRL agreed to provide the Agency with data to support the efficacy of Rofecoxib through 12 months in protocols 034 and 035 including both primary and secondary measures. In addition, MRL has noted an error on page 22 of the Agency's OA efficacy review.

By this letter and attachments, MRL is providing responses to both of these issues.

Efficacy of Rofecoxib Through 12 Months - Merck Response:

Attachment 1 provides the appropriate tables highlighting all observed data for the primary endpoints (WOMAC) for Protocols 034 and 035 that were applied to the 12 month treatment period. Attachment 2 provides the appropriate tables highlighting the data averaged over the 12 month treatment period (Intention–to-Treat Approach) for the secondary endpoints for Protocols 034 and 035.

The results support the conclusion that Rofecoxib is efficacious through 12 months on both primary and secondary endpoints.

Efficacy Review - Merck Response:

page 22 of the OA efficacy review in bold text, the reviewer indicated that tistically significant differences in efficacy were observed in protocol 040 (Rofecoxib Ibuprofen) in favor of Ibuprofen for patient global assessment of response to therapy d investigator global assessment or response to therapy. These statements are, in fact, correct. The statistically significant differences for these endpoints were in favor of 25 g Rofecoxib vs. Ibuprofen. Attachment 3 provides the appropriate tables highlighting e difference.

e results support the conclusion that statistically significant differences in efficacy are favor of 25 mg Rofecoxib vs. Ibuprofen.

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

you have any questions or need additional information please contact Robert lverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. 10) 397-2383.

Sincerely,

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

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ttachments

ederal Express #1
esk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Maria L. Villalba, HFD-550, CRP2 N334, Federal Express #2

Robert E. Silverman, M.D., Ph.D.
Senior Director
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NEW CORRESP
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April 5, 1999

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Robert J. DeLap, M.D., Acting Director
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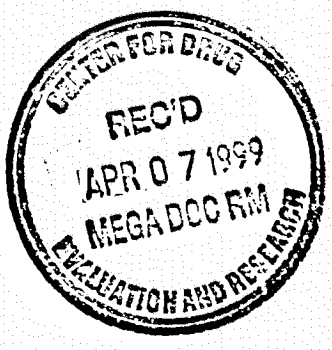
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets
General Correspondence

Reference is made to the above New Drug Application (NDA); an Arthritis Advisory Committee (AAC) Session scheduled for April 20, 1999; a pre-Advisory Committee Meeting between representatives of Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. and the Agency scheduled for April 8 at 10:30a.m.; and the FDA briefing document distributed to the MRL and the Advisory Committee participants on March 30, 1999.

MRL is highly appreciative of the opportunity to read the Agency's briefing materials distributed on March 30 and looks forward to seeing the segments of this material that are still forthcoming. It is our strong desire to make the AAC hearing as productive an interchange as possible and our ability to know the perspective of the Agency on the various aspects of our NDA, before the hearing, will allow us to direct our attention to those issues of particular interest and importance to the Agency.

MRL's prime objective for the April 8 meeting is that, at its conclusion, both MRL and the Agency will have a mutual understanding of what will be the focus(es) for the AAC discussion on April 20. We understand that the Agency has not yet had the opportunity to crystallize the specific questions for the Advisory Committee. However, it would be helpful to understand the Agency's topics of primary focus for the meeting to insure the appropriate focus for the MRL presentations.

In this spirit of collaboration, MRL proposes the following Agenda for the April 8 meeting.

DRAFT AGENDA
April 8, 1999

I. Agency's proposed issues for AAC consideration
II. Overview of the Agency presentation to the AAC
III. MRL's perspective on issues/reviewer's comments in Agency briefing documents
    1. Elderly OA study (Protocol 058)
    2. Long-term OA efficacy (Protocols 034 & 035)
    3. Duration of analgesia
    4. Clinical Pharmacology in patients with hepatic insufficiency (Protocol 057)
    5. Others, as the discussion develops
IV. Overview of MRL presentation to the AAC

MRL participants in the April 8 meeting are (tentatively) listed below.

Dr. Seidenberg	Clinical Research
Dr. Simon	Clinical Research
Dr. Nies	Clinical Sciences
Dr. Gertz	Clinical Pharmacology
Dr. Williams	Biostatistics
Dr. Patrick	Pre-clinical Toxicology
Dr. Baillie	Drug Metabolism
Dr. Vyas	Drug Metabolism
Dr. Goldmann	Regulatory Affairs
Dr. Silverman	Regulatory Affairs
Dr. Perlmutter	Basic Research

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/shilling/ltr/639
Federal Express #1

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

Robert E. Silverman, M.D., Ph.D.
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March 31, 1999

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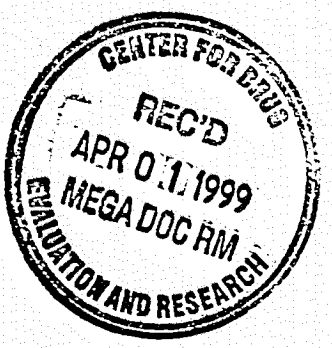

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA) and a telephone conversation between Dr. Silverman, Merck Research Laboratories (MRL), a Division of Merck and Company, Inc. and Drs. Wilson, Weir and Ms. Cook (FDA) on March 24, 1999, concerning the results of the rodent carcinogenicity studies submitted in the NDA. The Agency requested copies of correspondence between MRL and FDA relevant to the early termination of the high dose groups in the mouse carcinogenicity studies.

By this letter and attachments, MRL is responding to the Agency's request. Attached are copies of the following:

1. Submission to IND [redacted]
2. MRL Record of Call between Dr. Silverman and Drs. Coulter and Chen on May 19, 1997 (memo dated May 22, 1997)
3. Submission to IND [redacted]
4. MRL Record of Call between Dr. Silverman and Drs. Coulter and Chen on September 8, 1997 (memo dated September 9, 1997)

As documented in the above attachments, the early termination of the high dose groups (300, 100 and 60 [males] mg/kg/d) were undertaken with the Agency's concurrence. The females at 60 mg/kg/d were continued to study conclusion and the results from this group are reported in the NDA.

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/shilling/ltr/636
Attachment

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Susan Wilson, HFD-550, CRP2 N368, Federal Express #1

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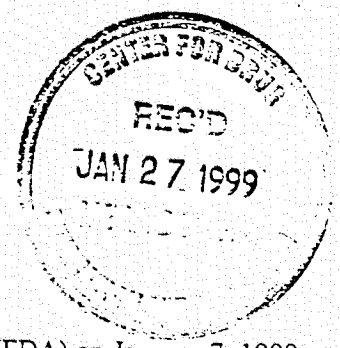

muary 26, 1999

obert J. DeLap, M.D., Ph.D., Acting Director
ivision of Anti-Inflammatory, Analgesic and
phthalmic Drug Products, HFD-550
enter for Drug Evaluation and Research (ODE V)
ood and Drug Administration
201 Corporate Blvd.
ockville, MD 20850

ear Dr. DeLap:

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

eference is made to the above New Drug Application, and a telefax from Ms. S. Cook (FDA) on January 7, 1999 ontaining several requests for additional information from the Biopharmacology reviewer. By this letter and ttachment, MRL is providing responses to those requests.

[redacted]

MRL Response: The requested information was submitted to the FDA under separate cover on January 11, 1999.

FDA Comment 2: Individual PK and PD data should be submitted for all studies submitted under the Human harmacokinetics and Biopharmaceutics section of the NDA. Preliminary review of the submission indicates that ne individual PD data were not submitted for study P051. Please submit individual data for both PK and PD neasurements for study P051 and other studies if not already submitted.

MRL Response: The requested data for Protocol 051 are provided in Attachment 1. This tabular information was rovided in NDA 21-042; Item 11 Case Report Tabulations / Protocol 051 Tabulations / Patient Diary.