

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

Desk Copy (cover letter only):  
Ms. Sandra Cook, HFD 550, CRP2 N317, Federal Express #1  
Desk Copy (with attachments)  
Dr. Lawrence Goldkind, HFD 180, PKLN 6B45, Federal Express #1

Q\robinson\defusco\endoscopy

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

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

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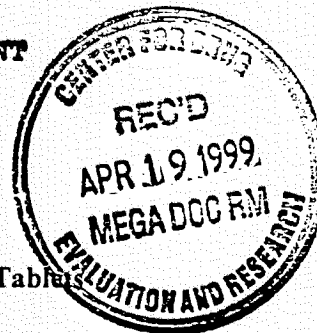
April 16, 1999



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

ORIG AMENDMENT

*EM*



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 telephone conversation between Dr. R. Silverman (Merck Research Laboratories (MRL), a division of Merck & Company, Inc. and Ms. S. Cook (FDA) on April 15, 1999 with a request from the Medical Officer.

By this letter and attachments, MRL is responding to the Agency's request.

**FDA Comment:** Please provide a SAS dataset which contains the time of rescue medication use on days 2 to 5 for patients in MK-0966 Protocol 072.

**MRL Response:** Per your request, a SAS dataset has been created which contains the time of rescue medication use on days 2 to 5 for patients in MK-0966 Protocol 072. Other variables in the dataset are described in Attachment 1, (including output from SAS PROC CONTENTS) which describes the dataset contained in the transport file. Note that each patient has at least one record for each of days 2 to 5 in which he/she took a dose of study medication. The discontinuation visit normally occurred on the day after the patients last dose of study medication. The time and date of rescue medication use and the number of tablets taken will be missing if the patient did take study medication but did not take rescue medication. The trial start date and the date of the discontinuation visit are provided for each patient. The time of study medication was not recorded in a few instances. These are for allocation number 9010 on 08MAR98, allocation number 9226 on 19APR98 and 20APR98, and allocation number 9300 on 17JAN98.

The dataset is provided in a SAS transport file. The code to be submitted in SAS to convert the transport file into a useable SAS dataset is included in Attachment 2.

BEST POSSIBLE COPY

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

DUPLICATE

UC

Merck & Co., Inc.  
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April 19, 1999

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



Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA) submitted November 23, 1998; a teleconference between Merck Research Laboratories (MRL) and the FDA on March 22, 1999; and a follow-up conversation on March 26, 1999 whereby Dr. Goldkind (FDA) requested copies of source documentation of the endoscopists reports.

Reference is also made to our submission of April 15, 1999 in which the requested reports were provided to the Agency. It has been identified that Volume 9 in the eleven volume submission was incomplete. Enclosed is a replacement Volume 9 that has been corrected. We apologize for any inconvenience this error has caused the Agency.

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,

A handwritten signature in black ink, appearing to be 'R. Silverman', written over a horizontal line.

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

Attachment  
Federal Express #1

Desk Copy (cover letter only):

Ms. Sandra Cook, HFD 550, CRP2 N317, Federal Express #1

Desk Copy (with attachment, Volume 9)

Dr. Lawrence Goldkind, HFD 180, PKLN 6B45, Federal Express #2

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

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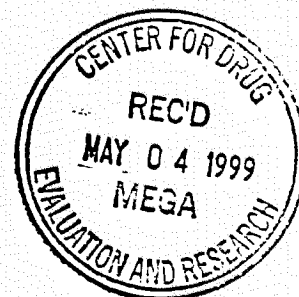
April 30, 1999

NEW CORRESP

NC



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 an e-mail to Dr. R. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. on April 27, 1999 from Ms. S. Cook (FDA) with a request from Dr. Villalba.

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

**FDA Comment:** Table E-158 gives valuable and reassuring information regarding adverse events by age in the 6-week OA trials. Please provide a similar table including data from the 6-month and one-year OA trials.

**MRL Response:** The requested tables are attached. Table 1 contains the 6-month data and Table 2 presents the one-year data. These tables have an identical format as Table E-158 of the Integrated Summary of Safety from the original NDA. The following 3 age groups are used: less than 65 years old, 65 years or greater, and 75 years or greater. The 65 years or greater group contains all the patients reported in the 75 years or greater group (for example, a patient age 77 is reported in both the 65 years or greater and the 75 years or greater group). The adverse experiences are columns and the treatment-by-age groups are rows. The body systems are bolded and to the right are the specific clinical adverse experiences for that body system. In general, these data confirm the findings in the Elderly OA Study (Protocol 058). The adverse experience profile in the elderly is similar to younger patients.


Robert J. DeLap, M.D., Acting Director  
NDA 21-042: VIOXX™ (Rofecoxib) Tablets

Page Two

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/tr/645

Attachments

Federal Express #1

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

Dr. Maria Villalba, HFD-550, CRP2 N334, Federal Express #1

ORIGINAL

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

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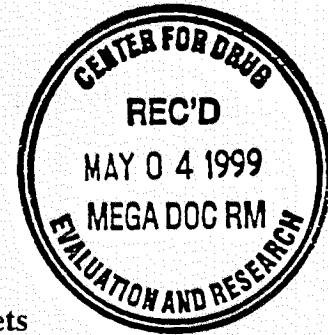
May 4, 1999



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

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BM



Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA) submitted November 23, 1998; a teleconference between Merck Research Laboratories (MRL), a division of Merck & Co., Inc. and the FDA on March 22, 1999; and a follow-up conversation on March 26, 1999 whereby Dr. Goldkind (FDA) requested copies of source documentation of the endoscopists reports.

**FDA Request:** Please provide copies of the endoscopists reports from the following sites in Protocols 044 and 045:

- Protocol 044: 4, 6, 19, 24, 32, 33
- Protocol 045: 9, 10, 18, 20, 21, 30

**MRL Response:** As partial response on April 15, 1999, MRL submitted Case Report Forms and endoscopy notes for the following investigators

- |              |         |
|--------------|---------|
| Dr. Genta    | 044-004 |
| Dr. Johanson | 044-006 |
| Dr. Shah     | 044-019 |
| Dr. Zizic    | 044-024 |
| Dr. Schwartz | 044-032 |
| Dr. Stern    | 044-033 |
| Dr. Graham   | 045-018 |
| Dr. Cello    | 045-030 |

Robert DeLap, M.D., Ph.D., Acting Director  
NDA 21-042: VIOXX™ (Rofecoxib) Tablets  
Response to FDA Request for Information  
Page 2

Attached to this letter are the Case Report Forms and endoscopy notes for the remaining investigators not included in the April 15, 1999 submission:

Dr. Maldonado-Cocco	045-009
Dr. Hawkey	045-010
Dr. Fueller	045-020
Dr. Beaulieu	045-021

In the process of assembling this request, it has come to our attention that some documents were missing. See Attachment 1 for more details.

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

Desk Copy (cover letter only):

Ms. Sandra Cook, HFD 550, CRP2 N317, Federal Express #1

Desk Copy (with attachments)

Dr. Lawrence Goldkind, HFD 180, PKLN 6B45, Federal Express #2

Q:\robinson\defusco\endoscopy2

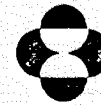
Robert E. Silverman, M.D., Ph.D.  
Senior Director  
Regulatory Affairs

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May 6, 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



**MERCK**  
Research Laboratories

ORIGINAL

BM

~~FOR AMENDMENT~~

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 to Dr. R. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. on April 29, 1999 from Ms. S. Cook (FDA) with a request from the hematology reviewer.

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

**FDA Comment.** Regarding the anemia and reticulocytosis data contained in the four month safety update, please provide the cross tabulations or case report forms for those individuals with either a decrease in hemoglobin, hematocrit or for the new patient with reticulocytosis.

**MRL Response:** " The attachment contains additional clinical information on the 9 patients from Table 56 in the Safety Update Report. These nine patients experienced an adverse event of hemoglobin decrease, hematocrit decrease or reticulocytosis during the SUR reporting period. The distribution of patients was: 1, 5, 1, and 2 in the 12.5, 25, 50-mg rofecoxib and diclofenac group respectively."

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/tr/647

Attachment

Federal Express #1

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

Dr. Ann Farrell, HFD-180, PKLN 6B-45, Federal Express #2 (w/attachment)



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

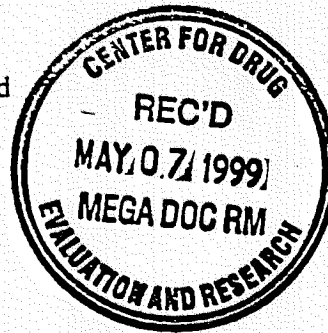
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May 6, 1999

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:

CRP2 AMENDMENT

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

Reference is made to the above New Drug Application (NDA); and a telephone call to Dr. D. Patrick, Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. on May 5, 1999 from Dr. Susan Wilson (FDA).

By this letter, MRL is providing a response to the Agency's request.

**FDA Request:** Please provide the historical control range for vertebral malformations in rabbits.

**MRL Response:** The overall historical control range for vertebral malformations (cervical, thoracic and lumbar vertebrae combined) is 0-1.974%. When broken down by region of vertebral column, the historical control incidences are:

Cervical:	0-0.909%
Thoracic:	0-1.818%
Lumbar:	0-1.299%

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/tr/652

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

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

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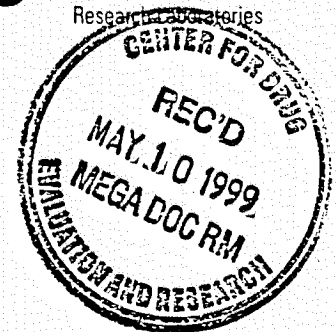
May 6, 1999

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



**MERCK**

Research Laboratories



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BM

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 to Dr. R. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. on May 6, 1999 from Ms. S. Cook (FDA) with a request from the medical reviewer.

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

**FDA Comment:** Please provide a Table of Adverse Experiences with incidence  $\geq 2\%$  in any VIOXX treatment group from the six-month OA trials (044, 045, first six months of 034 and 035) instead of the 6-week data presented in Table 1 of the proposed label. Data should include VIOXX 12.5, 25 and 50 mg doses.

**MRL Response:** Table 1 is provided in response to today's request for a 6 month clinical adverse experience table. MRL would like to highlight several issues with this table. First there is a differential exposure for treatment groups. The exposure was maximal for the rofecoxib and diclofenac groups and approximately one-third less for the placebo and ibuprofen groups. The placebo group underwent a planned discontinuation after 4 months of therapy in the two endoscopy studies that it was used. The ibuprofen patients also derive from the same two endoscopy studies and a significant number of these patients were discontinued early due to endoscopic ulcers. Therefore, we have provided Table 2 which is the four month cut of the two endoscopy studies as presented at the April 20, 1999 advisory meeting.

The 50 mg dose of rofecoxib is not recommended for use in OA. Presentation of 50 mg safety data in this table might indicate support for use of this dose in patients with OA. Therefore for OA, the 6 week Table, provided in the original NDA, accurately reflects

the safety profile of rofecoxib with respect to placebo and ibuprofen at the recommended dose in the OA population. The issue with the adverse experiences of edema and hypertension at the 50 mg dose could be addressed with a sentence in this section.

The use of 50 mg is recommended only for analgesia, supported by analgesia studies of one to 5 days. A summary table of adverse experiences of healthy patients from the dental pain and dysmenorrhea is included (Table 3). Table 4 reports the safety profile from the 5 day post-operative orthopedic study in hospitalized patients using 50 mg of rofecoxib.

We look forward to further discussion on the presentation of AE information in the product circular during the label negotiations to come.

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/648  
Attachment  
Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1 (w/att.)  
Dr. Maria Villalba, HFD-550, CRP2 N334, Federal Express #1 (w/att.)

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

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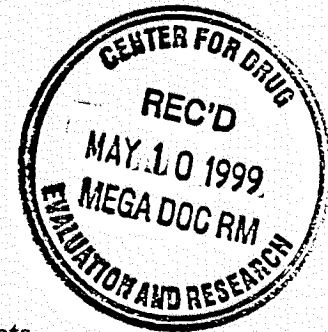
May 7, 1999



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

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BL



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 to Dr. R. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. on May 6, 1999 from Ms. S. Cook (FDA).

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

**FDA Comment:** Please clarify how many subjects received 1000 mg single dose and 250 mg for 2 weeks mentioned in the OVERDOSE section of the label.

**MRL Response:** Exposure to high doses ( $\geq 250$  mg) of VIOXX are delineated in the original NDA, Clinical Documentation (Item 8), Part H. Product Abuse and Overdosage Information. Specifically, in Protocol 002 (Single Dose Study), 6 of 8 normal volunteers received active drug in the 1000 mg panel. Normal volunteers received multiple doses of 250 mg for studies up to 14 days in Protocol 014 (14 day study, 12 patients), Protocol 011 (10 day study, 12 patients) and Protocol 009 (7 day study, 51 patients).

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.

Robert J. DeLap, M.D., Acting Director  
NDA 21-042: VIOXX (Rofecoxib) Tablets

Page Two

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,

A handwritten signature in black ink, appearing to read 'R. Silverman', with a long horizontal line extending to the right.

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

q/shilling/tr/653A

Federal Express #1

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

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

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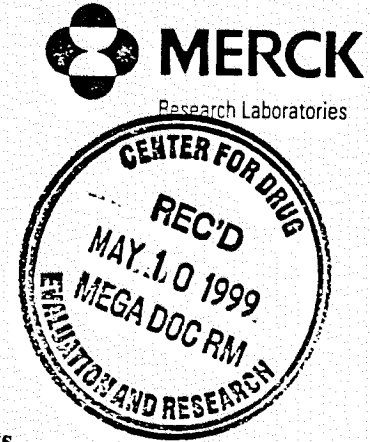
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May 7, 1999

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 an e-mail to Dr. R. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. on May 6 from Ms. S. Cook (FDA) with a request from Dr. Villalba.

By this letter, MRL is providing a response to the Agency's request.

**FDA Requests:** Did you do an analysis of efficacy across studies by age (as they did for safety. It is very possible that it is there in the NDA but I can not find it.

**MRL Response:** The analyses of OA efficacy stratified by age for the 6 week studies (029,033,040 combined) can be found in the NDA, Item 8 (Clinical Documentation), Clinical Reference 247. Analyses of the 6 month efficacy results from 034 and 035, by age, can be found in Reference 236(pp70-72). We have not performed any analyses, by age, that pools all the OA studies. The results for each of the study sets noted above corroborate each other that there is no significant effect of age on the efficacy of rofecoxib.

Attachment 1 contains a copy of the six month combined analysis of efficacy stratified by age for Protocols 034 and 035 from Reference 236. Attachment 2 contains a copy of the six week efficacy data stratified by age for Protocols 029, 033, and 034 from Reference 247.

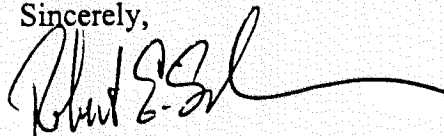
We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Robert J. DeLap, M.D., Acting Director  
NDA 21-042: VIOXX (Rofecoxib) Tablets

Page 2

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/tr/650

Attachment

Federal Express #1

Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1  
Dr. Maria Villalba, HFD-550, CRP2 N 334, Federal Express #1 (w.att.)

APPEARS THIS WAY  
ON ORIGINAL