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

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

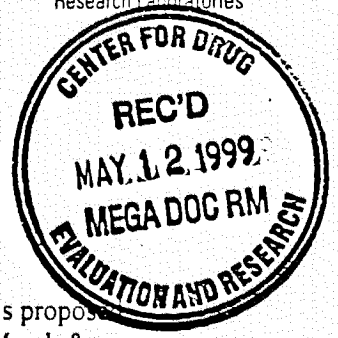
BL

ORIG AMENDMENT

May 10, 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
9201 Corporate Boulevard
Rockville, MD 20850

MERCK
Research Laboratories



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 the Agency's proposed product circular provided to Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. by e-mail on May 7, 1999. By this letter and attachments, MRL is providing its comments and counterproposal to the Agency's proposal.

To facilitate review where appropriate, we have attached data from the NDA. The attached counterproposal is based on the Agency's May 7 proposal. In the left column the Agency's proposed labeling is presented with strike outs and underlined additions constituting MRL's response. For each of these proposed changes there is a corresponding comment or rationale to support the change in the right column.

In general, MRL's counterproposal is made in consideration of the available data and established product labeling precedents in this therapeutic area demonstrated by existing product labeling for NSAIDs and the recently approved circular for celecoxib.

We look forward to reaching a timely and mutually satisfactory consensus on final product labeling for VIOXX.

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/654
Attachment
Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1

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

Merck & Co., Inc.
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NEW CORRESP

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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

GENERAL CORRESPONDENCE

Reference is made to the above New Drug Application (NDA) and to the Arthritis Advisory Committee Meeting held on April 20, 1999.

Attached, for your reference, are copies of additional slides that were not provided to the Agency prior to the meeting.

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

Q\robinson\defusco\slides

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Robert E. Silverman, M.D., Ph.D.
Senior Director
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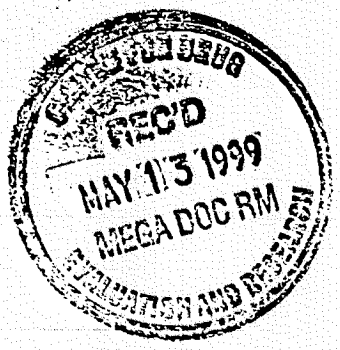
Tel 610 397 2944
215 652 5000



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ORIG AMENDMENT

May 11, 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
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 a teleconference today between representatives of FDA and Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. Additional information requested by the Agency during the teleconference is attached.

Attachment 1 contains the requested information from the carcinogenicity studies for celecoxib that was not reflected in product labeling.

Attachment 2 provides the requested corrected AUC ratios for the preclinical pharmacology sections of the proposed label.

Attachment 3 provides the requested information related to clinical pharmacology aspects of the proposed label.

Attachment 4 provides the requested information related to adverse events of: anemia; abnormal liver function tests; and dose related increases in edema and hypertension with celecoxib.

Attachments 5 and 6 provide the requested information related to combined analysis of the two endoscopy studies (Protocols 044 and 045).

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/657
Attachment
Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1 (w/att.)

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

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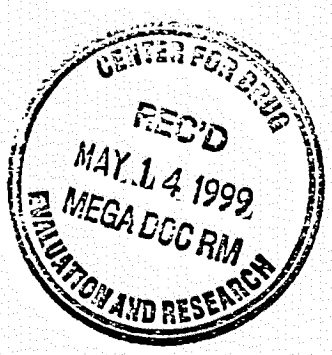
May 13, 1999

MERCK
Research Laboratories

ORIG AMENDMENT



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 (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 chemistry reviewer.

By this letter, we are responding to Comments 12 through 14. Comments 1 through 11 were previously provided in our submission dated May 12, 1999.

FDA Comment 12: The NDC number on label for Unit Dose package of 100 for both 12.5 mg and 25 mg blisters appears to be NDC 0006-0074-28 and not NDC 0006-0074-01.

MRL Response: In a discussion with the FDA Office of Compliance and FDA Product Information Management Branch concerning a similar issue involving the labeling of PEPCID RPD™ and the future labeling of hospital unit doses, the FDA requested that if a package entity can be subdivided into units of one when they are presented to the end user, the NDC number must uniquely distinguish the package entity as a "unit of one" instead of the "salable" unit (in this case, the package of 100 tablets).

The "Package Code" of the NDC appearing on the "salable unit" and as referenced in the "How Supplied" section of the product package circular will be listed as the "salable" unit of 100 tablets (-28).

Following the situation with PEPCID RPD™, Merck decided that, in order to comply with the FDA's requirements concerning the NDC and to accommodate Merck's desire to retain NDC bar codes, we would revise the methodology for assigning "Package Codes" rather than remove the NDC from the blister indefinitely.

The final outcome was that the FDA strongly encouraged that Merck revise our methodology for assigning "Package Codes" in order to designate a unique "Package Code" for all labeling components based on the level of packaging up to the "salable" unit.

FDA Comment 13: The package insert should include "Rx" after the storage statement and before the company name and address.

MRL Response: Merck accepts this addition to the Package Insert; however, the regulation states that the text should be "Rx only." Therefore, we have included "Rx only" in the Package Insert and on the label components.

FDA Comment 14: The storage statement in the labeling should also include [see USP Controlled Room Temperature].

MRL Response: Merck accepts FDA's request to include the phrase [redacted] following the specific storage temperature statement, "[redacted]" This statement will be added to the HOW SUPPLIED section of the package circular immediately. In order to meet the packaging requirements in time for product launch, the other labeling components (cartons, labels, blisters) have either finished printing at risk or are currently in the printing process. Merck requests that we be allowed to use these components which contain the statement "[redacted]" and commit to add the statement [redacted] at the first printing of these components beyond the production of materials necessary for product launch.

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/660
Attachment
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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DESK COPY

May 18, 1999

MERCK
Research Laboratories

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 (NDA) and to an e-mail to Dr. R. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. on May 14, 1999 from Ms. S. Cook (FDA) with request from Dr. Villalba.

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

FDA Comment: Please direct me to the table for Patient Discontinuation due to Adverse Events in study 068 (RA dose ranging) and their CRF's or narratives in the SUR.

Please clarify what is the data source "other than CRF's". I am particularly interested in having additional information for AN 5034 (quadrantopia on day 8 during treatment with rofecoxib 50 mg in study 068). 1729 (renal insufficiency in study 058) and 2530 (necrotizing angiitis and pneumonia in study 068). (Data from table 99)

MRL Response: A total of 3.0, 3.2, 4.7 and 6.2 % of patients in the placebo, 5, 25, and 50-mg rofecoxib groups, respectively discontinued for a clinical adverse experience in Protocol 068. There were no statistical differences in the incidence among the groups. In general, the causes for discontinuation were consistent with previous clinical studies. Attachment 1 provides a listing of all patients discontinued for a clinical adverse experience by treatment group. Case report forms are supplied for each patient in Attachment 2.

In reference to the second part of this request the term "data sources other than CRFs" refers to serious adverse experiences reported to the Merck Research Laboratory's Worldwide Adverse Experience System (WAES) that occurred after the in-house cutoff date for the Safety Update Report of 04SEP98. A discussion of this is present on page

303 of the Safety Update Report. These WAES reports are sent to the FDA in compliance with the reporting guidelines for serious adverse experiences.

The WAES reports for AN 1729 (Protocol 058) and AN 2530 (Protocol 068) are supplied in Attachment 3. The request for AN 5034 probably refers to Protocol 044 and not Protocol 068. This patient experienced a serious adverse experience of CVA while in the study and was discontinued from therapy. The report of quadrantanopia is a sequelae of this episode. As this patient was discontinued for an adverse experience, the complete set of case report forms are available electronically in Item 12 of 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\662

Attachment

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 (w/att.)

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

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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
NDA 21-052: VIOXX™ (Rofecoxib) Oral Suspension
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 19, 1999, and the FDA chemistry reviewers. During this teleconference, Dr. Ho requested that MRL provide additional information in support of the tablets and oral suspension review.

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

RE: (Rofecoxib) Tablets

Comment 1:

Please provide additional data (*i.e.* 3 and 9 months) for MK-0966 Tablets stored in

Response 1:

Tables 1 and 2 (attached) include market container stability study (MCSS) data for 3 lots of each strength stored in
Please note, the summary of the MCSS "Other Data" included on pages 409-411 of the application are applicable to the stability observed for the MCSS lots stored in the opaque

Comment 2:

Please clarify the initial production batches which will be placed on stability.

Response2:

The first three production lots of each strength, released for the market, in each package type, will be placed on stability according to the submitted protocol (page 425 of the NDA 21-042).

Comment 3:

Provide additional information on the [redacted] in future NDA annual reports.

Response3:

Merck & Co. Inc. will clarify the [redacted] in upcoming NDA annual report updates.

RE: (Rofecoxib) Oral Suspension

Comment 1:

Provide additional information on the [redacted] in future NDA annual reports.

Response1:

Merck & Co. Inc. will clarify the [redacted] in upcoming NDA annual reports.

Comment 2:

Provide additional information [redacted] during the market container stability studies.

Response 2:

During the market container stability studies (MCSS), Merck

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/668

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

EXCLUSIVITY SUMMARY for NDA #21-042 SUPPL #____

Trade Name: Vioxx Tablets

Generic Name: rofecoxib 12.5 mg and 25 mg tablets

Applicant Name: Merck Research Laboratories HFD-550

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /X/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____
   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 YEARS

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

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