A Comment 3: Please fill out the attached sheet for each study.

RL Response: The requested Clinical Pharmacology/Biopharmaceutics Study Summary Sheets are provided in achment 2. The Clinical Study Report Synposes are attached to the corresponding Study Summary Sheets.

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

you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 7-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

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

ttachments

ederal Express #1

esk Copy/attachments: Ms. Sandra Cook, Project Manager, HFD-550, CRP2 N317
3 deskcopies with hardcopy attachments

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
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

January 11, 1999

DESK COPY

MERCK
Research Laboratories

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

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) and requests for additional information from the Agency telefaxed to Merck Research Laboratories (MRL) on November 19, 1998 (from the Chemistry reviewer) and January 7, 1999 (from the Biopharmaceutics reviewer).

By this letter and attachments, MRL is providing the information requested on November 19, 1998, and a response to the first request in the January 7, 1999 telefax. Responses to the other Agency requests in January 7, 1999 will be provided under separate cover.

From the Agency telefax of November 19, 1998

FDA Comment 1: Construct dissolution profiles

FDA Comment 2: Perform physical/chemical test

FDA Comment 1: The dissolution methods and specification

The final dissolution methods and specification should be submitted in the NDA.

MRL Response: The final dissolution method

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 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

mcs/q/ltr/582

Attachment

Federal Express #1

Desk Copy: Ms. Sandy Cook, Project Manager, HFD-550, CRP2 N317 (3 copies)

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

DUPLICATE

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

December 16, 1998

These copies are
OFFICIAL FDA Copies
not desk copies.

MERCK
Research Laboratories

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

Dear Dr. DeLap:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets

Reference is made to the above New Drug Application (NDA) submitted on November 23, 1998 and an FDA facsimile transmission on December 10, 1998 requesting additional desk copies of Clinical Documentation.

Attached, as partial response to the fax request on December 10, 1998, are the following Clinical Study Reports from Item 8 (Clinical Documentation) of NDA 21-042:

Protocol Number	Title	NDA Volume (s)
P009	MRL Clinical Study Report: A Double-Blind, Randomized, Active- and Placebo-Controlled Study to Compare the Effects of L-748,731, Ibuprofen, and Aspirin on the Gastric and Duodenal Mucosa of Healthy Volunteers (Protocol 009).	1.100-1.101
P041	MRL Clinical Study Report: A Double-Blind, Placebo-Controlled, Four-Period Crossover Study in Healthy Volunteers to Determine the Effects of Treatment with MK-0966 and Indomethacin for Seven Days on Small Intestinal Permeability (Protocol 041).	1.148-1.149

Protocol Number	Title	NDA Volume (s)
P044	MRL Clinical Study Report, Multicenter Study: A Multicenter, Randomized, Parallel-Group, Active- and Placebo-Controlled, Double-Blind Study, Conducted Under In-House Blinding Conditions, to Determine the Incidence of Gastroduodenal Ulceration After 12 Weeks of Treatment with MK-0966, Ibuprofen, or Placebo with a 12-Week Continuation Period (Protocol 044).	1.151-1.154
P044C	MRL Clinical Study Report, Multicenter Study: A Combined Analysis Of Two Identically Designed Multicenter, Double-Blind, Randomized, Parallel Group, Active And Placebo-Controlled Studies To DetermineThe Incidence Of Gastroduodenal Ulceration After 12 Weeks Of Treatment with MK-0966, Ibuprofen Or Placebo With A 12-Week Continuation Period (Protocol 044/045).	1.154-1.156
P045	MRL Clinical Study Report. Multicenter Study: A Multicenter, Randomized. Parallel-Group. Active- and Placebo-Controlled, Double-Blind Study. Conducted Under In-House Blinding Conditions. to Determine the Incidence of Gastroduodenal Ulceration After 12 Weeks of Treatment with MK-0966, Ibuprofen, or Placebo with a 12-Week Continuation Period (Protocol 045).	1.156-1.160
P050	MRL Clinical Study Report: A Randomized, Double-Blind, Active- and Placebo- Controlled Study With MK-0966, Ibuprofen, and Placebo to Evaluate the Gastrointestinal Blood Loss In Normal Healthy Volunteers During a Four-Week Treatment Period (Protocol 050).	1.162-1.163
P069	MRL Clinical Study Report. Multicenter Study: MK-0966 Phase III Gastrointestinal Clinical Event Monitoring Plan and Case Review Committee Procedures (Protocol 069).	1.181-1.182

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

Q:/Michener/DeFusco/NDA21-042A

Attachments provided for desk copies only

Desk copy: Sandra Cook (including attachments)

Federal Express

APPEARS THIS WAY
ON ORIGINAL

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

ORIGINAL

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2310
215 652 5000
Email larry_bell@merck.com

NC

November 23, 1998

These copies are OFFICIAL FDA Copies not desk copies

MERCK
Research Laboratories

Central Document Room
Food & Drug Administration
12229 Wilkins Avenue
Rockville, MD 20850

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 24 1998
MEGA DOC RM

Original New Drug Application
ELECTRONIC SUBMISSION

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

By copy of this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., is providing to the Technology Support Service Staff (TSSS) one (1) [redacted] hereafter referred to as the hard disk, which contains the Original New Drug Applications (NDAs) for NDA 21-042: VIOXX™ Tablets and NDA 21-052: VIOXX™ Oral Suspension (Rofecoxib).

VIOXX™ is indicated for the acute and chronic treatment of the signs and symptoms of osteoarthritis, relief of pain, and treatment of primary dysmenorrhea.

The hard (paper) copy of these Original New Drug Applications are also being submitted to the Agency on November 23, 1998. Additionally, a DLT Tape [redacted] which contains the archive electronic version of Items 11 and 12 (Case Report Tabulations and Case Report Forms, respectively) of NDA 21-042 is being submitted with the paper copy (volume 278 of 278).

The hard disk is to be installed on the MRL-dedicated network server at the Agency. It is MRL's anticipation that the hard disk will be installed in a timely manner after delivery to TSSS.

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

A list of reviewers from the Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products Division who should be provided access to this electronic submission from their desktops may be obtained from Ms. Sandra Cook, Project Manager.

Please notify MRL's Regulatory Agency Relations (RAR) Office (301/881-9000) when the disk installation is successfully completed and access from the reviewers' desktops is functional.

When an action has been taken on these submissions and the hard disk is no longer needed, MRL will make arrangements to retrieve it from the FDA. The FDA will be responsible for the "sanitization" of the hard disk before MRL removes it from TSSS. We further understand that, in the future, information submitted in electronic form may be retained indefinitely by the Agency, as an archival copy of the application, in the event that a complete paper submission is not filed.

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

There are five attachments to this letter:

Attachment 1	An NDA Table of Contents of the accompanying electronic submission.
Attachment 2	A Difference Report identifying differences between the electronic version of this submission and the hard copy submission.
Attachment 3	Installation Instructions detailing how to install the hard disks in the server.
Attachment 4	Documentation regarding the development procedures performed at MRL for this electronic submission.
Attachment 5	A complete list of file names.

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

During the time that the hard disks are actively being used, MRL will provide technical support. Any questions relating to these hard disks should be addressed to me (610/397-2310) or, in my absence, Marie Dray (301/881-9000).

Sincerely,

Larry Bell, M.D.
Senior Director
Regulatory Affairs

Q:ALCD\COX2\COVERES

Attachments

HAND DELIVERED

cc (cover letter only):

Mr. D. Moss, Div. of Technology Support Services Staff, HFD-70 – Federal Express No. 2
Mr. K. Edmunds, Div. of Technology Support Services Staff, HFD-70 – Federal Express No. 3

cc (cover letter with attachments):

Ms. Sandra Cook, Project Manager, HFD-550 - HAND DELIVERED
NDA 21-042 and NDA 21-052, HFD-550 (2 copies), Federal Express No. 4

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

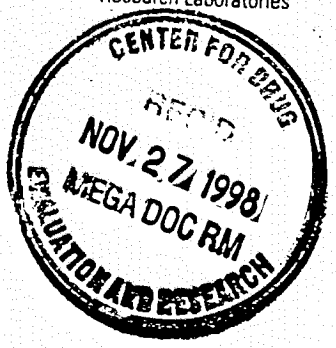
Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

November 25, 1998

DUPLICATE

MERCK
Research Laboratories

CORRESP
NC



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
1201 Corporate Blvd.
Rockville, Maryland 20850

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

Dear Dr. DeLap:

Reference is made to the above original new drug applications submitted on November 23, 1998 and to a letter providing desk copies of the key volumes to Ms. Sandra Cook.

Please note that the cover letter providing desk copies inadvertently had the incorrect spelling of the generic name for VIOXX™. The correct spelling is as follows: Rofecoxib. This error is isolated to the cover letter only.

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

I:\CAT\CDF\21042GC

Federal Express No.

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

December 10, 1998

MERCK
Research Laboratories

Ms. Sandra Cook
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

Dear Ms. Cook:

NDA 21-042: VIOXX™ (Rofecoxib) Tablets

Reference is made to the above New Drug Application (NDA) submitted on November 23, 1998; a letter providing desk copies of the key volumes of the NDA; and a telephone conversation on December 8, 1998 with Dr. Robert E. Silverman (MRL) whereby you requested an additional desk copy of Item 10 (Statistical Documentation).

Attached, as requested, is an additional copy of the VIOXX™ Statistical Documentation.

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

Q:/Michener/DeFusco/NDA21-042

Attachments

Federal Express

NDA ORIG AMENDMENT & DUPLICATE

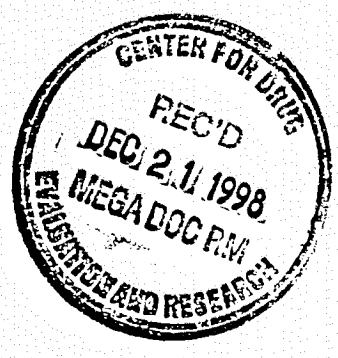
Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

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

These copies are
OFFICIAL FDA Copies
not desk copies.

December 18, 1998

MERCK
Research Laboratories



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

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application and a telefax from Ms. S. Cook (FDA) and Dr. R. Silverman (Merck Research Laboratories [MRL]) on December 10, 1998 containing requests from the Medical Reviewer.

By this letter and attachments, MRL is providing responses to the December 10 requests.

FDA Request: Is Protocol 068 dose ranging study included in the NDA? If so, where?

MRL Response: Protocol 068, a dose finding study in patients with rheumatoid arthritis, is not included in the NDA. This study is still ongoing.

FDA Request: Please provide one table with all trials (just the protocol number) and indicate which ones are considered pivotal or supportive studies for each indication.

MRL Response: The requested tables are attached (one for analgesia studies and one for osteoarthritis studies). As noted on the table of osteoarthritis studies, MRL has characterized the special GI studies (Protocols 044, 045 and 069) as "pivotal" because of the important focus of the clinical development program on GI safety issues. These studies, however, do not provide pivotal efficacy data to support an efficacy claim in osteoarthritis.

FDA Request: Please provide a desk copy of the following volumes: 100, 148, 151, 154, 156, 162, 181.

MRL Response: The requested copies were provided under separate cover on December 16, 1998.

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 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

mcs/q/ltr/581

Attachment

Federal Express #1

Desk Copy: Ms. Sandy Cook, Project Manager, HFD-550, CRP2 N317

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
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

DESK COPY

December 22, 1998

MERCK
Research Laboratories

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Center for Drug Evaluation and Research (ODE V)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 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 and a telephone conversation between Ms. S. Cook (FDA) and Dr. R. Silverman (Merck Research Laboratories [MRL]) on December 15, 1998 during which the Agency made several requests for information. By this letter and attachment, MRL is providing responses to those requests.

FDA Request: Provide a listing of all ongoing clinical studies with VIOXX being conducted under IND 46,894 that have not been reported in NDA 21-042.

MRL Response: The requested list is provided by attachment. This table has been updated and edited from a previous listing of all ongoing and completed studies that was submitted to FDA on September 3, 1998 (IND [redacted]

FDA Request: Indicate where body weights for the rat and mouse carcinogenicity studies, including standard deviations and interval changes, can be found in NDA 21-042.

MRL Response: The requested body weight information can be found in NDA 21-042 in Item 5 Nonclinical Pharmacology and Toxicology, Part E Oncogenic/Carcinogenic Potential. The full reports of each study are included in References (subpart E.6). Within each report (references E-1 [rat]; E-3 and E-5 [mouse]) both average and individual body weight data is provided in Tables A-1 through A-4 for each study.

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.