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/586

Attachment

Federal Express #1

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

APPEARS THIS WAY
ON ORIGINAL

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

ORIGINAL

NDA ORIG AMENDMENT

BS

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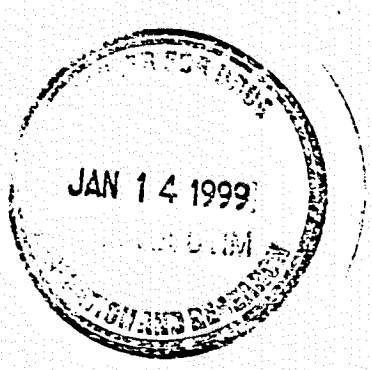
Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

January 13, 1999

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, a telefax from Ms. S. Cook (FDA) on December 31, 1998, and a telephone conversation between Ms. S. Cook (FDA) and Dr. R. Silverman (Merck Research Laboratories [MRL]) on January 11, 1998 during which the Agency made several requests for information. By this letter and attachment, MRL is providing responses to those requests.

FDA Request: Please submit desk copies of the following volumes (for the analgesia studies): 97, 98, 116, 117, 144, 145, 163, 164, 167, 168, 169, 170, 179, 180, 181, 183, and 184.

MRL Response: The requested volumes were submitted to the FDA under separate cover on January 6, 1998.

FDA Request: Please provide, or specify the location in the NDA, statistical analyses of the time specific measurements of pain intensity differences (PID), pain relief scores (PR) and pain relief and intensity differences (PRID) for studies # 027, 051, 066, 071, 038, 055, 056, 072. Use the baseline observation carried forward (BOCF) technique for missing values for the first 24 hours.

MRL Response: The requested analyses are provided in Attachment 1. The analytical methods are identical to those used to produce the 5-page summaries in the original NDA application; however, the data is different because Pain Relief (PR) and Pain Intensity (PI) values which were missing due to patient use of rescue medication were estimated

with baseline PR (i.e. PR=0) and PI observations. BOCF analyses are depicted in graphic and tabular output. Patients in Protocols 027, 038, and 051 who were previously excluded from analyses because they remedicated 90 (Protocols 027 and 051) or 120 (Protocol 038) minutes postdose were included for these analyses. PR, PID, PRID were analyzed. In general, results of these analyses were consistent with those presented in the original NDA submission.

FDA Request: Please provide the data sets for studies 010, 029, 029-10, 029-20, 029-30, 034-10, 035-10, 058, 058-10.

MRL Response: MRL is providing one (1) Compact Disk (CD) which contains additional SAS datasets in support of the Statistical Documentation.

We have taken precautions to ensure that any software on the 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 2 User Instructions for SAS Datasets

Attachment 3 Complete Listing of File Names

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

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

Merck & Co., Inc.
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215 652 5000

January 18, 1999

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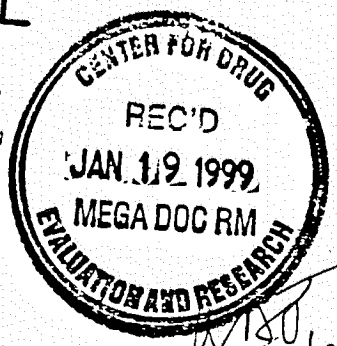
MERCK
Research Laboratories

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

DUPLICATE
NDA ORIG AMENDMENT
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) and a telefax from the Agency on January 7, 1999 containing requests from the GI medical reviewer for additional information. By this letter and attachments, Merck Research Laboratories (MRL) is providing responses to the January 7 requests.

3/30/99
ISI

FDA Request 1: Please supply all endoscopy reports and coding sheets used to ascertain data as well as a list of patients identified with ulcers and "PUB"s.

MRL Response: Osteoarthritic patients with endoscopic ulcers were identified in the two large 6-month endoscopy studies, Protocols 044 and 045. Complete endoscopic information is presented on these patients, in the following tables, listings, and case report forms.

- Attachment 1 contains two lists of allocation numbers with treatment assignments for patients who met the protocol definition for gastroduodenal ulcer in each of the Phase III endoscopy studies (MK-0966 Protocols 044 and 045).

- Attached are listing tables (reproduced from Appendix 4.10.2) of the Clinical Study Reports provided in NDA 21-042 for Protocols 044 and 045: Attachments 2A and 3A, respectively) of patients who met the protocol definition for gastroduodenal ulcer in the Phase III endoscopy studies. Ulcer patients are organized by investigator site. Within each investigational site, the results are presented by treatment group.

- For all ulcer patients from the endoscopy studies (Protocols 044 and 045), we have attached the printed case report forms of the endoscopy data (Protocols 044 and 045: Attachments 2B and 3B, respectively). For each anatomic location within the upper GI tract (esophagus, stomach, duodenum), these forms convey information on the

extent of ulceration or erosion, and any comments that were recorded on the original report in the workbook. For each patient, the information is organized in temporal sequence, beginning with the baseline endoscopy and ending with the latest endoscopy the patient underwent.

The patients are organized as in Attachments 2A and 3A. Ulcer patients are organized by investigator site. Within each investigational site, the results are presented by treatment group.

- Patients with "PUB"s are addressed in the accompanying response to FDA Request #2.

FDA Request 2: Please provide a list of patients presented to the GI committee for adjudication of PUBs.

MRL Response: Enclosed are listing tables and complete adjudication packages for all MK-0966 patients presented to the GI committee for adjudication of PUBs.

- Attachment 4 provides a copy of Table 31 from the Protocol 069 ("Pooled PUB Analysis") Clinical Study Report submitted in NDA 21-042, that lists the 55 patients who were included in the Protocol 069 analysis, organized by treatment group.

- Attachment 5 provides a copy of Appendix Table 4.2.1 from the Protocol 069 Clinical Study Report that lists seven (7) patients who were adjudicated by the GI committee but not included in the Protocol 069 analysis (as prespecified in the Data Analysis Plan) due to the fact that the suspected upper GI event occurred greater than 14 days after the discontinuation of study medication. Patients are organized by treatment group.

- Attachment 6 provides a copy of Appendix Table 4.7 (from the Protocol 069 Clinical Study Report) that lists the above 62 patients, organized by case number. This table also includes the final adjudication ruling of the GI committee.

- A total of 65 patients were referred to the GI committee for adjudication. In addition to the 62 discussed above, three (3) patients were sent to the GI committee in error. In each of these cases, the investigator did not complete and sign the Significant Gastrointestinal Event form and indicated that a potential upper GI event in these patients was not suspected. These three patients were either preliminarily or completely adjudicated by the GI committee but were not included in the Protocol 069 analysis (as prespecified in the Data Analysis Plan) or in the Clinical Study Report. These three patients were: Case # 005 (Protocol 035, AN8176; Diclofenac

150 mg daily); Case # 008 (Protocol 034, AN5810; MK-0966 12.5 mg daily); and Case # 022 (Protocol 040, AN8746; Ibuprofen 2400 mg daily).

- PUB adjudication packages for all 65 patients (including the above three cases sent to the committee in error) are provided in Attachment 7, organized by treatment group.

- Some PUB patients from the endoscopy studies (Protocols 044 and 045) had endoscopy data additionally reported on Protocol 044 or 045 case report forms. These case report forms can be found in Attachments 2B and 3B which addresses patients with ulcers from 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 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/mcs/ltr/589

Federal Express #1

Desk Copy: Ms. Sandra Cook, Project Manager, HFD-550, CRP2 N317
Federal Express #1 (Cover Letter Only)
Dr. Larry Goldkind, Medical Reviewer, HFD-180, PKLN 6B-45
5600 Fishers Lane
Rockville, MD 20857
Federal Express #2 (w/Attachments)

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

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
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Email larry_bell@merck.com

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January 27, 1999

NC
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MERCK
Research Laboratories

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

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

Reference is made to the above New Drug Application, and the original Submission (ES) submitted to the Agency on November 23, 1998. In the process of reviewing the ES, Merck Research Laboratories (MRL) has found that some initial data was inadvertently omitted from the Chemical and Pharmaceutical Manufacturing and Control Documentation of the assay and dissolution stability EXCEL spreadsheets. By this letter and attachment, MRL is providing a replacement for the EXCEL spreadsheets in a comprehensive dataset which includes the initial data.

This information should be copied to the [redacted] currently in use at the Agency NDA 21-042: VIOXX™ (Rofecoxib) electronic submission. Upon completion of the copy process, please notify our MRL Regulatory Agency Relations (RAR) Office in Rockville, MD (301.881.9000).

MRL is providing one (1) Compact Disk (CD), [redacted] which contains the comprehensive dataset in support of the CMC tablet assay and dissolution stability data.

We have taken precautions to ensure that any software on the 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 User Instructions for CD-ROM Copy

Attachment 2 Complete Listing of File Names

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 & Company, 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 (610.397.2383).

Sincerely,

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

APPEARS THIS WAY
ON ORIGINAL

Attachments

Enclosures:
Compact Disk

Federal Express - #1

cc: (cover letter only)

Mr. D. Moss, Div. of Technology Support Services Staff, HFD-70 - Federal Express #2
Mr. K. Edmunds, Div. of Technology Support Services Staff, HFD-70 - Fed. Ex. #3

cc: (cover letter with attachments)
Ms. Sandra Cook, Project Manager, HFD-550 - Federal Express #4
Dr. Robert J. DeLap, Acting Director, NDA 21-042, HFD-550 - Federal Express #5

q:/floyd/fda/letter/0128

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

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Tel 610 397 2944
215 652 5000

February 1, 1999

MERCK
Research Laboratories

Robert J. DeLap, M.D., Ph.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

NDA ORIG AMENDMENT
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, and an encrypted email from Ms. S. Cook (FDA) on January 25, 1999 during which the Agency made a request for information. By this letter and attachments, MRL is providing a response to the request.

FDA Request: An NME can be categorically excluded if the EIC is [redacted] and there are no extraordinary circumstances (like the drug comes from a wild plant). The categorical exclusion claim should include a statement certifying that to Merck's best knowledge no extraordinary circumstances exist. In addition, the calculations should have been based on the total active ingredient that will be used for both applications.

MRL Response: The Categorical Exclusions to support the MK-0966 Tablets (Attachment 1) and Oral Suspension (Attachment 2) have been revised. The document has been updated based upon comments from the FDA. Specifically, the statement at the end of the filing has been revised to state that "To Merck's best knowledge no extraordinary circumstances exist in regards to this action." Also, text was added to verify that the EIC was calculated based upon both forms of the drug substance.

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

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

DUPLICATE

Merck & Co., Inc.
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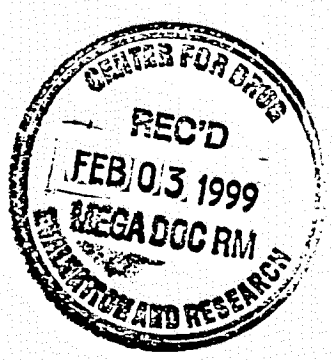
February 2, 1999

MERCK
Research Laboratories

NEW 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
9201 Corporate Blvd.
Rockville, Maryland 20850



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 a telephone conversation between Ms. S. Cook (FDA) and Dr. R. Silverman (MRL) on January 22, 1999 requesting additional desk copies of Clinical Documentation.

By copy of this letter, we are sending the following volumes to Ms. Kati Johnson (FDA): 71-74, 96, 99, 100, 101, 114, 115, 176, and 177.

Please note these volumes were copied exactly from the original NDA, therefore, there may be additional information attached which was not requested.

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\21042VOLUMES

Federal Express #:

Desk Copy (Cover Letter Only): Ms. Sandra Cook, Proj. Mgr., HFD-550, N322
Federal Express #1

Desk Copy w/attachments: Ms. Kati Johnson, Chief Project Manager, HFD-180, Room 6B45
Federal Express #2

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
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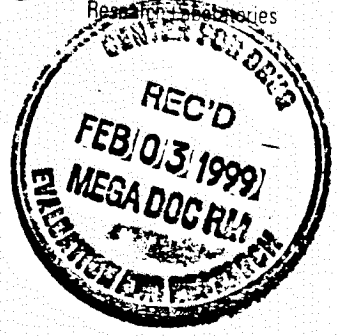

February 2, 1999

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

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 an e-mail from Ms. Sandra Cook (FDA) on January 29, 1999 requesting additional desk copies of Clinical Documentation for the Cardio-Renal Reviewer, Dr. Juan Pelayo.

By copy of this letter, we are sending the following Clinical Study Reports (CSR) to Dr. Pelayo: 010, 029, 029C, 033, 034, 034C, 035, 040, 044, 045, and 058.

Please note these volumes were copied exactly from the original NDA, therefore, there may be partial CSR's attached which were not requested.

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\21042REQUEST

Federal Express #:

Desk Copy (Cover Letter Only): Ms. Sandra Cook, Proj. Mgr., HFD-550, N322
Federal Express #1

Desk Copy w/attachments: Dr. Juan Pelayo, HFD-110, Room 5073
Federal Express #2

DUPLICATE

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

BM

ORIG AMENDMENT

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
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215 652 5000

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February 5, 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 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 2, 1999 containing a request for additional information from the medical reviewer. By this letter and attachments, MRL is providing a response to the Agency's request.

FDA Comment: Please provide the raw data with no imputation for missing values, of time specific pain intensity and pain relief measurements from time 0 through 12/24 hours for studies 004, 027, 051, 066, 071, 038, 055, 056, 072. I would like to see the data as series of measurements over time rather than separate data for each visit. If the data is in the application, please provide location or provide the data in SAS transfer files or in an Excel format (I prefer the Excel but they are not obligated to provide this rather than the SAS format.)

MRL Response: The SAS datasets provided as part of the Statistical Documentation (Item 10) in NDA 21-042 include the requested data for the Phase III Protocols 055, 056, 066, 071 and 072. Attached are instructions for extracting the requested raw data values for these protocols. Specific efficacy datasets for the Phase II studies, 004, 027, 038 and 051 were not provided with the original NDA, based upon discussions between MRL and the Agency at a Pre-NDA conference held on December 11, 1997. In light of the request of February 2, 1999, for this information, MRL is now assembling appropriate SAS datasets for these studies. We anticipate submission of this information to the Agency within the next two weeks.

DUPLICATE

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/590

Attachment

Federal Express

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

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

Merck & Co., Inc.
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Tel 610 397 2944
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February 5, 1999

[redacted] AMENDMENT
BZ

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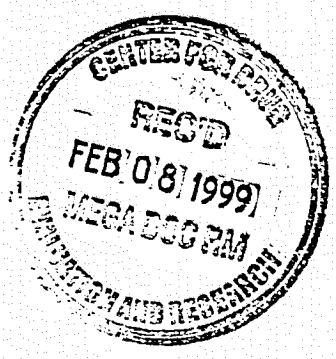

Robert J. DeLap, M.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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 2, 1999, containing a request for clarification from the medical reviewer and statistician. By this letter and attachment, MRL is providing a response to the Agency's request.

FDA Comment: Please clarify where the "'PRE-SPECIFIED INTEGRATED ANALYSIS" that was used to generate the best fit curve for dose-response analysis (Studies 010 and 029). This relates to figure D-4, D-5 and D-6 in Section D of the Clinical Documentation Volume (vol. 1.94)

MRL Response: The intent to conduct the integrated analysis from Protocols 010 and 029 was pre-specified in the data analysis section of the original submission of Protocol 029 (page 35 of the Protocol; submitted [redacted] which is also included in the Clinical Study Report for Protocol 029 from the NDA, as excerpted here:

> **Pooled Analyses**
> The data from this trial may be pooled with that from the MK-0966 Pilot OA Study (Protocol 010) to further examine the dose-response relationship of MK-0966 in OA. This would be reported in an exploratory document, separate from the report of this study.

q/mcs/ltr/591

DUPLICATE

Subsequent to the analyses of the individual studies, MRL carried out the integrated analysis. Attached is the MRL internal report of this analysis which was the basis for the discussion in the NDA referenced in the Agency's comment. The figures included in the attached report were reproduced as the above noted figures D-4, D-5 and D-6 in the NDA with only a reversal of the ordinate scale to conform with the presentation style used throughout the NDA. In the NDA, a downward slope corresponds to improvement in efficacy parameters for the graphical presentations.

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

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