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

Merck & Co., Inc.
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Fax 610 397 2516
Tel 610 397 2944
215 652 5000

DESK COPY

February 19, 1999

MERCK
Research Laboratories

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

AMENDMENT TO PENDING APPLICATION

Dear Dr. DeLap:

Please refer to the New Drug Application referenced above submitted November 23, 1998. Also, refer to an agreement reached with the Agency and mentioned in the NDA (Chemical and Pharmaceutical Manufacturing and Controls Documentation, Page C-88) regarding the submission of additional stability data. Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. committed to amending the NDA when additional stability data became available to support a 24 month shelf-life in all packages. MRL also committed to submit this information no later than 3 months prior to the PDUFA deadline.

Please find enclosed 18 month stability data for all packages along with a full statistical evaluation of all available data to support a 24 month expiration. MRL is requesting, via this submission, a 24 month expiration date for all packages. The additional data contained in this submission demonstrates that the product continues to be stable and supports a proposed expiry of 24 months.

Electronic review aids in the format of updated Excel spreadsheets containing this data will be submitted in the near future when available.

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\21042\DATA

Federal Express No. 1:

Desk Copy with Attachments:
Ms. Sandra Cook, CSO, HFD-550 – Fed. Exp. No. 1:
Ms. Debra Pagano – Philadelphia District Office – Fed. Exp. No. 2:

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

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February 23, 1999

MERCK
Research Laboratories

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

Reference is made to the above New Drug Application (NDA) submitted November 23, 1998.

It was recently discovered by Merck Research Laboratories (MRL) that final revisions to the attached table and associated narrative description were not incorporated into the Clinical Study Report (CSR) for Protocol 044: Patients Exceeding the Predefined Limits of Change at One or More Visits Versus Two or More Visits Over the Entire Study (Table 061). This CSR can be found throughout the NDAs mentioned above as Reference Number P044.

By copy of this letter, we are providing replacement pages 235 and 236 for CSR 044.

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
Desk copy w/attachments: Ms. Sandra Cook, Project Manager, HFD-550, Room N-322
Q\robinson\defusco\vioxx

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

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DUPLICATE

March 4, 1999

NEW CORRESP
NC

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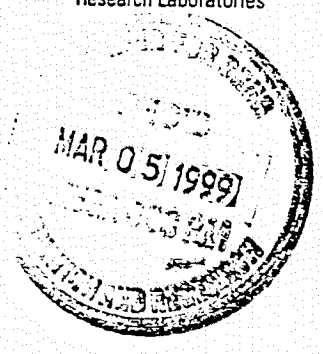
Research Laboratories



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

Reference is made to the above New Drug Application (NDA) and a request from Dr. Ho (FDA) by telephone to Dr. Silverman (Merck Research Laboratories [MRL]) on March 3, 1999, for the geographic address and CFN number for the facility that performed the stability testing for drug product manufactured at the manufacturing site proposed in the NDA

By this letter, MRL is providing the requested information which was also provided by telephone to Dr. Ho on March 3, 1999.

As discussed on March 3, this facility has both manufacturing and research operations on-site. The stability testing included in the NDA on material from was conducted in the research laboratories.

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/607

Federal Express #1

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

Larry P. Bell, M.D.
Senior Director
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March 5, 1999

NDA ORIG AMENDMENT
BC

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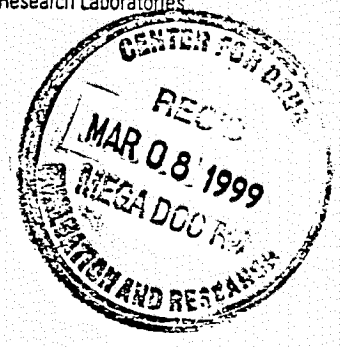
Research Laboratories



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

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

Reference is made to the above New Drug Applications submitted to the Agency on November 23, and to an amendment (chemistry) submitted on February 19, which provided 18 month stability data for all proposed market packages along with a full statistical evaluation of all available data to support a 24-month expiry. By this letter and attachment, MRL is providing EXCEL spreadsheets containing stability data as promised in the February 19, 1999 submission.

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 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

Attachments

Enclosures:
Compact Disk (CD # SM8BP0311974)

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. #2

cc: (cover letter with attachments)
Dr. Robert J. DeLap, Acting Director, NDA 21-042, HFD-550 - Federal Express #3

cc: (Cover letter, attachments)
Ms. Sandra Cook, Project Manager, HFD-550 - Federal Express #3

Q\robinson\defusco\diskettes

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

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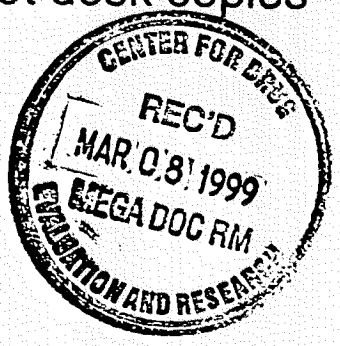
March 5, 1999



MERCK
Research Laboratories

BB

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. S. Cook (FDA) on March 2, 1999 with a request from the Pharmacokinetic Reviewer.

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

FDA Comment 1: In study P042, the statistical analysis is based on pooled data across Parts I and II. Since the randomization was done within each part, the reviewer believes that the analysis should be conducted separately for Parts I and II. In addition, period and sequence effects should be included in the final ANOVA model to evaluate the treatment effect.

MRL Response: To address all pharmacokinetic objectives of the protocol with equal precision, the analysis was based on combined Parts I and II. Separate analyses of Parts I and II for their respective objectives and a combined analysis for the inter-Part objectives would yield results based on different precision of variance. This could have led to inconsistent conclusions. As per the protocol, data from Parts I and II were analyzed separately in order to justify pooling Parts I and II to make treatment comparisons across the parts. Tests for period and carryover effect were carried out prior to pooling data across both parts. Both period and carryover effect needed to be assumed negligible to permit the combined analysis of Parts I and II because treatments are confounded with periods when the data from Parts I and II are combined for analysis. A significant period effect was observed in the first part of the study. The effect of period on the results was assessed as follows; observations were adjusted for period assuming that the period effect was linear across periods. A straight line was fitted to assess the change in $AUC_{(0-24)}$ with period. The slope of this line was used to adjust the response for period effect by subtracting an appropriate factor of the slope of this line from each individual observation. Since the treatment effect for the adjusted data was comparable to that observed for the unadjusted data, it was concluded that the period effect, though significant, does not affect the overall conclusions of the study. Hence the results reported in the Clinical Study Report (P042) are based on the data pooled across Parts I and II using analyses techniques described below per described in the protocol prior to unblinding of the results and summarized below.

Method used:

For Part I, the ANOVA model contained terms for subject, treatment, period and carryover effects. The carryover effect was dropped from the model because it was not significant, as specified in the protocol. Between-treatment comparisons of the pharmacokinetic parameters, i.e., $AUC_{(0-24)}$, C_{max} and T_{max}, were based on the final model.

Data from Part II was analyzed using an ANOVA model containing terms for sequence, subject within sequence, treatment and period effects. The period effect was dropped from the model because it was not significant, as specified in the protocol. Between-treatment comparisons were based on the final model.

If period and carryover effects were not significant, all pair-wise between-treatment comparisons of the pharmacokinetic parameters, for data pooled across both parts, was planned to be analyzed by a single ANOVA model containing terms subject and treatment effects. As mentioned above, this was done to make all treatment comparisons with the same degree of precision. Furthermore, since period effects across study Parts are confounded with treatment, period effect could not be included in the final ANOVA model. Also note that sequence effect is accounted for by the subject effect. The subject effect is equivalent to substitution of sequence effect and subject-within-sequence effect into the ANOVA model. Hence, the final ANOVA model did account for sequence effect.

As described above, since the overall results of treatment means for each group separately were clinically unaltered when adjusted for period effects compared to when unadjusted, the pooling of the data was justified. This permitted comparisons of treatments from both parts of the study to be made with equal precision. This approach also provides greater precision for estimation of the within-subject estimate of the variability term and hence enhances precision of the computation of the corresponding confidence interval calculations for the geometric mean ratios for AUC and Cmax.

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/605
Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
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NDA ORIG AMENDMENT

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March 5, 1999

BS

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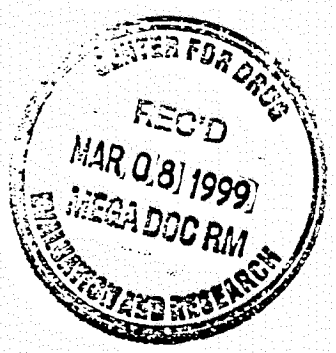
5600 Fishers Lane
Rockville, MD 20857



Dear Dr. DeLap:

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

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. S. Cook (FDA) on March 2, 1999 with several requests from the Statistical Reviewer.

By this letter, we are responding to the Agency's first request. The response to the second request will be forthcoming under separate cover.

FDA Comment 1: Please provide the SAS data set and program (Cox's PH model) that generates study by treatment interaction statistic (p=0.231) for study 44c.

MRL Response: The SAS program which generated the above noted p-value from the combined analysis of Protocols 044 and 045 is attached. The input data for this program is 'endosevt' which was sent to FDA in the statistical electronic filing (a part of the combined analysis of Protocols 044 and 045).

As can be seen in the attached SAS outputs, the model chi-square from the Cox PH model without the interaction terms is 103.039 with 4 degrees of freedom. The model chi-square from the Cox PH model with the interaction terms is 107.328 with 7 degrees of freedom. The statistic for testing study by treatment interaction is a chi-square statistic which is 107.328-103.039=4.289 with 7-4=3 degrees of freedom. Thus, the p-value is approximately 0.231.

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/604

Attachment

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

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

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March 9, 1999

NEW CORRESP

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

NC

Dear Dr. DeLap:

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

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. S. Cook (FDA) on March 2, 1999 with several requests from the Medical Reviewer.

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

FDA Comment 1: Please provide the intention to treat analysis of the data from study 041 and 050. It is illegible in the electronic submission. Also, please provide the results of the raw data on the 51CR EDTA/L-rhamnose ratio from the study, before geometric transformation.

In a subsequent teleconference, the reviewer requested an analysis of the ^{51}Cr EDTA/L-rhamnose ratios before geometric mean transformation.

MRL Response: Hard copies of the intention to treat analyses for studies 041 and 050 are included in Attachments 1 and 2. We apologize for the small print in these analyses. On some computers, legibility improves greatly with the "zoom in" tool, or after printing a hard copy.

Raw data are also requested. These were provided in the Case Report Tabulations for protocol 041 in the original NDA; the table is entitled "Permeability Assessment". The data are not transformed. We are providing a hard copy of the listing table (Attachment 3) with this response, to avert any risk of poor legibility.

This response contains arithmetic mean data for the ^{51}Cr EDTA/L-rhamnose ratios. These were computed for baseline and Day 7. The Day 7/baseline ratio without log transformation was computed and analyzed using an ANCOVA model with factors: treatment, subject, carryover and baseline.

As pointed out in the CSR, consumption of alcohol and other protocol violations can affect assessments of permeability. Therefore, per-protocol analysis was considered as the primary analysis and the intention-to-treat analysis was considered a supportive analysis. As indicated by the increasing SD with increasing mean (Day 7) in Tables 1 and 2, a log transformation to the data is necessary in order to satisfy the homogeneity and normality assumptions for the analysis. This transformation was prespecified in the protocol, based on review of the distribution of data from individual subjects in a prior permeability study at the same investigational site.

Results based on data without log transformation provided here are for reference purposes only; no conclusions should be drawn from them because of departures from assumptions necessary for valid ANOVA conclusions. The sample sizes presented in the analysis tables 3 and 4 are for those who had both baseline and Day 7 values. Since Protocol 041 had a cross-over design, Least Squares (LS) means adjusted for period, subject, carryover (and also baseline for Day 7 value and Day 7/baseline ratio) are presented in the analysis tables.

In these analyses, treatments are compared based on the difference of Day 7 to Day 1 ratios. The results indicate that indomethacin differs from placebo, while rofecoxib does not. The prespecified comparability bound is based explicitly on the geometric mean ratio for rofecoxib and placebo. Therefore, a formal assessment of comparability to placebo cannot be made using the data as summarized herein.

Table 1

Summary Statistics for Permeability Assessments

Per-Protocol

Parameter	Treatment	Baseline		Day 7	
		N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
^{51}Cr EDTA/L-rhamnose	Placebo	29	0.039(0.013)	29	0.040(0.020)
	MK-0966 25 mg	29	0.039(0.018)	29	0.033(0.013)
	MK-0966 50 mg	27	0.039(0.018)	27	0.043(0.039)
	Indomethacin 150 mg	26	0.039(0.015)	26	0.062(0.056)

Table 2

Summary Statistics for Permeability Assessments

Intention-to-Treat

Parameter	Treatment	Baseline		Day 7	
		N	Arithmetic Mean (SD)	N	Arithmetic Mean (SD)
^{51}Cr EDTA/L-rhamnose	Placebo	38	0.036(0.014)	38	0.037(0.019)
	MK-0966 25 mg	38	0.037(0.016)	39	0.031(0.012)
	MK-0966 50 mg	38	0.036(0.016)	37	0.040(0.034)
	Indomethacin 150 mg	36	0.038(0.017)	36	0.064(0.056)

Table 3

Per-Protocol Analysis of ^{51}Cr EDTA/L-rhamnose Urinary Excretion Ratio

Treatment	N	Baseline LS Mean	Day 7 LS Mean	Day 7/Baseline Ratio LS Mean	95% CI for Day 7/Baseline Ratio
Placebo	29	0.038	0.038	1.07	(0.78, 1.36)
MK-0966 25 mg	29	0.039	0.029	0.84	(0.56, 1.12)
MK-0966 50 mg	27	0.038	0.044	1.21	(0.91, 1.51)
Indomethacin 150 mg	26	0.041	0.072	1.83	(1.51, 2.15)

Between-Treatment Comparison	Between-treatment Difference of Day 7/Baseline Ratios	95% CI for Between-treatment Difference	p-Value
MK-0966 25 mg vs Placebo	-0.23	(-0.64, 0.17)	0.259
MK-0966 50 mg vs Placebo	0.14	(-0.28, 0.55)	0.509
Indomethacin 150 mg vs Placebo	0.75	(0.32, 1.19)	0.001
MK-0966 50 mg vs MK-0966 25 mg	0.37	(-0.05, 0.79)	0.081
Indomethacin 150 mg vs MK-0966 25 mg	0.99	(0.55, 1.43)	<0.001
Indomethacin 150 mg vs MK-0966 50 mg	0.62	(0.19, 1.04)	0.006

Effect	P-value
Treatment	<0.001
Baseline	<0.001
Period	0.893
Carry-over	0.074

Pooled SD for log Percent of Baseline	0.733

Table 4

Intention-to-Treat Analysis of ^{51}Cr EDTA/L-rhamnose Urinary Excretion Ratio

Treatment	N	Baseline LS Mean	Day 7 LS Mean	Day 7/Baseline Ratio LS Mean	95% CI for Day 7/Baseline Ratio
Placebo	38	0.035	0.036	1.08	(0.83, 1.33)
MK-0966 25 mg	38	0.036	0.027	0.83	(0.59, 1.08)
MK-0966 50 mg	37	0.037	0.042	1.21	(0.96, 1.46)
Indomethacin 150 mg	36	0.040	0.068	1.87	(1.61, 2.13)

Between-Treatment Comparison	Between-treatment Difference of Day 7/Baseline Ratios	95% CI for Between-treatment Difference	p-Value
MK-0966 25 mg vs Placebo	-0.25	(-0.60, 0.10)	0.164
MK-0966 50 mg vs Placebo	0.13	(-0.23, 0.49)	0.478
Indomethacin 150 mg vs Placebo	0.79	(0.43, 1.15)	<0.001
MK-0966 50 mg vs MK-0966 25 mg	0.38	(0.03, 0.73)	0.035
Indomethacin 150 mg vs MK-0966 25 mg	1.04	(0.67, 1.40)	<0.001
Indomethacin 150 mg vs MK-0966 50 mg	0.66	(0.30, 1.02)	<0.001

Effect	P-value
Treatment	<0.001
Baseline	<0.001
Period	0.208
Carry-over	0.013

Pooled SD for log Percent of Baseline	0.726