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/631

Attachment

Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Lawrence Goldkind, HFD-180, PKLN 6B-24, Federal Express #2

Robert E. Silverman, M.D., Ph.D.
Senior Director
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March 17, 1999

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Ms. Sandra Cook, Project Manager
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550, Rm. N317
Office of Drug Evaluation V (CDER)
Food and Drug Administration
9201 Corporate Blvd.
Rockville, Maryland 20857

Draft Background Package for Arthritis Advisory Committee

Dear Ms. Cook:

Reference is made to the above New Drug Application submitted November 23, 1998 and to the upcoming Arthritis Advisory Committee Meeting scheduled for April 20, 1999.

By copy of this letter we are providing 10 copies of MRL's draft background package for the Agency's review. This draft does not include a brief synopsis which will be placed at the front of the document that is still in preparation, and a copy of our proposed product label.

We would appreciate any comments you may have. Since we need to finalize this document for the Advisory Committee by next week, please send your comments to my attention by the end of business on Monday, March 22, 1999. We apologize for the short time we have allowed for your consideration.

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

Federal Express

Q\robinson\defusco\brpkg

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

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DUPLICATE

March 18, 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

NEW CORRESP
NC

CENTER FOR DRUG
REC'D
MAR 22 1999
MEGA DOC RM
EVALUATION AND RESEARCH

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 16, 1999 with requests from the Pharm Reviewer.

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

FDA Comment 1: Please re-analyze your BE study #070 for 25 mg (suspension vs. tablet). Include sequence as a factor in the ANOVA model.

MRL Response: Based on the linear models theory for designs with three or more periods, we used a model with the following terms: subject, period, and treatment. This ANOVA model yields identical results for the period & treatment effects as the ANOVA model with the following terms: sequence, subject within sequence, period, and treatment. The other effects explain the exact same variability. The subject effect can be further partitioned into the following components: Sequence and Subject within Sequence. Please note that in the balance case, the type III Sum of Squares and the corresponding degrees of freedom of the Sequence effect, plus the Subject within Sequence effect equals the type III Sum of Squares for the Subject effect alone. Either parameterization yields identical treatment LSmeans, GMR's, 90% CI's, p-values, and corresponding within-subject variance estimate. Both parameterizations of the ANOVA model (the original from the CSR and the one requested by FDA) are included in Attachment 1. Relevant SAS output from the GLM models are also included for completeness.

FDA Comment 2: Please provide Child-Pugh scores (including the scores for all components) for all patients with hepatic insufficiency (Study #057). Please provide them in table format. The sample table is being faxed to you.

MRL Response: Attachment 2 is the response to this request.

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/627

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 18, 1999

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ORIG AMENDMENT

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 16, 1999 with a request from the Pharm Reviewer.

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

FDA Comment: We have received your response dated March 12, 1999 to our request of conducting a separate analysis for Part I and Part II including period and sequence effects in the ANOVA model. In your response, period effect was included in the analysis for Part I; period and sequence effects were included in the analysis for Part II. For the combined analysis, neither period nor sequence effect was included in the model.

As indicated in our original comment, please submit the results of separate analysis for Part I and II including subject, period, sequence and treatment effects in the ANOVA model. In addition, geometric mean ratio (GMR) and 90% confidence interval of GMR need to be calculated for each comparison. If the sponsor wishes to conduct the combined analysis, subject, period, sequence and treatment effects should also be all included in the model.

MRL Response:

- Per your request, GMR's and 90% CI's have been amended (Attachment 1) to the response submitted on March 12, 1999. The separate analyses accounting for sequence, subject within sequence, period, and treatment were initially submitted in that response. As a point of clarification, in Part I, the sequence effects were accounted for by the subject effects in the regular crossover ANOVA model which was employed (See Section I of March 12th response). A model containing terms for sequence, subject within sequence, period and treatment yields identical results as a model containing the terms subject, period and treatment. This is due to the fact that the sequence and subject within sequence effects

account for the exact same variability as the subject effects. Attachment 2 includes a detailed analysis for the model containing terms for sequence, subject within sequence, period and treatment.

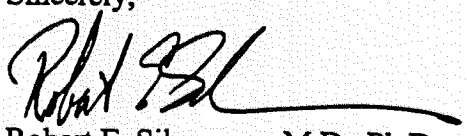
- GMR's and 90% confidence intervals for all treatment comparisons derived from separate ANOVA models for Parts I and II are provided in Attachment 3. These GMR's and confidence intervals were computed using the variability measurements from the individual parts and combining them using the usual t-distribution methods for differences between means on the log scale.

- Finally, analyses were done for the combined (Parts I and II) data with a model containing terms for sequence, subject within sequence, period, and treatment. As expected, period and treatment are confounded, therefore treatment effects were not estimable. In order to estimate the adjusted treatment effects, three dummy variables, prt1prd1, prt1prd2, and prt2prd1, were created to partition the degrees of freedom associated with period. This enables the estimation of treatment effect. Attachment 4 contains details on this analysis. Note that the results for this analysis are identical to those seen with the model containing terms for subject and treatment that was provided in the March 12, 1999 (see Part III) response.

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.

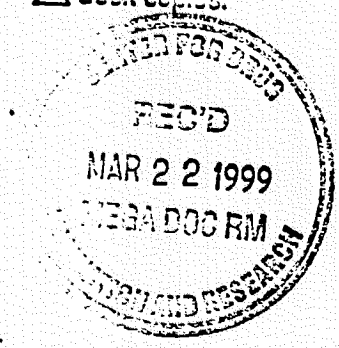
Sincerely,



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

q/shilling/ltr/626
Attachments
Federal Express #1
Desk Copy/attachments: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Dan Wang, HFD-880, CRP2 N363, Federal Express #2

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



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MERCK
Research Laboratories

March 18, 1999

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

ORIG AMENDMENT

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 a telephone conversation between Dr. Pelayo, (FDA) and Dr. Silverman, (Merck Research Laboratories [MRL]) on March 15, 1999, during which Dr. Pelayo made a request for information on electrolyte data from clinical studies.

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

FDA Request: Identify which clinical protocols contain data on serum bicarbonate, chloride, magnesium and phosphorous and where this data can be found in the NDA.

MRL Response: Serum magnesium and phosphorous were not assess in the clinical program. Bicarbonate and chloride were measured in Protocols 044 and 045, the two 6-month OA endoscopy studies. This data can be found in the Case Report Tabulations by protocol and patient in the electronic NDA as PDF files (also Appendix 4.16.1 of each clinical study report [Clinical Documentation, References P044 and P045]) in the electronic NDA. Additionally, this data can be found in the SAS transport files provided as part of the electronic NDA, as described in the User Manual for the electronic NDA. Attached is page 34 from that manual which describes the access to the SAS transport files.

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/633
Attachment

Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Juan Pelayo, HFD-110, WOC2 2095, Federal Express #2

APPEARS THIS WAY
ON ORIGINAL

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

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March 19, 1999

NDA ORIG AMENDMENT

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Research Laboratories

BM
1 (HFD-110)

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 a telephone conversation between Ms. Sandra Cook, (FDA) and Dr. Silverman, (Merck Research Laboratories [MRL]) on March 16, 1999, during which the Agency made a request from the Cardiorenal Reviewer (Dr. Juan Pelayo).

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

FDA Request: Please provide survival plots and cumulative incidence tables for lab AE's increased serum creatinine, hyperkalemia, and proteinuria. Also provide these tables & plots for the corresponding pre-defined limits of change.

MRL Response: Per your request, we have analyzed safety data for the selected laboratory adverse experiences and laboratory values exceeding the predefined limits of change using survival analysis methods. Attachment 1 reports the results, including dropout-adjusted cumulative incidence rates for the combined population of all OA studies and plots of the associated estimated survival distributions. Interpretation of these results must be made with caution because of the confounding of protocol-type with treatment groups (doses of Rofecoxib and NSAID comparators) and treatment duration. Not all treatments were studied in all protocols; hence, some results from these analyses could be influenced by factors of protocol-type and/or treatment duration, not only by the actual treatments themselves. In addition, since sample sizes decrease substantially between the 1 year and 86 week time points, results at the latter time points must be viewed with added caution because they are more highly variable. This cannot be easily shown on the survival plots because of the large number of treatment groups, but is shown via patient counts and confidence intervals on the summary tables.

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:\amirault\fda\100

Attachment

Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Juan Pelayo, HFD-110, WOC2 5073, Federal Express #2

Robert E. Silverman, M.D., Ph.D.
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March 19, 1999

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NDA ORIG AMENDMENT
RM

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 telephone conversation between Ms. Cook and Dr. Goldkind (FDA) and Dr. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on March 17, 1999; a follow-up e-mail from Ms. Cook on March 18, 1999; and a conversation between Dr. Goldmann (MRL) and Dr. DeLap and Ms. Walling (FDA) on March 19, 1999. During the March 17th conversation the Agency requested an additional analysis for GI events that was clarified in the March 18th e-mail.

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

FDA Request: Please reanalyze the incidence of clinical events in Protocol 069 after excluding the 14 cases identified in the attached list. The rationale for excluding each of these cases is provided, for information.

MRL Response: The analysis is provided with this response (Table 1). The relative risk for MK-0966 vs NSAID over the 12 month treatment period was 0.45 (95% CI 0.24, 0.85, p=0.012). This is similar to that observed in the original analysis.

As discussed between Dr. Goldmann, Dr. DeLap and Ms. Walling, MRL has very little information on the FDA's rationale for this request, but in the spirit of open exchange, we detail, herein, our reservations about the scientific validity of the analysis, from the information available to us at this time. These reservations stem mainly from the potential for bias. We also provide our perspective on the stated rationale for excluding and including certain cases.

Table 1

Survival Analysis for Incidence of Confirmed plus Unconfirmed Upper-GI PUBs (Excluding 14 Cases Identified by FDA)

Time Point	Number of Patients with Incidence			Rate per 100 Patient-Years			Cumulative Incidence[#] (%) at Each Time Point		
	Placebo (N= 514)	MK-0966 (N=3357)	NSAIDs (N=1564)	Placebo	MK-0966	NSAIDs	Placebo	MK-0966	NSAIDs
6 Weeks	1	4	10	1.76	1.05	5.68	0.22	0.12	0.69
4 Months	2	13	15	1.79	1.71	4.49	0.57	0.62	1.32
6 Months	n/a	15	18	n/a	1.50	4.19	n/a	0.75	1.79
12 Months	n/a	20	19	n/a	1.40	3.09	n/a	1.33	2.06

Overall Summary Statistics for Between-Treatment Comparison

		Cumulative Incidence Difference (%)	95% CI for Cumulative Incidence Diff. (%)	Relative Risk[*]	95% CI for Relative Risk	p-Value[**]
Primary Results:	MK-0966 vs. NSAIDs (across first 12 Months)	-0.73	(-1.93, 0.47)	0.45	(0.24, 0.85)	0.012
Other Results:	MK-0966 vs. NSAIDs (across first 6 Weeks)	-0.56	(-1.00, -0.12)	0.19	(0.06, 0.59)	0.001
	MK-0966 vs. NSAIDs (across first 4 Months)	-0.70	(-1.48, 0.09)	0.38	(0.18, 0.80)	0.008
	MK-0966 vs. NSAIDs (across first 6 Months)	-1.04	(-2.00, -0.08)	0.36	(0.18, 0.72)	0.002
Placebo Results:	NSAIDs vs. Placebo (across first 4 Months)	0.75	(-0.32, 1.82)	2.59	(0.59, 11.31)	0.190
	MK-0966 vs. Placebo (across first 4 Months)	0.05	(-0.83, 0.94)	0.96	(0.22, 4.29)	0.962

Cumulative incidence from the survival analysis, it may not equal (number of patients with incidence/N) x 100.

* From the Cox Proportional Hazards Model.

** From the log-rank test for the comparison of the cumulative incidence curves.

General Comments

The request is for an analysis based on a repeat adjudication of the 55 cases of perforation ulcer or bleed that form the basis of Protocol 069. This study was a combined analysis of the Phase IIB/III study program. It represents a prospectively defined evaluation of the incidence of perforations, ulcers and bleeds.

This combined analysis of randomized, double-blind trials was undertaken with the attention to rigorous design we employed in our individual trials. The steps taken to avoid bias included a prespecified case definition (developed based on literature and expert input) and a prespecified data analysis plan. Most importantly, a blinded internal coordinating center and a blinded external review committee were established to avoid bias in areas that required expert judgment about potentially unclear situations. The blinded review committee consisted of two expert gastroenterologists and an epidemiologist, all of whom are extremely well qualified to review such cases, by reason of training, expertise, and record of publication. As with any pivotal trial, documentation was provided to the Agency in advance of unblinding of the study endpoints.

We took care to detail the steps to minimize potential bias in the adjudication process, to facilitate review by FDA. The report of Protocol 069 specifically details the time of adjudication relative to the time of study unblinding. This led FDA to ask a follow-up question that required a detailed review of adjudication records, to provide assurance that unblinded personnel did not influence the outcome of the adjudication process or the analysis.

These actions by MRL and FDA were designed to minimize potential bias, and to serve the common goal of providing an objective, unbiased comparison of rofecoxib to NSAIDs. The GI reviewer noted that for Celebrex, the definition of significant GI event was "not defined in the studies in a way to prospectively or statistically evaluate... claims". Under such circumstances, a re-adjudication can perhaps be as valid as an original adjudication. However, in the case of Protocol 069, the original adjudication was made in a fully prespecified, blinded manner. Any analyses based on an unblinded, post-hoc readjudication must be viewed as a type of sensitivity analysis, carrying less weight than the primary, prespecified, blinded analyses. We also note that none of the sensitivity analyses provided in the report of protocol 069 involved post hoc readjudication of individual cases.

Specific Cases

Our primary concerns with this request are methodologic, as outlined above. However, given a decision to proceed with a case by case re-adjudication, we appreciate the Agency's willingness to provide a rationale for each exclusion (Attachment 1). Technical issues with the handling of selected cases are provided below.

Case 062, diclofenac: The reviewer excludes this case of GI hemorrhage. We believe this decision reflects potential misinterpretation of an endoscopy report. The reviewer

noted that the patient had a hemoglobin of 13.5, which had dropped to 10.1 g/dl. A concurrent endoscopy revealed grade 1 esophagitis (endoscopists report). A colonoscopy was negative. The reviewer excludes this case on the basis that "anemia was present when esophagitis wasn't even erosive. Hgb rose while esophagitis slightly worsens." The endoscopist stated explicitly in his report that the patient's esophagitis was grade 1 by the Savary Miller scale, and later progressed to grade 2.

The key issue is the grading scale. The Savary Miller scale is used widely internationally: Grade 1 on this scale includes erosive change of the esophagus. Grade 2 involves confluent but non circumferential erosive changes. In the U.S., the Hetzel Dent scale is used more commonly: Grade 1 corresponds to erythema and edema without erosive change, as noted by the reviewer, while grade 2 requires erosive change. Therefore, erosive esophagitis was documented as being present at the time of the decreased hematocrit, and having worsened over the course of treatment.

Case 058, placebo: The reviewer excludes this case, based on credibility of the report of melena. We agree with the committee's blinded determination. The physician's narrative stated that there was a two week history of melena confirmed by the physician, and believed that the diagnosis had been confirmed. This determination was made while all parties were blinded.

There appears to be a typographical error under case 042—this case was an ibuprofen case, not MK-0966 50 mg.

Finally, we note that the reviewer allowed three of eleven rescheduled endoscopy cases (which occurred outside of the +/- 7 day windows) to remain in the analysis (Cases 029, 032, 060). The basis for these decisions is not available to us.

- In Case 029, the patient reported abdominal pain beginning on relative day 1 and occurring continuously from relative days 10 to 99; an endoscopy was performed, per protocol, on relative day 95 because the patient had been discontinued due to peripheral edema. The protocol required endoscopy in cases of early discontinuation.

- In Case 032, "the endoscopist was on vacation" and the Week-12 scheduled endoscopy was consequently performed outside of the +/- 7 day window. No GI symptoms were reported.

- In Case 60, the patient reported epigastric pain beginning two days prior to initiation of study medication, continuing intermittently until relative day 86. The endoscopy form from the visit at which the ulcer was detected (relative day 96) reads "visit date deviation was simply for scheduling reasons (patient's personal problems)".

For all three of these cases, notes on the worksheets, database, and/or case report forms as well as letters signed by the investigators confirm that the events were rescheduled