Robert E. Silverman, M.D., Ph.D.
Senior Director
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March 25, 1999

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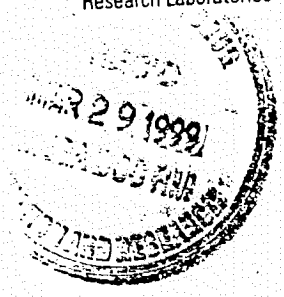
Research Laboratories



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
Response to FDA Request

Reference is made to the above New Drug Application, and a telephone conversation between Ms. Sandra Cook (FDA) and Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on March 23, 1998, during which the Agency made a request for information from the Cardiorenal Reviewer (Dr. Juan Pelayo).

By this letter and attachment, MRL is providing a response to this request.

FDA Comment: Please provide plots of pre-defined limit of change for decreased HCO^-_3 and increased Cl^- laboratory values from Protocols 044 and 045. Also break out by treatment groups and provide life tables for the corresponding pre-defined limits of change.

Merck Response: There was no pre-specified analysis of serum bicarbonate and chloride in the Data Analysis Plan for the phase II/III OA program. As discussed in an earlier reply, the two 6-month endoscopy studies, Protocols 044 and 045, did collect this laboratory data on all patients. The following post hoc analyses will be presented for both serum bicarbonate and chloride:

- Graphs of the percent mean change from baseline
- A predefined limits of change analysis

Overall, the effects on these electrolytes were similar among all active treatment groups. The mean change in serum bicarbonate and chloride was clinically and statistically insignificant (less than 1% for both the 25 and 50 mg rofecoxib groups). Similar numbers of patients exceeded the predefined limits of change for serum bicarbonate and chloride in the active treatment groups. The changes with rofecoxib and ibuprofen were not statistically different compared to placebo.

In the interpretation of these results, two points need to be considered. First, the 50 mg rofecoxib group is two to four times the clinical OA dose. Even at this high dose, the effects on the electrolytes was clinically and statistically insignificant. Second, both the placebo and ibuprofen groups had approximately a third less exposure compared with the rofecoxib groups. This affects

the interpretation of the predefined limits of change analysis as there were fewer laboratory examinations performed on these groups.

Mean Percent Change from Baseline

The mean percent change from baseline in serum bicarbonate was 1.3, -0.4, -0.9 and –1.2 % in the placebo, 25-, 50-mg rofecoxib and ibuprofen groups, respectively (Figure 1). The mean percent change from baseline in serum chloride was 0.1, 0.7, 0.6 and 0.6 % in the placebo, 25-, 50-mg rofecoxib and ibuprofen groups, respectively (Figure 2). No placebo values are recorded after Week 16 (except for the post study visit) as there was a planned discontinuation of this treatment group at Week 16.

Predefined Limits of Change Analysis

A predefined limit of change parameter was not pre-specified for these electrolytes. In this post hoc analysis a conservative approach was taken. The limit for serum bicarbonate was a decrease of 1 mEq/L or greater from baseline and the value below the LLN. The limit for serum chloride was an increase in 1 mEq/L or greater from baseline and the value above the ULN. The number of patients exceeding the predefined limits of change was similar for all treatment groups (Table 1). Both the placebo and ibuprofen groups had approximately a third less exposure.

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,

Eric A. Floyd for

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

q:\amirault\fda\105

Attachments

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

Robert E. Silverman, M.D., Ph.D.
Senior Director
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March 31, 1999

ORIG AMENDMENT

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Robert J. DeLap, M.D., Acting Director
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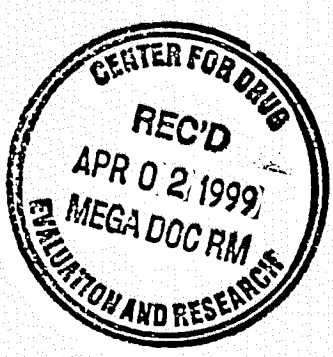

Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA); responses to Agency requests concerning additional analyses of GI clinical events submitted on March 16, 19 and 23, 1999; an e-mail request for additional analyses from Ms. Cook (FDA) on March 25; and a series of teleconferences between FDA and Merck Research Laboratories (MRL), a Division of Merck & Company, Inc. on March 24, 27 and 29 to clarify the Agency's requests.

By this letter and attachments, MRL is providing responses to the Agency's requests as agreed during the March 29 teleconference.

FDA Requests: Please reanalyze the PUB 069 database including the cases listed in Attachment 1 (e-mail from S. Cook to R. Silverman, March 25, 1999). It would be of value to know if there is documentation of physician witnessed melena as defined in the protocol for patient 058. Also, please break down the analyses by rofecoxib dose and individual NSAID comparators.

MRL Response: General Issues

The requested analyses of the lists of 37 cases and 11 cases are provided below, beginning with Attachment 2.

MRL's general concerns regarding the re-adjudication of PUB cases from the Protocol 069 database have been outlined in previous responses. As was clarified during conversations with the GI reviewer, the lists of cases below represent the reviewer's re-adjudication of confirmed cases, based on the prespecified protocol case definitions. We

note that "mixing" the adjudications of the blinded committee with unblinded re-adjudications appears to weight these two methods equally.

With regard to the question about Case number 58, all information obtained by MRL was provided in the data package submitted previously. Because that considerable time has elapsed and the study is unblinded, additional data have not been sought. It should be noted, that the prespecified case definition required "physician documented frank melena (distinguished from other dark stool, e.g. that due to bismuth salts)", rather than "physician witnessed" melena. The investigator narrative stated that "the patient reported a description of melanotic stools, confirmed by the physician...", and the blinded case review committee adjudicated this as a confirmed, complicated case, based on the above, prespecified definition.

Ambiguous situations occur in clinical medicine, and there can easily be disagreement about details cases. The protocol was designed to deal with these ambiguities by minimizing bias through blinding, and assigning resolution of ambiguity to unbiased experts. Though MRL might have differed with some of the determinations, no attempt was made to influence or re-adjudicate decisions, because they were made while blinded, by an external committee, and according to criteria that were pre-specified in the protocol that had been sent to FDA prior to blinding.

The Agency has also requested information on the rate of events in individual dosage groups, for each of the analyses agreed upon in our telephone conversation of March 29. Although we understand that the Agency wishes to evaluate individual doses and are providing the analyses, we feel that the original combined analysis remains most appropriate. The Protocol 069 Clinical Study was conducted using a prespecified set of studies, a single primary hypothesis, and predefined methods of data handling and analysis. The hypothesis referred to a general question, concerning rofecoxib (pooled doses), and comparator NSAIDs (pooled treatments). Pooling allowed an examination of a group of patients receiving on average 24.7 mg rofecoxib daily, which is very close to the highest dose that is being proposed for chronic treatment of OA.

To assure that pooling across doses was valid, Protocol 069 was re-analyzed after stratifying by protocol type. These analyses demonstrated virtually identical results to the prespecified non-stratified analysis, suggesting a lack of confounding by protocol type for the analysis of rofecoxib (all doses) and comparator NSAIDs (pooled treatments) and supporting the prespecified combined analysis approach. In other words, the analysis is compatible with a stratified approach based on comparing rofecoxib to NSAIDs within each protocol type and combining to estimate an overall single relative risk. Similar levels of consistency are observed in a non-stratified analysis of the 37 cases adjudicated

by the Agency as confirmed and an analysis stratified by protocol type (Attachment 3); this also lends supports to the validity of a combined approach.

Complicated Events vs Perforations, Obstructions, Bleeds (POBs)

The list of 11 cases identifies patients who experienced complicated events, according to the definition in the protocol. However, neither the protocol nor the data analysis plan contained a pre-specified hypothesis concerning complicated cases. The report of Protocol 069 does contain a post hoc exploratory analysis of such cases. The estimates of risk reduction favored rofecoxib over NSAID, and were consistent with those of the original analyses.

Given that perforations, obstructions and bleeds have been identified by some as the most clinically relevant set of events, a different approach is necessary in order to estimate the relative occurrence of POBs on rofecoxib and NSAID. Crude rate analyses of POBs have been performed on the Protocol 069 database and were provided to the Agency on March 17. Corresponding survival analyses will be provided under separate cover.

It is important to distinguish between complicated events as defined in the protocol and perforations, obstructions, and bleeds (POBs). The protocol 069 definition of complicated event includes cases of giant ulcer and endoscopically visible vessel. Many investigators currently believe that giant ulcers and endoscopically visible vessels do not themselves represent complications, as evidenced by the fact that these events have not been assessed for other drugs (e.g. celecoxib).

Results

The current request is to analyze a list of 37 cases, and a list of 11 cases. The first contains cases that the reviewer has re-adjudicated as confirmed (complicated plus uncomplicated), and the second contains the subset of these cases that the reviewer has re-adjudicated as complicated.

Confirmed (Complicated and Uncomplicated; N=37)

The 37 cases designated on the first list are the same as those analyzed in the MRL response to FDA submitted on March 23, 1999; therefore, the results are the same. In this analysis (Attachment 3), rofecoxib remained significantly superior to NSAID, relative risk 0.51 (95% CI 0.26, 1.00; p=0.045). The result of this analysis is consistent with the original analyses presented in the report of Protocol 069. We have also provided, for the 37 cases, a table (Attachment 4) by type of protocol and by treatment

within type of protocol (analogous to Table 17 from the Protocol 069 Clinical Study Report).

A breakdown by dose is also provided (Attachment 5). In this analysis, cumulative incidences for each rofecoxib dose and NSAID comparator are displayed at 6, 12, 24, 52 and 86 weeks. The results of this analysis must be interpreted with caution, because of confounding of treatment groups by type of protocol. More specifically, not all individual NSAIDs, or doses of MK-0966 were studied in all protocols; the protocols differed in duration of treatment; and some protocols had greater restrictions on concurrent medication for GI adverse events than others (e.g., H_2 receptor antagonists were completely prohibited in the endoscopy studies, but not in OA efficacy studies). The placebo group was stopped at 16 weeks; therefore, information beyond 12 weeks reflects only one month of planned experience. The rofecoxib 50 mg data prior to six months come primarily from Protocols 044 and 045, however, after six months, only Protocol 029 contributed rofecoxib 50 mg data. Nabumetone was included only in Protocol 058, and the numbers of patients on nabumetone were small. Therefore, some of the apparent differences between doses and individual NSAID comparators may be due in part to differences between protocol types, rather than differences between the treatments. The pooled analysis and prespecified hypothesis do not suffer from these limitations, because every study contained rofecoxib and a comparator NSAID.

In addition, sample sizes decreased substantially at and after end-of-study time points, especially between the 1 year and 86 week time points; therefore, results at the latter time points must be viewed with added caution because they are more highly variable. This is shown via patient counts and confidence intervals on the summary tables.

Confirmed, complicated cases (N=11)

In this analysis (Attachment 6), rofecoxib is numerically superior to NSAID, and the point estimate of difference is the same as that observed for the list of 37 cases above, however statistical significance is lost in this small number of cases, relative risk 0.51 (95% CI 0.16, 1.69; p=0.263). The results of this analysis are identical with the original analyses of confirmed, complicated cases presented in the report of Protocol 069.

We have also provided, for the 11 cases, a table (Attachment 7) by type of protocol and by treatment within type of protocol.

A breakdown by dose is also provided (Attachment 8). In this analysis, cumulative incidences for each rofecoxib dose and NSAID comparator are displayed at 6, 12, 24, 52 and 86 weeks. This analysis obviously carries the same cautions regarding interpretation

outlined above for the by-dose analysis of the 37 cases, particularly because of the very small number of events.

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/ltr637

Federal Express #1

Attachment

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.
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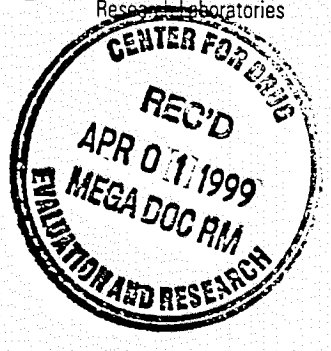

March 31, 1999

Robert J. DeLap, M.D., Ph.D., Acting Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Food and Drug Administration
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 fax sent by Ms. Sandra Cook, (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. on March 23, 1999, that contained the following comments from the reviewing pharmacologist (Dr. Wilson) on MRL's draft background package for the April 20, 1999 Advisory Committee meeting.

MRL appreciates the Agency's comprehensive and insightful review. By this letter, MRL is providing a response to the Agency's comments.

FDA Comment 1: On page 3 [2.1, 2nd paragraph] and 5 [2.3.2; 1st paragraph, there are statements which indicate that there were no gastric lesions/ulcerations observed following administration of rofecoxib. Admittedly, this is the case for a number of the studies. However, following combination of ulcers, erosions, perforations, and scarring for a given anatomical area of the stomach [e.g. glandular], there was a slight increase in the incidence of gastric lesions [Study #TT95-601-0 and Study #TT96-603-0;1] compared to the control animals. Therefore, these statements should be modified to reflect these findings.

MRL Response: We agree with the Agency that there were a few instances of glandular lesions in the stomachs of rodents in a few studies [Study TT #95-601-0 and Study TT #96-603-0] compared to control animals. The incidence of the gastric lesions is extremely low and, in each animal noted by the Agency, represents spontaneously induced stress erosions/ulcers in rodents which are secondary to the debilitated state of the animals caused by intestinal ulceration/peritonitis. As reported in the literature and as we have observed in toxicity studies, stress-induced ulcers (erosions) in the glandular portion of the stomach secondary to a variety of stress etiologies including, body weight decrements, have been observed in rodents. It is also important to note that gastric ulceration was not observed in dogs, the nonrodent species used to evaluate the toxicity of rofecoxib. Therefore, the background package has been modified to indicate that gastric ulceration is not directly related to rofecoxib.

FDA Comment 2: On page 7 [2.4.4 **Metabolism**], the following statement is made. "The principal metabolites observed in man have also been identified in the animal species, demonstrating that the toxicity profiles of both rofecoxib and its metabolites have been adequately assessed in animal safety studies." Please provide a tabular presentation of the clinical and nonclinical pharmacokinetic data [including AUC] that supports this statement. Although, the toxicity of L-755,190 has been evaluated, the nonclinical evaluation of the major metabolite in humans [*cis* and *trans*-dihydro-rofecoxib] does not appear to have been as extensively evaluated. If this information is not available, this statement should be modified or deleted.

MRL Response: All principal metabolites observed in man have been observed in one or more of the animal species used in the preclinical toxicity studies. Because rofecoxib has a low order of toxicity, preclinical studies could be completed in animal species at dosages far in excess of the clinically relevant dosage. As a consequence, the exposure of the preclinical species to rofecoxib and the predominant human metabolites could be achieved at exposures in excess of those expected at the clinical dosage.

The dihydrohydroxy acid metabolites (DHHA) of rofecoxib were quantitated in 0-24 hr urine samples of rats, dogs and humans after oral administration of ^{14}C-labeled rofecoxib. The results (table below) clearly demonstrate that both rats and dogs are exposed to one or both of these metabolites in several fold excess to that expected in humans after a 25 mg dose, the highest OA dosage.

Assays to quantitate these metabolites in plasma have not been developed and thus information on systemic exposure as determined by plasma AUC is not available.

Exposures to cis- and trans-dihydro-rofecoxib in rat, dog and human

Species	Dose	Percent of Dose (0-24 hr, urine)				
		Rofecoxib Eq. [Total C14]	Cis-dihydro-rofecoxib	Trans-dihydro-rofecoxib	Total DHHA	Amount
Rat	100 mg/kg	5%	0.18%	0.21%	1.14%	1.14 mg/kg
Dog	5 mg/kg	16.8%		10.5%	10.5%	0.52 mg/kg
Human	2.5 mg/kg (125 mg total dose)	37.1%	8.5%	12.4%	20.9%	0.52 mg/kg (26 mg)
Human	0.5 mg/kg (highest OA dosage)					0.1 mg/kg (5.2 mg)

Further, dihydro-rofecoxib has been shown not to be active against the human COX-1 or COX-2 isozymes with IC_{50}s greater than 50 μM. The observed toxicity profile of rofecoxib represents a subset of the mechanism based toxicity seen with nonspecific COX inhibitors. Since the principal human metabolites are inactive, there do not appear to be any toxicities attributable to these metabolites that are present in animals administered high doses of rofecoxib. It is for these reasons that we believe that rofecoxib and the metabolites pertinent in human exposure have been assessed in the preclinical toxicity studies.

FDA Comment 3: Qualitative statements referring to the margin of safety or to does which exceed clinical doses [e.g. p. 9:2.5.1, 2nd paragraph and p. 10; 2.5.1.2, 2nd paragraph] should be clarified by the inclusion of a quantitative measure [multiple of the human clinical dose based on AUC].

MRL Response: The paragraph cited in the Agency's comments represents general introductory statements. Specific details about margins of safety are discussed within the pertinent sections of the background package.

FDA Comment 4: On page 11 [2.5.3, 3rd paragraph], it is stated that the "NOEL for intestinal ulcers in rats was ....5 mg/kg/day ... after approximately 27 weeks. However, there was a single female rat in the 5 mg/kg/day group [Study #TT 95-045-0] which, at the Week 27 interim sacrifice, had a small intestinal ulcer. This is considered a treatment-related effect. Therefore, the NOEL for this time point should be 2 mg/kg/day.

MRL Response: The text has been revised to correct the typographical error.

FDA Comment 5: The increase in incomplete ossification in the rabbit study [Study #TT 95-704-0] at 25 mg/kg/day was comparable to that observed at 50 mg/kg/day and that the NOAEL for this finding should be 10 and not 25 mg/kg/day.

MRL Response: We agree with the Agency that there is a slight increase in incomplete ossification in the fetuses/litters from the 50 mg/kg/day group in the rabbit study [TT #95-704-0]. At 50 mg/kg/day, the increase in incomplete ossification is accounted for by a slight increase in the number of incomplete metacarpal ossifications with no other ossification sites showing significant differences from controls. The Agency has concluded that there is an increase in incomplete ossifications at 25 mg/kg/day. We believe this increase in incomplete ossifications at 25 mg/kg/day is not treatment-related since there is no increase in the incidence of fetuses with incomplete metacarpal ossification when compared to controls (18 at 25 mg/kg/day vs. 17 in the controls). The overall incidence of incomplete ossifications of fetuses in the 25 mg/kg/day group above the concurrent controls is due to a disproportionately high number of fetuses with incomplete ossification of the sternebra. In our opinion the higher incidence of incomplete ossification of the sternebra represents biological variation and is not related to administration of rofecoxib based on the following data. The incidence of incomplete ossification of the sternebra is not dose-dependent (20 at 25 mg/kg/day vs. 12 at 50 mg/kg/day), is due to one litter (8/20 from one litter) and the overall incidence excluding this one litter is not remarkably different from the historical control incidence (10.3% at 25 mg/kg/day vs. 8.9% for the historical control incidence) and within the historical range (2.5 to 14.6%).

Although we disagree with the position of the Agency, we have modified the text to indicate that there is an increase in the incomplete ossification of the metacarpus at 50 mg/kg/day and that the clear NOEL for incomplete ossifications is $\geq$ 10 mg/kg/day.

FDA Comment 6: Results from the cross-fostering study [Study #TT 95-730-0] should be included in the discussion of postweaning effects [2.6.3; p13, 5th paragraph]. This study indicates that pup survival is decreased following gestational as well as lactational exposure to rofecoxib. This finding is considered an important component of the toxicological profile of the drug.

MRL Response: We agree with the Agency's position and have indicated there were perinatal/postnatal effects in the background document. These effects are as a consequence of both gestational and lactational exposure as confirmed in the cross-fostering study (TT #95-730-0). To clarify that point, an additional sentence has been added to the background document to indicate the results of the cross-fostering 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.

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

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Federal Express #1
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Dr. Susan Wilson, HFD-550, CRP2 N368, Federal Express #1

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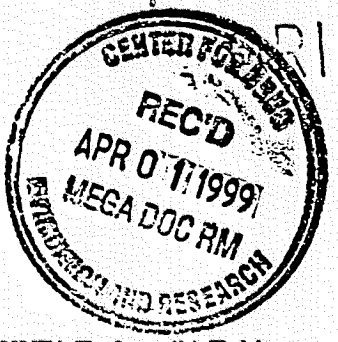
March 31, 1999



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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 submission on March 17, 1999, from Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., that contained a set of tables of crude rate analyses (number of patients with events / number of patients exposed to drug), based on patients with upper GI perforations, obstructions and bleeds ("POBs") from the Protocol 069 combined analysis.

By this letter and attachments MRL is providing, for the FDA's reference, a number of time-to-event survival analyses of Protocol 069 POB data. Results of the survival analyses are attached in Tables 1-5. The patients analyzed by survival method in the attached tables correspond exactly to the patients analyzed by crude method in the March 17th submission (i.e. Table 1 from March 17 corresponds directly to Table 1, attached).

A specific listing of clinical cases used in these analyses appears in Tables 6-7 (also provided in the March 17th submission on crude rate analyses).

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.

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Senior Director, Regulatory Affairs

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Attachments

Federal Express #1
Desk Copy: Ms. Sandra Cook, HFD-550, CRP2 N317, Federal Express #1
Dr. Lawrence Goldkind, HFD-180, PKLN 6B45, Federal Express #2

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April 1, 1999

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5600 Fishers Lane
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Dear Dr. DeLap:

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

Reference is made to the above New Drug Application (NDA) and two e-mails sent to Dr. R. Silverman, Merck Research laboratories (MRL), a Division of Merck & Company. Inc from Ms. S. Cook (FDA) on March 24 and 25, 1999 with requests from Dr. Wilson (FDA Pharm/Tox reviewer).

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

FDA Comment 1 (e-mail of March 24): Historical control data from the labs in which the carcinogenicity studies were conducted for:

1. mice - Crl:CD-1[IBR]
2. rats - ad libitum fed as well as restricted diet animals

This data should include, in addition to ranges, data from individual studies which have been conducted within the last 5 years, preferably. Please indicate when the studies were conducted.

MRL Response: The historical control data for all tumor types observed in the Vioxx™ carcinogenicity studies are included in Appendix 1 (mice) and Appendix 2 (rats). The data includes results from rat and mouse carcinogenicity studies performed at Merck Research Laboratories in our Safety Assessment facilities at West Point, PA, USA, and _____, in accordance with Standard Operating Procedures.

The rat carcinogenicity studies were done either via ad libitum or diet optimized feeding regimens and are so annotated on the tables. All studies were conducted using Sprague-Dawley rats acquired from _____/Laboratories.

The mouse carcinogenicity studies include studies of 21 to 24 months duration. The duration of the studies is indicated on the tables. All studies were conducted utilizing Crl:CD-1 mice from [redacted] Laboratories.

In addition to the historical control incidence by study, data from four studies in which animals were given different dietary regimens (without drug treatment) are also provided. The year the study was conducted can be determined from the study TT number. The first two digits represent the year the study was initiated.

FDA Comment 2 (e-mail of March 25): Please provide individual study data for historical control values for oral developmental toxicity studies in rats and rabbits. Also please indicate dates of studies as well as supplier of animals. Study data from the past five years would be preferred.

MRL Response: Attached is the fetal alteration historical control data for rabbits (Appendix 3) and rats (Appendix 4) for the types of alterations noted in the Vioxx™ studies. The data includes all individual studies for the past five- and ten-year periods. The year the study was initiated can be determined from the study TT number. The first two digits indicate the year initiated. All rabbit developmental toxicity studies were conducted using New Zealand White Rabbits from Covance Laboratories. All rat developmental toxicity studies were conducted with Sprague-Dawley rats from [redacted] Laboratories.

FDA Comment 3 (e-mail of March 25): Please provide historical control values [both summary and individual study data] for ossification data. Please indicate dates of studies as well as supplier of animals. Study data from the past five years would be preferred.

MRL Response: Both the summary and individual study ossification data for rabbits (Appendix 5) and rats (Appendix 6) are provided. The data represents the results of the past ten years. The source of the animals used in the studies is detailed in Response #2.

FDA Comment 4 (e-mail of March 25):. Please provide historical control values [both summary and individual study data] for mortality from 2-year bioassays in mice and rats. Please indicate dates of studies as well as supplier of animals. Study data from the past five years would be preferred. Also data for rats should be from diet restricted studies.

MRL Response: The historical control values for mortality from the rat and mouse carcinogenicity studies are provided in Appendix 7 and Appendix 8, respectively. The date and source of animals for the studies are annotated on the individual study mortality tables.