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December 18, 2001

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Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products

MERCK

c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Bull:

NDA 21-042/S-007: VIOXX™ (Rofecoxib Tablets)

Response to FDA Request for Information

Reference is made to the above cited supplemental New Drug Application (sNDA) submitted as an electronic archive on June 29, 2000, a fax containing requests for information concerning the VIGOR database and the Alzheimer's studies dated December 5, 2001 from Ms. Barbara Gould (FDA) to Dr. Robert E. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc.; and a partial response dated November 26, 2001 containing the Alzheimer's data.

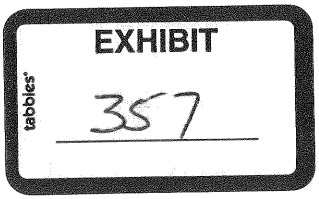
By this submission, we are providing the remaining response to the requested information.

FDA Request #1

Please clarify whether the safety monitoring board and the IRB overseeing these studies are aware of the excess in total cause mortality in the Vioxx 25 mg group as compared to placebo (p=0.026) and the trend against Vioxx 25 mg on CV mortality compared to placebo.

MRL Response #1

Mortality in the Alzheimer's disease program was fully discussed in recent responses of October 8, 2001, November 5, 2001, and November 26, 2001 and in the July 12, 2001 Safety Update Report (SUR). In final data from Protocols 091 and 126, 18 patients in the rofecoxib group and 11 in the placebo group died; in interim data from Protocol 078, additional 15 patients in the rofecoxib group and 9 in the placebo group died. Although there was a significant difference between rofecoxib and placebo groups in overall mortality based on the total number of deaths in all 3 protocols combined, there were no notable trends in the data. Examination of the most frequent causes of death reveals that 4 and 7 patients in the rofecoxib and placebo groups, respectively, died due to malignancies; 8 and 5 died from infectious causes (some associated with underlying malignancies); 4 and 1 died due to trauma; and 10 and 6 patients in the rofecoxib and placebo groups, respectively, died from a cardiovascular adverse experience. Based on these data, it was concluded that the difference between rofecoxib and placebo in overall mortality does not reflect any increases in particular types of events to suggest causality. In a similar analysis of mortality in the osteoarthritis program, there was statistically significant decreased mortality with rofecoxib compared to other NSAIDs combined. The small numeric differences between rofecoxib and comparators in overall mortality, although statistically significant in one program in favor of rofecoxib and in the other against rofecoxib, are most consistent with chance fluctuations.



Although there is a small imbalance in cardiovascular deaths between the 2 groups in the Alzheimer's disease studies, MRL does not agree with the Agency that there is a trend against rofecoxib for cardiovascular mortality (10 vs 6 events, p = 0.21). The data presented in the July 2001 SUR demonstrate that there is no excess of cardiovascular events in the Alzheimer's disease program. In fact, if there is any trend in the data on cardiovascular events, it is in favor of rofecoxib over placebo.

With regard to dissemination of these data, individual study site IRBs, rather than a single, central IRB are providing oversight for the 078 study. There is no data safety monitoring board. MRL has not provided these data to the individual IRBs because MRL does not believe that a safety issue has been identified. Moreover, the 078 study is still under study blind both to personnel at study sites and to personnel at MRL monitoring these studies. In the absence of a compelling and clear safety issue, MRL has not broken study blind to individuals involved in these studies. Of the 47 investigative sites involved in Protocol 078 (44 of which are still continuing), 24 sites were also involved in either Protocol 091 and/or Protocol 126. The IRBs for these 24 sites, along with all of the IRBs involved in Protocols 091 and/or 126, were notified of the results of Protocol 091 and of the reasons for discontinuing Protocol 126 (see response to Question #2 for further discussion). We have not been notified of any concerns by any IRB about continuing Protocol 078.

FDA Request #2

Have these oversight groups commented on the ethics of continuing study 078 in light of the mortality data and the fact that study 126 was deemed futile because of lack of efficacy in study 091?

MRL Response #2

Three studies were initiated in the Alzheimer's disease program. These 3 studies were designed to answer 2 clinical questions: 1) Does VIOXX™ slow the progression of clinical symptoms of Alzheimer's disease (Protocols 091 and 126) and 2) Does VIOXX delay conversion of Mild Cognitive Impairment to Alzheimer's disease (Protocol 078)?

Protocols 091 and 126 studied the treatment of patients with established Alzheimer's disease. The results of Protocol 091 became available in 1Q01 and demonstrated that VIOXX did not differentiate from placebo in slowing the clinical symptoms of Alzheimer's disease as assessed by the ADAS-Cog and CIBIC-plus. Protocol # 126, which was identical in design to protocol # 091, was thus terminated early in March 2001 with LPO in May 2001.

In contrast to these studies, Protocol 078 studies the treatment of patients with Mild Cognitive Impairment without Alzheimer's disease and investigates whether treatment delays conversion from Mild Cognitive Impairment to Alzheimer's disease – i.e. it is a prevention study, not a treatment study, and asks a very different question from Protocols 091 or 126. As was elegantly demonstrated in the epidemiologic study by In 't Veld and colleagues in the *New England Journal of Medicine* [Vol 345(21): 1515-1521,2001; Attachment #1], there are compelling data that NSAIDs appear to be effective at preventing the onset of Alzheimer's disease.

Data from this study also suggest that duration of NSAID treatment is related to reduction in relative risk of developing Alzheimer's disease and that NSAID treatment may need to be taken for 2 or more years to significantly reduce the development of disease.

The results of Protocol 091 confirmed in a prospective manner the prediction from the findings of In 't Veld and colleagues that rofecoxib would not be effective in treating established Alzheimer's disease. MRL believes that the results of Protocol 091 will be of interest to the medical community and a manuscript describing the results of Protocol 091 is in preparation. MRL discontinued its other parallel protocol studying the treatment of established Alzheimer's disease (Protocol 126). In contrast, the

recently published epidemiologic data would tend to reinforce the rationale for continuing Protocol 078 for the prevention of the onset of Alzheimer's disease. If successful, Protocol 078 would be the first prospective study to demonstrate the results suggested by epidemiologic studies that an NSAID (in this case, VIOXX) can significantly delay the onset of Alzheimer's disease.

All information is in electronic format as indicated in the Table of Contents for this amendment.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

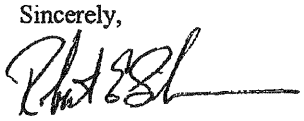
All the information is contained on one CD and is not more than 100MB. We have taken precautions to ensure that the content of the CD are free of computer viruses (Norton AntiVirus® 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

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

We consider the filing of this amendment 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.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (484)344-2944 or, in my absence, Bonnie J. Goldmann, M.D. (484)344-2383.

Sincerely,



Robert E. Silverman, M.D., Ph.D.
Senior Director
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Federal Express

Desk Copy: (cover letter only) Ms. Barbara Gould, Project Manager
HFD- 550, Room N353

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