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U.S. House of Representatives
Committee on Energy and Commerce
Washington, DC 20515–6115

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November 23, 2004

Lester M. Crawford, D.V. M., Ph.D.
Acting Commissioner of Food and Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Crawford:

As part of its continuing oversight of the public health and the safety of prescription drugs, the Committee on Energy and Commerce is examining issues surrounding the recent withdrawal of a non-steroidal anti-inflammatory drug (NSAID) Cox-2 inhibitor called rofecoxib, known commercially as Vioxx, by its manufacturer Merck & Co., Inc. ("Merck").

On September 30, 2004, Merck publicly announced a voluntary worldwide withdrawal of Vioxx, a medicine approved by the Food and Drug Administration ("FDA") in 1999 for use in treating osteoarthritis and the management of acute pain in adults, and later, for rheumatoid arthritis. The publicly reported reason for this withdrawal was new data from a three-year clinical trial that showed a two-fold increase in cardiovascular adverse events in patients taking Vioxx. The study, which was halted, reportedly showed an increase in heart attacks and strokes in patients beginning 18 months after treatment with Vioxx, as compared with those patients on placebo. We are seeking more information about: (1) What did the FDA know about these cardiovascular adverse events associated with Vioxx? (2) When did the FDA know about this information? (3) Did the FDA take adequate action in response to cardiovascular safety concerns associated with Vioxx?

Recent press reports regarding prior studies of Vioxx have raised serious questions about cardiovascular adverse events associated with Vioxx. According to the

FDA's September 30, 2004, Public Health Advisory regarding Vioxx, in June 2000, Merck submitted a safety study to the agency called Vioxx Gastrointestinal Outcomes Research ("VIGOR"), which found an increased risk of serious cardiovascular events in patients taking Vioxx as compared to patients taking naproxen. In April 2002, FDA implemented labeling changes to Vioxx to reflect the increase in risk of cardiovascular events, such as heart attack and stroke. The passage of almost two years between the time that the FDA was first provided the VIGOR study results and the resulting labeling changes to the drug, raises concerns that the FDA's regulatory process for reviewing this safety information may not have been adequate to ensure that the public was informed in a timely manner of this increased risk. During this time period, millions of patients in the United States were prescribed Vioxx, unaware of this increased safety risk. We are seeking information about the FDA's decision-making process during this time period to determine if the agency should have acted more quickly to implement a labeling change to Vioxx, reflective of the two-fold increase in cardiovascular adverse events that were found in the VIGOR study. We are also interested in learning what subsequent actions the agency undertook to look more closely at the cardiovascular safety risks associated with Vioxx and what conclusions the agency ultimately drew concerning whether the VIGOR cardiovascular adverse events were actually due to a protective effect of naproxen, and not due to an increased safety risk of Vioxx, as Merck asserted at the FDA's February 8, 2001, Advisory Committee meeting.

Additional studies, besides VIGOR, have also shown an apparent increased risk of heart attack by persons taking Vioxx. For example, in August 2001, Dr. Eric Topol published a study in the Journal of the American Medical Association finding that the available data about the drug raised concerns about the risk of cardiovascular events. In April 2004, Dr. Daniel Solomon published a study in Circulation showing a 24% increased risk of heart attack in persons taking Vioxx as compared with those taking Celebrex.

It has also been reported that the FDA initiated a study to review cardiovascular adverse events in Cox-2 inhibitor drugs, including Vioxx and Celebrex. This FDA study focused on 1.4 million Kaiser Permanente patients given Vioxx or Celebrex, both of which are Cox-2 inhibitor drugs, from the time Vioxx was first approved in 1999 through 2003. Press reports have indicated that the study's lead author, Dr. David Graham, an associate director of science in the FDA's Office of Drug Safety ("ODS"), the division of FDA responsible for reviewing post-marketing safety data of drugs, concluded that an estimated 27,000 heart attacks and sudden cardiac deaths "would have been avoided" had the patients used Celebrex rather than Vioxx. Although not based on clinical trial data, the safety questions raised by these projections are of serious concern, particularly in light of the information about cardiovascular adverse events associated with Vioxx emerging several years earlier in the VIGOR study and other studies. We are interested in learning about why and when the FDA initiated their study of Cox-2 inhibitors and cardiovascular adverse events and whether the FDA reviewed any additional

cardiovascular safety data concerning Vioxx between the VIGOR study and the study conducted by Dr. Graham.

Finally, there have been several recent press reports alleging that FDA officials pressured Dr. Graham into "watering down" his conclusions in his report and further, that FDA attempted to prevent Dr. Graham from presenting his findings at a scheduled epidemiology conference on August 25, 2004, because the agency had funded the study and Dr. Graham's conclusions would represent an "alternative FDA opinion." Two FDA internal e-mails to an ODS supervisor from Dr. Anne Trontell and from Dr. Graham seem to support these allegations. The first e-mail, dated August 12, 2004, is from Anne Trontell, a management level employee within ODS, to Paul Seligman, her supervisor within that division. In this e-mail, Dr. Trontell expresses concern over Dr. Graham's conclusions contained in a poster presentation that he was to present at a medical conference in France on the Vioxx safety review he recently completed and seems to be focused on the ramifications to the drug in the marketplace if the study has the imprimatur of an FDA employee. In another e-mail that has been widely reported on, dated August 13, 2004, Dr. Graham responds to suggestions by various senior FDA officials that he weaken some of his conclusions regarding the Vioxx data he reviewed, by stating: "I've gone about as far as I can without compromising my deeply-held conclusions about this safety question." We have grave concerns about this assertion.

In light of the Committee's jurisdiction over public health matters and concerns over the adequacy of FDA's review of safety issues of approved drugs, we are requesting that, pursuant to Rules X and XI of the U.S. House of Representatives, you provide the Committee with the information requested below by Tuesday, December 7, 2004:

1. All records relating to safety reviews and/or safety updates of Vioxx submitted by Merck, or any other third party, to the FDA, relating to cardiovascular adverse events.

2. All records relating to FDA's review of the VIGOR study, including, but not limited to, the VIGOR study and all records relating to the review of Vioxx by Dr. Shari Targum, Dr. Quia Li, and Dr. Lourdes Villalba.

3. Identify all FDA employees who reviewed and/or analyzed the VIGOR study, including the division of FDA, job title and employment status with the agency.

4. All internal communications between FDA employees relating to cardiovascular safety concerns about Vioxx, Bextra, or Celebrex, including, but not limited to, communications concerning Dr. Graham's report on Vioxx.

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In light of the Committee's jurisdiction over public health matters and concerns over the adequacy of FDA's review of safety issues of approved drugs, we are requesting that, pursuant to Rules X and XI of the U.S. House of Representatives, you provide the Committee with the information requested below by Monday, December 6, 2004:

1. All records relating to safety reviews and/or safety updates of Vioxx submitted by Merck, or any other third party, to the FDA, relating to cardiovascular adverse events.

2. All records relating to FDA's review of the VIGOR study, including, but not limited to, the VIGOR study and all records relating to the review of Vioxx by Dr. Shari Targum, Dr. Quia Li, and Dr. Lourdes Villalba.

3. Identify all FDA employees who reviewed and/or analyzed the VIGOR study, including the division of FDA, job title and employment status with the agency.

4. All internal communications between FDA employees relating to cardiovascular safety concerns about Vioxx, Bextra, or Celebrex, including, but not limited to, communications concerning Dr. Graham's report on Vioxx.

5. All records of Dr. David Graham, Dr. Robert Temple, Dr. Steven Galson, Dr. John Jenkins, Dr. Paul Seligman, Dr. Jonce Bull, Dr. Shari Targum and Dr. Anne Trontell relating to cardiovascular safety concerns of Vioxx or any other Cox-2 inhibitor.

6. All communications between the FDA and Merck relating to possible increases in cardiovascular events associated with Vioxx, including but not limited to, any proposed or actual labeling changes.

7. All records relating to FDA's decision in April 2002 to institute a labeling change to Vioxx to reflect the increased risk in adverse cardiovascular events.

8. All records relating to FDA's decision to review Kaiser-Permanente's database for cardiovascular events associated with Vioxx including, but not limited to, all drafts and the final report by Dr. David Graham.

9. All records of any FDA medical officer's safety and efficacy review for the original approval of Vioxx.

10. Minutes of all Advisory Committee meetings relating to cardiovascular risks of Cox-2 inhibitors.

11. All study reports conducted or initiated by the FDA relating to whether naproxen has a protective effect for cardiovascular events.

12. All records the FDA considered in reviewing whether the VIGOR study results on cardiovascular risks associated with Vioxx were due to a protective effect of naproxen.

13. All records relating to communications between or among FDA employees and the manufacturers of Cox-2 inhibitor drugs about cardiovascular adverse events.

14. All records relating to the potential study design of a Vioxx clinical trial to assess cardiovascular safety.

Please note that, for purposes of responding to this request, the terms "records" and "relating" should be interpreted in accordance with the attachment to this letter. If you have any questions about this matter, please contact Kelli Andrews, Majority Committee Counsel, at (202) 226-2424 or David Nelson, Minority Investigator, at (202) 226-3400.

Sincerely,

Joe Barton
Chairman

John D. Dingell
Ranking Member

cc: The Honorable Greg Walden, Vice Chairman
Subcommittee on Oversight and Investigations

The Honorable Peter Deutsch, Ranking Member
Subcommittee on Oversight and Investigations

Attachment

ATTACHMENT

1. The term "records" is to be construed in the broadest sense and shall mean any written or graphic material, however produced or reproduced, of any kind or description, consisting of the original and any non-identical copy (whether different from the original because of notes made on or attached to such copy or otherwise) and drafts and both sides thereof, whether printed or recorded electronically or magnetically or stored in any type of data bank, including, but not limited to, the following: correspondence, memoranda, records, summaries of personal conversations or interviews, minutes or records of meetings or conferences, opinions or reports of consultants, projections, statistical statements, drafts, contracts, agreements, purchase orders, invoices, confirmations, telegraphs, telexes, agendas, books, notes, pamphlets, periodicals, reports, studies, evaluations, opinions, logs, diaries, desk calendars, appointment books, tape recordings, video recordings, e-mails, voice mails, computer tapes, or other computer stored matter, magnetic tapes, microfilm, microfiche, punch cards, all other records kept by electronic, photographic, or mechanical means, charts, photographs, notebooks, drawings, plans, inter-office communications, intra-office and intra-departmental communications, transcripts, checks and canceled checks, bank statements, ledgers, books, records or statements of accounts, and papers and things similar to any of the foregoing, however denominated.

2. The terms "relating," "relate," or "regarding" as to any given subject means anything that constitutes, contains, embodies, identifies, deals with, or is in any manner whatsoever pertinent to that subject, including but not limited to records concerning the preparation of other records.