ONE HUNDRED EIGHTH CONGRESS

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

JOE BARTON, TEXAS
CHAIRMAN

November 23, 2004

Mr. Raymond V. Gilmartin
Chairman
Merck & Co., Inc.
One Merck Drive
P.O. Box 1150
Whitehouse Station, NJ 08889

Dear Mr. Gilmartin:

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 rofecoxib, known commercially as Vioxx, by 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 arthritis and acute, chronic pain in adults, due to a two-fold increase in cardiovascular events occurring after 18 months on the drug. In a public news release, Merck stated that its decision to withdraw the drug was based on data from a new, three-year placebo controlled clinical trial that was designed to assess the efficacy of Vioxx in preventing recurrence of colorectal polyps. The study, known as "APPROVe," which has been halted, showed an increase in heart attacks and strokes in patients beginning 18 months after treatment with Vioxx, as compared with those patients on placebo.

However, it is our understanding that as far back as 2000 — and only a year after Vioxx was first approved by the FDA — results from a Merck-sponsored study also showed a sharp increase in cardiovascular adverse events for patients taking Vioxx, that time as compared to patients taking naproxen. Further, recent press reports indicate that internal Merck e-mails suggest the company may have been aware of cardiovascular risks associated with Vioxx as early as 1996, prior to FDA approval, and may have tried to design a safety study in a way as to mask the cardiovascular risks to patients taking the drug. We note that prior to the company's September 30, 2004, withdrawal

announcement, Merck had never publicly acknowledged in its corporate press releases a link between Vioxx and increased cardiovascular risk. In light of the adverse event information concerning Vioxx prior to the APPROVe study, we are interested in finding out when Merck first learned about the potential cardiovascular risks associated with Vioxx and what actions the company undertook to further evaluate those risks and communicate them to the public.

In June 2000, Merck submitted a safety study to the FDA called Vioxx Gastrointestinal Outcomes Research ("VIGOR"), which found, among other things, a statistically significant increased risk of serious cardiovascular adverse events in patients taking Vioxx as compared to patients taking naproxen, even though studying cardiovascular adverse events was not a primary endpoint of the study. As Dr. Alise Reicin, a Merck official who presented the company's VIGOR data to the FDA in a February 8, 2001, Advisory Committee meeting, stated, "The one area where VIGOR demonstrated results which were different than those seen in the Phase IIb/III studies was in cardiovascular safety." In the VIGOR trial, the risk of a cardiovascular adverse event for patients taking Vioxx versus patients taking naproxen gained significance beginning six weeks after treatment and continued to widen after that time frame. At the February 8, 2001, Advisory Committee meeting, Merck presented data to the FDA, including a meta-analysis of several clinical trials of Vioxx, asserting that the increase in cardiovascular adverse events in the VIGOR trial was due to a protective effect by Naproxen, rather than an adverse effect of Vioxx. Dr. Reicin stated: "[I]n VIGOR, the imbalance in cardiovascular adverse events was due to naproxen reducing the risk of sustaining an event rather than rofecoxib increasing the risk." FDA officials who presented their analysis of the VIGOR data disputed some of Merck's assertions, and in particular, questioned the use of a meta-analysis spanning different doses of Vioxx and not encompassing longer-term use of the drug, as a basis for concluding the variance in cardiovascular events was not linked to the drug. We would like more information from the company about when and how it reached the conclusion that the VIGOR cardiovascular safety results were due to a protective effect of naproxen and whether the company revisited that conclusion at any time prior to receiving the most recent study results of the APPROVe trial.

Further, we understand that in April 2002, the FDA implemented labeling changes to Vioxx to reflect the increase in risk of cardiovascular events, such as heart attack and stroke. Given that almost two years passed between the time that Merck first provided the VIGOR study results to the FDA, which showed an increased risk of heart attack and stroke in patients taking Vioxx, and the resulting labeling changes to the drug, we are seeking information from the company on what its position was regarding any proposed and actual labeling changes concerning cardiovascular safety risks for patients taking Vioxx. We are also interested in learning what subsequent actions the company undertook, in light of the VIGOR cardiovascular results, to look more closely at the cardiovascular safety risks associated with Vioxx, as well as, the protective effect the company alleged that naproxen had in patients. If Merck examined any cardiovascular safety questions in other studies besides VIGOR about Vioxx prior to the results of the

APPROVe trial and determined there were no actionable cardiovascular safety issues, we would like to know why.

In addition, in an October 18, 2004, Washington Post article, some members of the Data Safety Monitoring Committee ("DSMC") in the APPROVe trial were interviewed concerning when they first noticed the signal of cardiovascular adverse events and when they determined that the trial should be halted. We are interested in learning more about the decision-making process by the DSMC in both the VIGOR trial and the APPROVe trial, since the process of evaluating cardiovascular adverse event data in each trial appears to be different. It is our understanding that the DSMC in the VIGOR study did not recommend halting the trial, despite the increase in cardiovascular events and we are interested in learning why this was the case. Reviewing the decision-making process by Merck concerning the potential cardiovascular safety risk of Vioxx from the time of the VIGOR study through the company's decision to remove the product from the marketplace will give us a clearer understanding of its practice of evaluating safety risks for an approved drug and insight into what, if any, input the FDA had in the post-market cardiovascular safety review of Vioxx.

Further, in a November 1, 2004, Wall Street Journal article, it was reported that various internal Merck marketing and/or sales training documents regarding Vioxx suggested downplaying the potential cardiovascular risks associated with the drug. For example, a Merck training document reportedly entitled "Dodge Ball Vioxx" listed various "obstacles" or questions that a physician may pose to a pharmaceutical sales representative about Vioxx, such as "The competition has been telling me that the incidence of heart attacks is greater with Vioxx than Celebrex." The document reportedly contains the company's suggested response for its marketing representatives to this, and other "obstacles" as being a simple, one-word answer in capital letters: "DODGE." Another document the Wall Street Journal reportedly reviewed was a Merck internal marketing document, addressed to all field personnel with responsibility for Vioxx, which was an "obstacle handling guide" for Vioxx. These reported documents raise questions about whether the company provided physicians and the public with complete and accurate information about the cardiovascular safety risks that were known by the company at the time these documents were written and disseminated to Merck employees.

Finally, we note that in 1999, the FDA approved Vioxx for use in the treatment of osteoarthritis, menstrual symptoms and for the management of acute pain in adults. The drug was subsequently approved by the FDA for treatment of rheumatoid arthritis in adults and children. Vioxx, a Cox-2 inhibitor, was demonstrated in a clinical trial to have a lower rate of gastrointestinal bleeding and ulcers than over-the-counter NSAIDS, such as ibuprofen and naproxen. As such, for people with a risk of gastrointestinal bleeding, which would most likely be due to chronic use of a pain reliever, Vioxx provided a prescription alternative to over-the-counter pain relief medications. It is our understanding that Merck primarily focused its advertising for Vioxx on the treatment of arthritis. According to the November 1, 2004, issue of Fortune magazine, Merck spent more than $500 million on advertising for Vioxx. Further, according to the Washington

Post article cited above, Merck spent $195 million on a direct to consumer advertising campaign for Vioxx. Moreover, it has been widely reported that over 20 million people in the United States alone were prescribed Vioxx since 1999. The high usage rate of Vioxx, considering its relatively narrow set of approved indications, raises questions about how Vioxx was being marketed and advertised by the company to physicians and patients.

In light of the Committee's Jurisdiction over public health matters, 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 to the FDA, relating to cardiovascular adverse events.

2. All records relating to Merck's review of the VIGOR study relating to cardiovascular adverse events, including, but not limited to, the meta-analysis that Merck performed in the wake of the VIGOR study results.

3. Identify all Merck employees who reviewed and/or analyzed the VIGOR cardiovascular study results, including the division of Merck in which they work, job title and current employment status with the company.

4. All records of any current or former Merck employee relating to questions or concerns about cardiovascular adverse events in Vioxx.

5. All records relating to any Data Safety and Monitoring Board of a Merck-sponsored study on Vioxx that considered cardiovascular adverse events including, but not limited to, meeting minutes, internal correspondence between or among Data Safety and Monitoring Board members and Merck employees, telephone conference call memos, and meeting notes.

6. For each Vioxx trial sponsored by Merck in which there was a Data Safety and Monitoring Board, provide the names of the members of the Board, their most recent employment information and the dates upon which they served on the Board.

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

8. All records relating to the April 2002 labeling change to Vioxx and the associated increase in cardiovascular adverse events.

9. All corporate minutes relating to any adverse events associated with Vioxx.

10. All study reports conducted, initiated or considered by Merck relating to whether naproxen has a protective effect for cardiovascular adverse events as compared to Vioxx or other Cox-2 inhibitors.

11. All records relating to Merck's review of the APPROVe study relating to cardiovascular adverse events.

12. All records relating to communications between Merck and the FDA regarding an agreement about notification by the FDA to Merck of any impending FDA announcements, decisions or release of information pertaining to a Merck pharmaceutical product.

13. All records relating to Merck's decision to withdraw Vioxx from the marketplace.

14. All records relating to the design of the VIGOR study as it relates to cardiovascular adverse events.

15. A listing of all studies of Vioxx performed, or in some manner sponsored, by Merck and the dates the study was started and completed.

16. For each study listed in Question 15, state whether the study was published in a peer-review medical journal and, if so, provide the name of the journal and the publication date.

17. All records relating to corporate sales force communications about cardiovascular adverse events associated with Vioxx: (1) between or among Merck employees and external marketing consultants or agents and (2) to physicians, hospitals and/or patients, including but not limited to, "Operation Dodgeball" records and "obstacle handling guides."

18. All records relating to the United Health study concerning Vioxx.

19. From the time Vioxx was first approved for use in the United States to the present, provide all data about monthly and annual Vioxx prescription and usage rates in the United States, in the aggregate and for all subcategories (e.g., states, major metropolitan areas, types of prescribers).

20. From the time Vioxx was approved for use in the United States to September 30, 2004, state the annual cost of advertising and marketing Vioxx in the U.S., including separate categories for the following costs: (a) direct to consumer marketing; (b) physician/hospital marketing; and (c) medical conferences.

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.