U.S. SENATE COMMITTEE ON
Finance
SENATOR CHUCK GRASSLEY, OF IOWA - CHAIRMAN
http://finance.senate.gov

For Immediate Release
Friday, October 15, 2004

Grassley questions Merck about communication with the FDA on Vioxx

WASHINGTON — Sen. Chuck Grassley is asking questions about, among other things, the communication between the Food and Drug Administration and Merck in the weeks leading up to the drug maker pulling its arthritis medicine Vioxx from the global marketplace last month.

Grassley, who is chairman of the Senate Committee on Finance, said that he has questions about an agreement between the Food and Drug Administration and Merck to give the drug company a head's up when the federal agency planned to publish a drug study that might negatively affect the drug company.

"The issue for doctors and their patients is, did the government agency that's supposed to regulate pharmaceuticals have an inappropriate agreement with Merck? And did a cozy relationship between the FDA and a pharmaceutical company allow a drug with known safety risks to stay on the market longer than it should have? Part of the answer may rest in what Merck was or was not telling the FDA," Grassley said.

Grassley has been conducting a congressional investigation of the way that the Food and Drug Administration dealt internally with information about problems with Vioxx. Earlier this year, he scrutinized the Food and Drug Administration's handling of research that suggested a link between the use of antidepressants and suicide among young people. Grassley is also examining allegations against the FDA regarding the inspection of a Red Cross facility.

The text of Grassley's letter to Merck & Co., Inc. follows here.

October 14, 2004

Mr. Raymond V. Gilmartin
Chairman, President & Chief Executive Officer
Merck & Co., Inc.
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100

Dear Mr. Gilmartin:

The U.S. Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs, and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage, including prescription drugs, under these programs.

On September 30, 2004, Merck & Co., Inc. (Merck) announced a world-wide withdrawal of Vioxx, its arthritis and acute pain medication. The FDA and Merck have known about potential cardiovascular risks associated with Vioxx for years. In 1999, the FDA approved Vioxx. Since 1999, there have been a number of studies showing an increased risk in cardiovascular complications among those taking Vioxx. One of these studies was the Merck-sponsored VIGOR study, which determined that there were more serious cardiovascular events occurring in patients taking Vioxx compared to patients taking naproxen, another anti-arthritic drug (patients with a recent history of heart attack or stroke were excluded from the study beforehand). In 2002, Dr. Wayne Ray published another study, which found a two-fold increase in heart attack and sudden death associated with high dose Vioxx. In 2004, a Merck-funded study—authored by eight researchers, including a Merck epidemiologist and seven doctors from Harvard Medical School and Brighham & Women's Hospital—found both low dose and high dose Vioxx increased the risk of heart attack. In light of all this clinical trial data, the FDA approved Vioxx for pediatric use, based on a three-month study, on August 19, 2004, and Merck announced Vioxx's pediatric approval on September 8, 2004.

However, on August 25, 2004—less than a week after FDA approved Vioxx for use in children—Dr. David Graham, an FDA epidemiologist, presented the results of his recent work on Vioxx at a conference in France. Dr. Graham's study found that patients taking low dose Vioxx have a 50% greater chance of suffering a heart attack and sudden cardiac death than patients using Celebrex. In addition, Dr. Graham noted that the risk of heart attack and sudden cardiac death in those patients taking the highest recommended daily dose of Vioxx was three times that of patients taking standard painkillers.

Recently, my staff interviewed Dr. Graham concerning drug safety problems at the FDA, including issues related to his Vioxx study. According to e-mails obtained by the Committee (see attached documents), Dr. Anne Trontell, Deputy Director of Drug Safety, wrote an email to some of her FDA colleagues on May 14, 2002, which stated:

> I was contacted by Dr. Braunstein of Merck asking why they were not informed about the submission and publication of the article in the link below. He indicated that after the Vioxx and aseptic meningitis letter was published a few years back and created a lot of press interest without Merck's prior awareness, *there had been an agreement that Merck would be informed prior to any FDA publication about one of their drug products*. Can any of you inform me about when this paper was submitted, who cleared it, and whether anyone attempted to inform the company? . . . FYI, Dr. Braunstein indicated that his supervisor, Dennis Urb (sp?) might contact FDA management about this event.
> (emphasis added).

Another email written by Dr. Trontell, dated August 12, 2004, raised issues with Dr. Graham's Vioxx study, and concluded that: "However this study is presented, the mfg (Merck?) needs to know before it becomes public so they can be prepared for extensive media attention that this will likely provoke." These emails show that Dr. Trontell was aware of an "agreement" with Merck as early as May 2004. It appears Dr. Trontell wanted to honor that agreement by notifying Merck about Dr. Graham's Vioxx study prior to him presenting his findings and conclusions in France.

Merck made its Vioxx announcement on September 30, 2004. When my Committee staff interviewed Dr. Graham, he stated that Dr. Paul Seligman, his supervisor, gave him a deadline of September 30, 2004, to finish the final manuscript of his Vioxx study. The *New York Times* reported that Merck notified the FDA that it was withdrawing Vioxx on Tuesday, September 28th. According to the *New York Times*, Merck first learned about new data on heart attacks and strokes when Dr. Peter S. Kim, president of Merck Research Labs, received a call on Thursday, September 23rd, from an "independent committee of scientists who were monitoring the colon polyp study."

Given the "agreement" between the FDA and Merck, as well as the timing of events surrounding Merck's withdrawal of Vioxx, many questions come to mind, specifically: who knew what and when? Accordingly, as chairman of the Committee, I request that Merck comply with the following requests for information and documents, in accordance with attached general instructions and definitions.

FIRST REQUEST

1. State whether "Dr. Braunstein" is a Merck employee and/or agent. If so, please include that person's full name, title, curriculum vitae and contact information.

2. State whether "Dennis Urb," is a Merck employee and/or agent. If so, please include that person's full name, title, curriculum vitae and contact information. If "Dennis Urb" is a phonetic spelling or misspelling of a known person, identify that Merck employee and/or agent.

3. Identify the person(s) and/or agent(s) (including full name, title and contact information) within or affiliated with Merck who is/are currently responsible for communicating with the FDA on drug safety matters generally and Vioxx specifically.

4. What type of "agreement" did Merck seek/obtain from FDA about receiving information prior to any FDA publication about one of Merck's drug products?

a) Does Merck ever request information and/or documents relating to any FDA study prior to its publication?

b) How much advance notice does Merck request?

c) Does Merck ever request to comment and/or provide comment(s) on any FDA study prior to its publication?

d) Why is it appropriate for a drug manufacturer to get a "heads-up" about FDA publications?

Please provide a detailed explanation, including events, circumstances, and/or examples relating to the aforementioned questions.

5. Between August 1, 2004, and September 30, 2004, did Merck request any information and/or document(s) (including, but not limited to abstracts, posters, or manuscripts) relating to Dr. Graham's Vioxx study? Please explain in detail the events and/or circumstances relating to any request including, but not limited to the name(s), date(s), and a detailed description of all communication(s) between the FDA and Merck.

6. Between August 1, 2004, and September 30, 2004, did the FDA provide Merck with any information and/or document(s) (including, but not limited to abstracts, posters, or manuscripts) relating to Dr. Graham's Vioxx study? Please explain in detail the events and/or circumstances relating to FDA providing any information and/or document(s), including, but not limited to the name(s), date(s), and a detailed description of all communication(s) between the FDA and Merck relating to Dr. Graham's Vioxx study. And please provide a copy of the document(s) provided by the FDA.

7. Between August 1, 2004, and September 30, 2004, did Merck request and/or initiate an "interim analysis" or review of the data by the "independent committee of scientists who were monitoring the colon polyp study"?

a) When did the "independent committee of scientists" begin its "interim analysis" or data review that showed the increased risk of heart attacks and strokes?

b) Was the "interim analysis" or data review by the "independent committee of scientists" planned or scheduled at the outset of the study?

c) If not, why did the "independent committee of scientists" begin the "interim analysis" or data review?

Please provide a detailed explanation, including, but not limited to the name(s), date(s), and a detailed description of all communication(s) between Merck and "the independent committee of scientists,"to each of the aforementioned questions.

8. From August 25, 2004, to August 30, 2004, provide a copy of all communication(s) between Merck and the FDA relating to Dr. Graham's Vioxx study (including, but not limited to email(s)).

SECOND REQUEST

9. From May 1, 2004, to October 14, 2004, provide a copy of all document(s) and communication(s) between Merck (including, but not limited to Dr. Braunstein and/or Dennis Urb) and the FDA relating to any actual or proposed agreement or arrangement, whether written or oral, regarding the FDA providing information to Merck prior to any FDA publication about one of Merck's drug products.

10. From May 1, 2004, to October 14, 2004, provide a copy of all communication(s) between Merck and the FDA relating to Vioxx (including, but not limited to email(s)).

11. From August 25, 2004, and September 30, 2004, provide a copy of all communication(s) relating to Merck's review of data for increased risk of heart attacks and strokes (including, but not limited to communication(s) between Merck, the FDA, or the "independent committee of scientists" (referred to in request number # above)).

12. What was Merck's association with the study published in the American Heart Association journal *Circulation* and authored by eight researchers, including a Merck epidemiologist and seven doctors from Harvard Medical School and Brighham & Women's Hospital?

a) Was Merck (including, but not limited to Dr. Carolyn Cannuscio) involved in designing the study's methodology, the collection and interpretation of the study data, and the writing of the study paper?

b) Did Merck have a role, either directly or indirectly, in the removal of Dr. Carolyn Cannuscio as an author of the study?

Please explain in detail the events and/or circumstances relating to the design and conduct of the study, and removal of Dr. Cannuscio as an author on this study, including, but not limited to the name(s), date(s), and a detailed description of all communication(s) between Merck, Dr. Cannuscio, and/or the American Heart Association journal *Circulation*.

13. From January 1, 2004, to May 18, 2004, provide a copy of all communication(s) relating to the removal of Dr. Cannuscio as an author on the Vioxx study published in *Circulation* (including, but not limited to email(s) between Merck, Dr. Cannuscio, and/or the American Heart Association journal *Circulation*).

14. From January 1, 1990 through October 14, 2004, provide a comfprehensive list of each clinical trial(s), study(ies), and/or data review(s) initiated by Merck relating to Vioxx and conducted in humans, including any conducted outside the United States. This request encompasses any trial(s), study(ies), and/or data review(s) (including, but not limited to all randomized placebo-controlled trials, open trials, active-controlled trials, ghost finding studies) conducted by Merck relating to Vioxx for any New Drug Application (NDA), Investigational New Drug (IND) application, *or for any reason* (including any trial(s), study(ies), and/or data review(s) conducted by any entity or agent engaged by Merck). For each trial/study/data review, provide the following information:

a) Identify each trial/study/data review by name and include a summary of the methodology, results, findings and conclusions;

b) State who requested it, who conducted it, where it was conducted (state the country), and for what purpose it was conducted;

c) State the date it was initiated and the date it was completed. If it was not completed, state in detail why it was not completed, who made the decision not to complete it, and at what point it was terminated;

d) State when and where it was published. If it was not published, state in detail why it was not published;

e) State when and for what purpose the trial/study was submitted to the FDA. If it was not submitted, state in detail why it was not submitted.

As Chairman of the Finance Committee, I request that Merck comply with the attached requests for information and documents in accordance with attached general instructions and definitions. Please provide the name and contact information, including an email address, for a person who will act as your company's point of contact by October 18, 2004. The first request for documents should be delivered no later than the close of business on October 27, 2004, and the second request for documents no later than the close of business on November 10, 2004, unless either is available sooner.

Sincerely,

Charles E. Grassley
Chairman