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

M E M O R A N D U M

TO: Reporters & Editors
FR: Jill Kozeny, 202/224-1308
RE: FDA announcement today
DA: Nov. 5, 2004

Sen. Chuck Grassley, Chairman of the Senate Committee on Finance, issued the following comment about the announcement today by the Food and Drug Administration of its new initiatives concerning the safety of medical products.

"The public must be able to have faith in the Food and Drug Administration. It's obvious that the leadership of the agency must take on what look like deep-rooted problems when it comes to putting public health and safety first and public relations second. Today's announcement is welcome, albeit late in coming. These initiatives need to take hold in a meaningful way and be more than an attempt to inoculate the agency in the face of alarming revelations."

Sen. Grassley also released a letter he sent to the Food and Drug Administration asking what actions the agency took in response to known risks about Vioxx. The text of the letter follows here.

November 5, 2004

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

Dear Dr. Crawford:

As the Committee on Finance (Committee) continues investigating the worldwide withdrawal of Vioxx by Merck & Co., Inc. (Merck), the Food and Drug Administration's regulatory role relating to Vioxx merits close scrutiny. As chairman of the Committee, I request that the FDA provide an expedited response to this letter.

Dr. Shari Targum, a Food and Drug Administration (FDA) Medical Officer, was the author of a consultation "to address a concern regarding risk of cardiovascular events with the use of [Vioxx]." Dr. Targum worked in the FDA, Division of Cardio-Renal Drug Products, and her consultation was directed to the FDA Division of Anti-Inflammatory Drug Products. Both of these divisions fall under the FDA's Center for Drug Evaluation and Research. Dr. Targum's consultation—commonly referred to as the Targum Memo—was considered by the Arthritis Advisory Committee in February 2001. The Advisory Committee recommended labeling and further study of Vioxx. Several concerns are noteworthy in the Targum Memo's Issues & Findings section, including the following:

> **2. Evaluation of CV events in other [Vioxx] studies that allowed ASA (085 and 090):** See Comments on 085 and 090. Despite lower dose, smaller sample size and aspirin use, *the trend is against [Vioxx]*.
>
> **3. Assessment of CV thrombotic risks in this database:** The VIGOR study was a large study with a longer drug exposure and follow-up than the two smaller studies (085 and 090). *The cardiovascular thrombotic event rates, while not high, were significantly different between the two groups; most striking were the myocardial infarction event rates.* Thus, to this Medical Reviewer, there are more cardiovascular thrombotic events in the [Vioxx] group than in the naproxen group; the time-to-event curves are different, favoring naproxen. *This Medical Reviewer is concluding that there is an increased risk of cardiovascular thrombotic events, particularly myocardial infarction, in the [Vioxx] group compared with the naproxen group.* More difficult is the question of a safety signal for [Vioxx]. As there is no placebo group, it will be difficult to assess the CV thrombotic risk with [Vioxx] use compared with no therapy at all. [Merck] provides several hypotheses to explain the data (see below);
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> **4. Assessment of [Merck]'s claim regarding CV risks:** [Merck] claims:
> - [Merck claims that the difference in myocardial infarctions between the two groups is primarily due to the antiplatelet effects of naproxen. *This hypothesis is not supported by any prospective placebo-controlled trials with naproxen. One can further argue that, no matter what the attribution, the results (from a cardiovascular standpoint) are favorable for naproxen* ...
>
> **5. Suggest labeling that would properly address CV risks:** It is difficult to write labeling at this point. As discussed with Dr. Villalba, we will be glad to discuss labeling with your Division. *It would be difficult to imagine inclusion of VIGOR results in the [Vioxx] labeling without mentioning cardiovascular safety results in the study description as well as the Warnings sections.*
>
> (Bold and underline in original; italics added).

Dr. Targum also included several recommendations in her consultation, including:

- [The Division of Anti-Inflammatory Drug Products] will need to consider the risks vs. benefits of [Vioxx] and naproxen. We will be glad to discuss this issue further with you.

- We would like to see further analysis of the updated Time-to Event table to answer the following questions: 1. How significant is this table; 2. What event rate is needed to detect a significant difference between [Vioxx] and naproxen.

- [The Division of Anti-Inflammatory Drug Products] should look at the VIGOR congestive heart failure results to clarify whether these events are related to edema, hypertension, or thrombotic events. You might ask [Merck] for further clarification.

- [The Division of Anti-Inflammatory Drug Products] might consider looking at celecoxib data to evaluate whether there is evidence of a class effect.

- It would be helpful if [Merck] could provide further cardiovascular safety data regarding long-term (>2 month) exposure of [Vioxx] 50 mg and above, both in rheumatoid arthritis and non-rheumatoid arthritis populations.

- As we have discussed, OPDRA should be asked to look at cardiovascular safety data for the COX-2 inhibitors.

In light of the Targum Memo, and the issues, comments, and recommendations found in it, please respond to the following:

1. Provide the Committee with a copy of the administrative file(s) relating to any Vioxx labeling change, including but not limited to the Vioxx labeling change approved in April 2002.

2. State whether or not the FDA took action on the issues, comments, and specifically the recommendations made in the Targum Memo. In your response, please list each recommendation in the Targum Memo and follow it with a detailed description of the specific action(s) taken by FDA in response to each recommendation. In addition, state why the cardiovascular safety results were not included in the Vioxx label warning section as per Dr. Targum's specific comment.

Thank you in advance for having your staff coordinate with my staff about this letter by no later than the close of business on November 8, 2004. Please provide the requested documents by November 12, 2004, unless they are available sooner. Your expedited response should be delivered to the Committee no later than November 17, 2004, unless it is available sooner.

Sincerely,
Charles E. Grassley
Chairman