

For Immediate Release
Tuesday, April 15, 2008

Grassley: new JAMA reports about Vioxx
buttress effort to require more transparency from drug makers

WASHINGTON — Senator Chuck Grassley is asking the drug maker Merck to respond to accounts in today’s Journal of the American Medical Association about the selective presentation of data to federal regulators and manipulation of scientific literature through ghost writers concerning the painkiller Vioxx, which was removed from the market in 2004 because of cardiovascular risks.

Grassley held a hearing of the Senate Committee on Finance more than three years ago, in the wake of the Vioxx scandal, to examine the relationship between the drug industry and the Food and Drug Administration and expose shortcomings in the drug safety system.

The studies and editorial appearing in today’s Journal of the American Medical Association describe documents made public in lawsuits against Vioxx where the company was not forthcoming about drug risks in its communication with the Food and Drug Administration. The Journal of the American Medical Association articles also detail how the drug maker sought out academic ghost writers to put their names on manufacturer-drafted studies about Vioxx.

“These reports reveal just how far a drug maker might go to market its product and try to bury information that might hurt sales even when that information directly affected the health and safety of the people taking their medicine,” Grassley said. “Revealing this kind of activity is very important in building pressure on the Food and Drug Administration to regulate, not accommodate drug makers. These new reports also underscore the value of transparency in making industry more accountable to the public.”

Grassley has sponsored legislation to require manufacturers of pharmaceutical drugs, devices and biologics to report payments to doctors for consulting, speeches and other services. He issued a report last year about the drug industry’s financial support of continuing medical education. Grassley also has pressed for greater transparency from the Food and Drug Administration through legislative and oversight initiatives.

The text of letters sent today from Grassley to Merck & Co., Inc. and Scientific Therapeutics Information, Inc. follows here.

April 15, 2008

Richard T. Clark
Chairman, President, and Chief Executive Officer
Merck & Co., Inc.
1 Merck Drive
Whitehouse Station, NJ 08889

Dear Mr. Clark:

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs. As a senior member of the United States Senate and as Ranking Member of the Committee, I have a special responsibility to protect the health of Medicare and Medicaid beneficiaries and safeguard taxpayer dollars authorized by Congress for these programs. This includes the responsibility to conduct oversight of the medical industry, including makers of pharmaceuticals and medical devices.

More than three years ago, on November 18, 2004, the Committee held a hearing titled, "FDA, Merck and VIOXX: Putting Patient Safety First?" At that hearing, I raised concerns not only about the almost two-year delay in updating the VIOXX label with important information about cardiovascular risks, but also Merck & Co., Inc.'s (Merck) aggressive marketing of VIOXX during that same timeframe when consumers and doctors were largely unaware of those risks.

I am writing today because additional findings regarding Merck's handling of VIOXX have come to light. Several studies based on a review of documents from recent litigation against your company were published today in the Journal of the American Medical Association (JAMA). In particular, one study seems to show selective reporting by Merck of mortality data from clinical trials of VIOXX that were conducted in patients with Alzheimer disease or cognitive impairment.

I am deeply troubled by the findings of this study. According to the authors, Merck misled the FDA by submitting initial mortality data from a trial called study 078 in July 2001 that minimized the appearance of an increased risk of death. FDA was not provided with the intention-to-treat analyses that the company had conducted in April 2001. The intention-to-treat mortality data from Merck's study 078 were not submitted to the FDA until 2003-about two years later.

The article also reports that the FDA raised questions about the safety data submitted in 2001 because of excess deaths seen in study 078, as well as in a separate study 091. According to the JAMA authors, Merck responded that it did not report the excess in deaths from this 091 study to the institutional review boards (IRBs) overseeing study 078. Thus, those individuals who enrolled in study 078 seem to have been left in the dark about a very serious risk. The people in the study had Alzheimer disease or cognitive impairment, and they are a vulnerable population who deserves special attention. Furthermore, Merck stated that there was no data and safety monitoring board (DSMB) in place for study 078. The authors argue that the mortality

findings might have led a DSMB to terminate study 078 before completion in the interest of protecting the human subjects that had volunteered.

It should be no surprise to you that VIOXX has been an interest of mine for several years now. Besides incurring over \$1 billion dollars in costs to our federal programs for this drug, it turned out that VIOXX was also causing heart attacks. Merck, with knowledge of the increased risk of heart attacks associated with VIOXX, proceeded to negotiate with FDA for label changes, while at the same time initiating an aggressive campaign to sell as much of the drug as possible. In fact, one FDA safety officer determined that VIOXX negatively affected tens of thousands of patients who took the drug.

Now we are learning that VIOXX not only increased the risk of heart attacks-it seems that it caused the death of certain patients. Had the federal government, namely the FDA known of this risk in 2001, instead of 2003, I am confident that the federal government would not have paid Merck \$1 billion dollars for the drug.

Another matter of concern that is also set forth in JAMA relates to allegations of ghost writing. I have been looking at this issue for about a year now. As I understand it, the practice of ghost writing involves company employees, or marketing or medical education companies, who draft review articles, editorials, and/or research papers. The companies then present the article to prominent doctors and scientists, particularly those affiliated with academic institutions, to sign on as authors, who become "guest" authors. The doctors and scientists agree to be authors on the articles even though they may not be intimately familiar with the underlying data and/or relevant documentation.

The 078 study, which was not published until 2005 (a year after VIOXX was withdrawn) appears to have employed several guest authors. According to another JAMA article entitled, "Guest Authorship and Ghostwriting in Publications Related to Rofecoxib," several court documents show that Merck hired a medical publishing company, Scientific Therapeutics Information, Inc. (STI), to:

- 1) draft manuscripts for the company's VIOXX studies; and
- 2) seek academic investigators to sign on as the primary author(s).

The JAMA authors published one email sent between STI and Merck that listed several manuscripts that STI was drafting on Merck's behalf. The email stated that, "At the request of John Romankiewicz, I am providing you with an update on development and estimated delivery dates for various publications related to VIOXX that STI is working on." John Romankiewicz is president of STI. The JAMA authors also note that in a document entitled, "VIOXX Publications Status Report," STI representatives wrote that a study draft had been sent to Merck for comments, but that an author for the publication still needed to be invited.

Articles published in medical and scientific journals are widely read and relied upon by practitioners. The information in these articles can have a significant impact on doctors' prescribing behavior and, in turn, on the American taxpayer, because the Medicare and Medicaid programs pay billions of dollars for prescription drugs. Thus, any attempt to manipulate the

scientific literature, that can in turn mislead doctors to prescribe drugs that may not work and/or cause harm to their patients, is just plain offensive.

Accordingly, please respond to the following questions and request for documents. When responding to each question, please repeat the enumerated request and follow with the appropriate response.

1. Please describe in detail how Merck determines when a DSMB is appropriate. What was the basis for Merck's decision to not establish a DSMB for study 078? Please provide all related communications and other documentation supporting that decision.
2. Please provide copies of the original protocols for studies 078 and 091. What was the original data analysis plan for the safety data in these studies? Please provide copies of all amendments to the data analysis plans and a timeline for all changes made in the data analysis plans.
3. Please provide a copy of communications, including but not limited to memoranda and email, and documentation of meetings and teleconferences related to Merck's decision to submit data to the FDA in July 2001 from study 078 based on an on-treatment analysis rather than an intention-to-treat analysis. Please explain why the intention-to-treat data were not submitted to the FDA until 2003.
4. When Merck became aware of the excess deaths seen in study 091, did the company inform IRBs overseeing any other VIOXX studies ongoing at the time? Was there a DSMB for 091? Please provide all communications about IRBs and DSMBs for study 091.
5. Please list all of the IRBs that provided oversight for study 078 and their members.
6. Please provide the Committee with a list of all VIOXX-related manuscripts or reports prepared by STI on behalf of Merck. For each study, research paper or article, please provide the following information
 - a) Title of study
 - b) Brief description
 - c) Period of time for which the work was done
 - d) Author who signed name onto study, research paper or article

- e) Fees that were paid to author
 - f) Extent of involvement/participation of the author in the drafting of the final manuscript
 - g) Journal where study or article was published
 - h) Charge to Merck for completed work
7. Please provide all internal and external correspondence and communications regarding each of these STI-prepared studies.
8. Were the primary authors of the article on study 078, "A Randomized, Double-Blind, Study of Rofecoxib in Patients with Mild Cognitive Impairment," directly involved in the conduct and/or review of study 078? Which authors of the published version of 078 were aware of the intention-to-treat analyses conducted in April 2001? Were these intention-to-treat analyses provided to the "guest" academic authors? Please identify all individuals and/or third party entities that contributed to the initial and final drafts of the manuscript. If a medical publishing company, such as STI, drafted the manuscript, please provide the following information:
- a) Name of the company
 - b) Fees that were paid to each author listed on the published article
 - c) Extent of involvement/participation of each author in the drafting of the final manuscript.

In cooperating with the Committee's review, no documents, records, data, or other information related to these matters, either directly or indirectly, shall be destroyed, modified, removed, or otherwise made inaccessible to the Committee.

Thank you in advance for your cooperation. Please provide the requested information and documents by no later than May 2, 2008.

Sincerely,
Charles E. Grassley
United States Senator
Ranking Member of the Committee on Finance

April 15, 2008

John A. Romankiewicz
President and Chief Executive Officer
Scientific Therapeutics Information, Inc.
505 Morris Ave
Springfield, NJ 07081

Dear Mr. Romankiewicz:

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs. As a senior member of the United States Senate and as Ranking Member of the Committee, I have a special responsibility to the more than 80 million Americans who receive health care coverage under those programs to ensure that beneficiaries receive drugs that are both safe and effective

I am writing to follow up on a letter I sent to you last October regarding ghost writing of medical studies. For the last three years, the Committee has been examining various aspects of the medical industry. More recently, I began examining a practice used by drug and device companies referred to as "medical ghostwriting." I have been informed that this practice involves marketing or medical education companies that draft review articles, editorials, and/or research papers. This information is then presented to prominent doctors and scientists, particularly those affiliated with academic institutions, to sign on as authors, whether or not they are intimately familiar with the underlying data and relevant documentation.

Specifically, I am concerned about several allegations of ghostwriting that have come to light in an article published today in the Journal of the American Medical Association (JAMA). This article points out that Scientific Therapeutics Information, Inc. (STI) drafted scientific studies on the painkiller VIOXX and then sought academics to sign on as the primary author(s). As I am sure you are aware, any attempt to meddle in the scientific literature can mislead doctors to prescribe drugs that may not work, or that may even be harmful. Such activity is also a concern to the federal government which pays out billions every year for drugs. In addition, there is a concern that such activities will make medical literature nothing more than an extension of drug or device marketing.

The JAMA authors published one email that was sent between STI and Merck, the makers of VIOXX. This email lists several manuscripts that STI was drafting on Merck's behalf. The email states that, "At the request of John Romankiewicz, I am providing you with an update on development and estimated delivery dates for various publications related to VIOXX that STI is working on."

The JAMA authors also note that in a document titled, "VIOXX Publications Status Report," STI representatives wrote that a study draft had been sent to Merck for comments, but that an author for the publication still needed to be invited.

I would also like to mention that my investigators found an email sent to your company by a professor at Northwestern University back in August 2000 (see attachment). In this email, the professor apparently declines payment for some type of work on a manuscript. He wrote, "I really do not feel it is appropriate to be paid for this type of work." This email was then forwarded on to several STI employees. You were copied on the response where one of the employees wrote, "We were offering him \$2000. Should I offer to issue the check as a research grant?"

Accordingly, I would appreciate your response to the following request for documents and responses to questions. When responding to each question, please repeat the enumerated request followed by the appropriate response.

1. Please provide the Committee with a list of all VIOXX-related manuscripts or reports prepared by STI on behalf of Merck for the period of January 1, 2000 through the present. For each study, please provide the following information
 - a. Title of study and/or report
 - b. Brief description
 - c. Period of time for which the work was done
 - d. Author who signed name onto study
 - e. Fees that were paid to author
 - f. Extent of involvement/participation of the author in the drafting of the final manuscript
 - g. Journal where study was published
 - h. Charge to Merck for completed work

2. Please provide all internal and external correspondence and communications regarding each of these studies.

In cooperating with the Committee's review, no documents, records, data, or other information related to these matters, either directly or indirectly, shall be destroyed, modified, removed, or otherwise made inaccessible to the Committee.

Thank you in advance for your continued cooperation. Please provide the requested information and documents by no later than May 2, 2008.

Sincerely,
Charles E. Grassley
United States Senator
Ranking Member of the Committee on Finance

Attachment