United States Senate

Committee on Finance

Washington, D.C. 20510

M E M O R A N D U M

TO: Reporters and Editors
FR: Carol Guthrie, 202/224-4515
for Sen. Max Baucus
Jill Kozeny, 202/224-4515
for Sen. Chuck Grassley
RE: Avandia (rosiglitazone)
DA: Monday, May 21, 2007

Sens. Max Baucus and Chuck Grassley, Chairman and Ranking Member of the Committee on Finance, today made comments and sent letters regarding the contents of a study just released by the The New England Journal of Medicine. The study is on cardiovascular problems linked to Avandia, a pharmaceutical used for the treatment of type 2 diabetes.

Comments from each senator are below, along with the text of their letters to the Food and Drug Administration and GlaxoSmithKline, the maker of Avandia. Sens. Baucus and Grassley are asking the Food and Drug Administration to tell them about what the FDA knew about Avandia and when they learned about it. The senators are asking the drug maker to respond to allegations that company executives sought to silence independent scientist(s) about risks with this particular drug.

Sen. Baucus' comment:

"What we are learning about the handling of Avandia by both GlaxoSmithKline and the FDA is appalling and unacceptable. Both the drug company and the FDA have some major explaining to do about what they knew about Avandia, when they knew it, and why they didn't take immediate action to protect patients. The number one priority for drug manufacturers and the FDA must be patient safety. Medicare and Medicaid patients—and all Americans—must never be put at risk like this again," Baucus said.

Sen. Grassley's comment:

"We need to know if this is another Vioxx, where the FDA sat on its hands and endangered lives. The FDA has talked a good game about how it's beefed up post-market surveillance over the last two years, but a case like this undermines that claim. It'll take more than administrative reforms to fix the system within the FDA. Congress ought to take advantage of the opportunity that we have right now with the FDA funding bill to make a real difference for public safety. Study after respected study has said that the FDA office responsible for post-market review of drug safety ought to have equal footing with the FDA's drug approval office. It's hard to understand how there's any resistance to this kind of reform if you care about public

safety and public access to the never ending flow of new information about pharmaceuticals. I won't stop making the case for giving the post-market review office real clout," Grassley said.

Baucus/Grassley letter to the FDA:

May 21, 2007

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner von Eschenbach:

The United States 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 under those programs to ensure that beneficiaries receive drugs that are both safe and effective.

Today, the New England Journal of Medicine published a study on adverse effects of rosiglitazone (Avandia), a pharmaceutical manufactured by GlaxoSmithKline (GSK) to treat type II diabetes. The study reported a 43% increase in the risk of myocardial infarctions/heart attacks in people taking Avandia and potentially a 64% increase in the risk of cardiovascular deaths. Since the Food and Drug Administration (FDA/Agency) approved Avandia in 1999, physicians have written tens of millions of prescriptions for the drug. This could mean tens of thousands of cardiovascular adverse events attributable to this drug.

Diabetics take Avandia to improve their overall health as well as avoid one of the major causes of death among diabetics, heart attacks. It is troubling to say the least that by taking Avandia, diabetics may be increasing their risk of the very adverse event that they hope to prevent by controlling their blood sugar. To make matters worse, American taxpayers have spent hundreds of millions of dollars on this drug through the Medicare and Medicaid programs.

In addition, the Committee has received reports that executives with GSK met with FDA officials in October 2005 and later in August 2006 after further exploring these cardiovascular problems. We understand that during the same time period, other concerns were raised by FDA employees.

Ironically, on May 9, 2007, Dr. Steven Galson, Director of the Center for Drug Evaluation and Research, testified before Congress that FDA guidance approved in March should protect the public against problems with pharmaceuticals such as what we are now seeing with Avandia. Dr. Galson testified, "The guidance affirms the Agency's commitment to communicate important drug safety information in a timely manner including in some situations when the Agency is still evaluating whether to take any regulatory action." Dr. Galson's testimony flies in the face of FDA's leisurely reaction to GSK's briefing over a year ago on

cardiovascular problems attributed to Avandia.

It appears that the new guidance on communicating drug safety information has not improved the FDA's ability to protect the American people in a timely manner. We are greatly concerned about these alleged missteps and would like to further understand why FDA has not taken any action.

In light of the serious concerns raised in this letter, we would like to have you personally brief us on Avandia. We request that Dr. Galson and the lead safety official in Office of Surveillance and Epidemiology who has been monitoring Avandia join you for the briefing.

Additionally, we would also appreciate responses to the following questions and requests for documents and records in advance of the briefing. Please respond by repeating the enumerated question, followed by the accompanying response.

1. When did you first become aware that Avandia may cause a higher incidence of myocardial infarctions, cardiovascular disease, and/or cardiovascular death?

2. How did the FDA first become aware of this problem? Describe in detail FDA's actions to address this problem.

3. Given the effects of Avandia on blood glucose levels and other cardiovascular risk factors like cholesterol levels and body weight, did the FDA consider requiring GSK to conduct a long-term randomized trial to demonstrate risks and/or benefits such as how Avandia affects heart attack risk? What were the discussions, if any, around this issue at the FDA? Did the FDA make the suggestion to GSK? If so, what was GSK's response? Please provide a complete account of the evolution of these discussions, including related communications, documents, and records.

4. Please provide a formal, detailed timeline of your agency's actions regarding Avandia beginning with the date on which FDA staff first became aware of this higher incidence of cardiovascular problems related to Avandia and/or were notified by GSK of these problems. This timeline should identify, among other things, any internal or external communications and/or meetings, including meetings with GSK. Please provide relevant documents and/or records.

5. Describe in detail actions that FDA has taken to investigate the potential for Avandia to cause cardiovascular problems since FDA was first advised or became aware of such risks.

6. Please provide all documents and/or records regarding Avandia since your agency first began examining whether patients taking the drug might be at a higher risk for myocardial infarctions, cardiovascular disease, or cardiovascular death.

7. Please identify all agency personnel (including full name, title and contact information) who have examined the issue of Avandia and myocardial infarctions, cardiovascular

disease, and/or cardiovascular death. Also, explain what role they played in investigating and/or communicating that Avandia may cause these adverse reactions. In responding to this question, please include internal and external communications.

8. When did the FDA first learn of the study and/or work of Dr. Steven Nissen, one of the authors of the New England Journal of Medicine article, regarding Avandia and myocardial infarctions? Please provide all communications, documents and records, both internal and external, regarding Dr. Nissen's study and/or work on Avandia.

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

We look forward to hearing from you regarding the concerns and questions set forth in this letter by no later than June 4, 2007 in accordance with the attached definitions and general instructions.

Sincerely,

Max Baucus
Chairman

Charles E. Grassley
Ranking Member

Baucus/Grassley letter to GlaxoSmithKline:

May 21, 2007

Mr. Christopher Viehbacher
President
U.S. Pharmaceuticals
GlaxoSmithKline
5 Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Viebacher:

The United States 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 under those programs to ensure that beneficiaries receive drugs that are both safe and effective.

Today, the New England Journal of Medicine published a study on the adverse effects for

rosiglitazone (Avandia), a pharmaceutical manufactured by GlaxoSmithKline (GSK) to treat type II diabetes. The study reported a 43% increase in the risk of myocardial infarctions/heart attacks in people taking Avandia and potentially a 64% increase in the risk of cardiovascular death. Since GSK began selling Avandia in 1999, physicians have written tens of millions of prescriptions for it. This could mean tens of thousands of cardiovascular adverse events attributable to Avandia.

Diabetics take Avandia to improve their overall health as well as avoid one of the major causes of death among diabetics, heart attacks. It is troubling to say the least that by taking Avandia, diabetics may be increasing their risk of the very adverse event that they hope to prevent by controlling their blood sugar. To make matters worse, American taxpayers have spent hundreds of millions of dollars on this drug through the Medicare and Medicaid programs.

One of the most immediate concerns to us are reports that GSK employees silenced one or more medical professionals who attempted to speak out about the potential for cardiovascular problems with Avandia. This allegation is very serious and warrants further investigation.

In addition, the Committee received reports that GSK executives met with FDA officials in October 2005 and later in August 2006.

In light of these allegations and concerns, we request a briefing for our Committee staff, focusing in particular on: (1) allegations that GSK executives sought to silence medical professional(s) regarding possible serious adverse events related to Avandia, and (2) the reports and any other information that GSK provided to the FDA regarding adverse events related to Avandia.

We also request that GSK provide responses to the following questions and requests for documents and records. Please respond by repeating the enumerated question, followed by the accompanying response.

1. When did GSK first become aware that Avandia may cause a higher incidence of myocardial infarctions, cardiovascular disease, and/or cardiovascular deaths? How did GSK first become aware of this problem?

2. Describe in detail what actions GSK took to address this problem. Please include copies of all responsive documents. In responding to this inquiry, please be specific as to what raised GSK's suspicion that people taking Avandia might be at a higher risk for cardiovascular problems.

3. When it was approved or soon after, there was evidence that Avandia improved the control of blood glucose but had adverse effects on other risk factors like weight and cholesterol. An important scientific question is whether Avandia thus reduces or increases the risk of heart attack in diabetics. Answering this question would require a large long-term randomized trial with heart attack as one potential outcome. Please provide all communications, documents, and records relevant to a discussion on conducting such a trial, from the time that the New Drug Application was first submitted

to the FDA. Did GSK conduct such a trial? If not, why not? What were the arguments for and against conducting such a trial? What was the decision-making process regarding such a trial?

4. Please provide a detailed timeline of GSK's actions regarding Avandia beginning with the date on which your company first became aware of the potential for a higher incidence of cardiovascular problems related to the use of Avandia and the time GSK notified the FDA of such potential. This timeline should identify specifically, among other things, any internal or external communications and/or meetings, including meetings with the FDA. Please provider relevant documents and/or records.

5. Please identify all GSK personnel (including full name, title and contact information) who have examined the issue of Avandia and myocardial infarctions, cardiovascular disease, and/or cardiovascular death. Also, explain what role they played in investigating and/or communicating that Avandia may increase the risk of these adverse reactions. In responding to this question, please include internal and external communications.

6. Please provide any and all contracts or similar instruments between GSK and any outside scientists/medical professionals regarding Avandia and efforts to either directly or indirectly limit that individual's ability to discuss adverse events related to Avandia. For each contract or similar instrument, please provide all related documents, records and/or communications.

7. Please identify any and all third parties (e.g., corporations, individuals, universities, etc.) engaged by GSK to examine, review, evaluate or analyze Avandia and/or the effects of its use. Please be sure to include the nature of the work performed and provide a copy of any and all draft and final products provided to GSK.

8. When did your company first learn about the study and/or work of Dr. Steven Nissen on Avandia and cardiovascular problems? Please provide all communications, documents and records, both internal and external, regarding Dr. Nissen's study and/or work on Avandia, including any consultants who may have been hired to examine/discuss Dr. Nissen's work.

In cooperating with the Committee's review, no documents, records, data or information related to these matters shall be destroyed, modified, removed or otherwise made inaccessible to the Committee. In addition, we would appreciate your identifying a GSK representative with whom we can discuss matters relating to Avandia as soon as possible.

We look forward to hearing from you regarding the allegations, concerns and questions set forth in this letter by no later than June 11, 2007, in accordance with the attached definitions and general instructions.

Sincerely,

Max Baucus

Chairman

Charles E. Grassley
Ranking Member