United States Senate
Committee on Finance

Sen. Chuck Grassley · Iowa
Ranking Member

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M E M O R A N D U M

TO: Reporters and Editors
FR: Jill Kozeny, 202/224-1308
for Sen. Chuck Grassley
RE: FDA Panel Meeting on Avandia
DA: Monday, July 30, 2007

Sen. Chuck Grassley issued the comment below about the FDA advisory board meeting today regarding the diabetes drug Avandia. Sen. Grassley is Ranking Member of the Committee on Finance and has sought legislative and administrative reforms to strengthen the FDA's post-market surveillance of pharmaceuticals.

Grassley Comment:

"It's good to see that scientists participating in the meeting today were able to hear from a range of views within the Food and Drug Administration, and that both the Office of New Drugs and the Office of Surveillance and Epidemiology were represented. As a result, the meeting considered the full deck instead of a stacked deck."

Background Information:

In January, Sen. Grassley and Sen. Christopher Dodd introduced, for the second time, two bills to revamp and prioritize the post-market surveillance process within the FDA and to greatly expand public access to information about all clinical trials through a registry and results database. Their bills are S.468, the Food and Drug Administration Safety Act of 2007, and S.467, the Fair Access to Clinical Trials Act of 2007. In May, Sen. Grassley offered an amendment to the Food and Drug Administration Revitalization Act of 2007 that would have made the FDA office that studies drugs after they're on the market an equal partner with the FDA office that initially approves drugs for all post-approval decisions related to the safety of drugs that are on the market. The amendment was defeated by only one vote.

Sen. Grassley has conducted active oversight of the FDA for the last three years and has put pressure on the drug safety agency to act with more independence and transparency in order to restore public confidence and strengthen public safety, especially when it comes to drugs

already on the market. Sen. Grassley has called the FDA's relationship with the drug industry "too cozy" and has revealed instances where agency leaders suppressed scientific dissent regarding agency actions and drug-safety recommendations.

Two Recent Letters on Avandia:

July 27, 2007

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

Dear Commissioner von Eschenbach:

As Ranking Member of the United States Committee on Finance (Committee), it is my duty under the Constitution to conduct oversight into the actions of the executive branch, including the activities of the Food and Drug Administration (FDA/Agency). As part of my ongoing inquiry into the diabetes drug, Avandia, I, along with Chairman Baucus, sent you a letter last Tuesday to address reports that two FDA medical experts had been removed from a safety review of Avandia (rosiglitazone) after they voiced concerns about the drug's safety. I also expressed concerns to you regarding an upcoming advisory committee meeting.

I am now writing you again regarding the joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (ACM) that is scheduled for July 30, 2007. Among other things, I am concerned about FDA's actions with regard to this meeting and possible conflicts of interests.

First, I reiterate that this meeting was organized by the Office of New Drugs (OND), the office that approved Avandia, instead of the Office of Surveillance and Epidemiology (OSE), which better understands post-marketing drug safety. The issues surrounding Avandia are, after all, about post-marketing safety. In addition, it has been reported to me that during a recent FDA meeting to prepare for Monday's ACM, a high level FDA official attempted to intimidate OSE staff members by informing all staff present that FDA is to speak with "one voice" on Monday. The problem, Dr. von Eschenbach, is that the "voice" with which FDA typically likes to speak when it comes to post-marketing drug safety is OND's voice, the same voice that put Avandia on the market.

Accordingly, I would appreciate receiving your immediate assurance that OSE will be permitted to voice its position with regard to Avandia at the ACM on Monday whether or not it concurs with OND. Specifically, I wish to ensure that the office that better understands the post-marketing safety questions related to Avandia may freely express its scientific opinion during this public meeting. In light of the fact that time is of the essence, please feel free to call

me or any member of my staff to respond to this inquiry.

Further, I am curious about a possible institutional conflict of interest that may have been overlooked by OND when it planned this ACM. I note that Dr. David J. Gordon with the National Institutes of Health (NIH) is a featured speaker and non-voting member of the Advisory Committee. He will be discussing the use of rosiglitazone in an ongoing NIH trial called BARI 2D. This study is apparently quite large and may involve a substantial investment of NIH resources.

In addition, the ACM also includes three other NIH experts who will be voting. While I do not doubt that Dr. Gordon will provide sound expert opinion on the NIH study, as will the other NIH officials, I wonder if there is an inherent institutional conflict of interest for NIH that was not considered by the FDA. More specifically, I wonder if a recommendation to remove or otherwise limit the use of Avandia will in any way negatively impact the ongoing NIH study, thereby influencing NIH officials. Your thoughts on this would be greatly appreciated.

Finally, I would like to speak with Dr. Gerald Dal Pan to fully understand OSE's role in organizing the July 30 ACM. I request a brief teleconference for tomorrow, Friday, July 27. I anticipate this call will take no more than 15 minutes of his time.

Commissioner von Eschenbach, I hope that you recognize the importance of gaining the trust of the American public on drug safety. I hope to work with you on this issue to ensure that the American people will all have an improved FDA in the future.

Sincerely,
Charles E. Grassley
Ranking Member

cc: Dr. Zerhouni

July 23, 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:

As Chairman and Ranking Member of the United States Committee on Finance (Committee), it is our duty under the Constitution to conduct oversight into the actions of the executive branch, including the activities of the Food and Drug Administration (FDA). The Committee has exclusive jurisdiction over the Medicare and Medicaid programs and a

responsibility to ensure that the more than 80 million Americans who receive health care coverage under these programs, and all Americans, receive drugs that are both safe and effective.

We continue to have concerns about FDA's process for ensuring drug safety and we have been closely following FDA's post-marketing activities on the diabetes drug, Avandia. On July 10th, we met with you regarding FDA's handling of post-marketing concerns generally and with Avandia specifically. At that time, we both voiced significant concerns that FDA was not letting science consistently guide decision-making at FDA. You agreed with us that open scientific discussions without fear of reprisal were essential to FDA's executing its mission. On June 4, 2007, Senator Grassley expressed specific concerns regarding FDA's treatment of Dr. Rosemary Johann-Liang, the former Deputy Director of the Division of Drug Risk Evaluation (DDRE) in the Office of Surveillance and Epidemiology (OSE), and urged you to take appropriate corrective actions. USA Today reported that the departure of Dr. Johann-Liang from her position in OSE was in part due to frustration with her job at the FDA. Dr. Johann-Liang had been verbally reprimanded for signing off on a recommendation that a black box label be placed on Avandia for congestive heart failure (CHF). "[T]he agency doesn't want to hear that there are problems," she told USA Today. She went on to say that, "I think in general, there is a culture of 'the drug is always innocent.'"

Suppression of dissent at the FDA is terribly troubling to both of us. Today, we are writing regarding another FDA employee who was removed from the review of Avandia after voicing safety concerns related to that drug. During a recent interview with Finance Committee staff, a senior medical officer in the Office of New Drugs (OND), who at one point was the primary reviewer for Avandia, told staff investigators that s/he was told to stop participation in the review of potential cardiovascular safety problems associated with Avandia. Since 2005, the senior medical officer believed that there was enough evidence to support a black box warning regarding the risk of CHF.

Interestingly, the senior medical officer's removal from the review happened at the same time that DDRE was recommending stricter labeling for Avandia, in particular a black box warning for CHF. What makes this allegation even more troubling is that numerous FDA employees told our investigators that this senior medical officer had the most experience with the drug class that includes Avandia. In fact, the senior medical officer had been looking at this particular drug class for about 6 years. It is our understanding that s/he was replaced by someone without experience in this drug class. The senior medical officer told our investigators, "It was the first time that this had happened to me, getting pulled off [a drug]." Another employee told our investigators, "OND does not like a black box."

Given our July 10th discussion, this new allegation is especially significant and raises our level of concern about FDA interference in safety decisions regarding Avandia and the joint Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (Advisory Committee) meeting scheduled for July 30 to discuss the safety of Avandia. We understand that OND has the lead responsibility for the upcoming advisory committee meeting instead of OSE and do not understand the logic behind this decision. The Government Accountability Office (GAO) reported that OSE's role in

advisory committee meetings was unclear and that OND generally set the agenda and determined who would present to the Advisory Committee and what issues would be discussed at meetings.

The GAO recommended that FDA clarify OSE's role. Clearly, we share GAO's concerns and have continuously expressed to you our clear sense that OND does not give post-marketing drug safety the attention and priority it deserves. When we met with you on July 10, you told us that you were working to give OSE greater control over drug safety. We would appreciate you keeping us apprised of your progress.

It also has been reported to us that a majority of the Advisory Committee members are coming from OND consultant pools rather than OSE consultant pools. We have been advised that the FDA personnel who will be sitting at the table with the Advisory Committee members and participating at the meeting break down as follows: two members of OSE to represent the post-marketing perspective and four members of OND to represent the pre-approval perspectives. Given that the focus of this meeting is the safety of Avandia in the post-marketing environment, we find this troubling.

Thank you for your prompt attention to this matter. We expect a response to the concerns set forth in this letter before the July 30, 2007 Advisory Committee meeting.

Sincerely,

Max Baucus
United States Senator
Chairman of the Committee on Finance

Chuck Grassley
United States Senator
Ranking Member of the Committee on Finance