**United States Senate**

# Committee on Finance

**Washington, D.C.**

For Immediate Release
Saturday, February 20, 2010

## Baucus, Grassley Release Finance Committee Report on Diabetes Drug Avandia, Express Concern About FDA's Role in Protecting Patients in Ongoing Avandia Study

WASHINGTON – Senator Max Baucus, Chairman of the Committee on Finance, and Senator Chuck Grassley, Ranking Member, today released a committee report based on a two-year inquiry of the diabetes drug Avandia. The senators also asked the Food and Drug Administration to describe what steps the agency has taken to protect patients in an ongoing Avandia clinical trial, and why the study is allowed to continue, given that the FDA itself estimated that the drug caused approximately 83,000 excess heart attacks between 1999 and 2007. In 2008, FDA officials called the clinical trial, as then-designed, "unethical and exploitative" of patients.

"There's a real problem when FDA's office that reviews drugs that are on the market is an unequal player in drug safety efforts," Grassley said. "It doesn't make any sense to have these experts, who study drugs after they have been on the market for several years, under the thumb of the officials who approved the drug in the first place and have a natural interest in defending that decision. The Avandia case may be the most alarming example of the problem with this set-up. Both the FDA and Congress need to take every step possible to establish independence for post-market surveillance. The Institute of Medicine has made recommendations. It's a matter of sound science and public safety."

"Americans have a right to know there are serious health risks associated with Avandia and GlaxoSmithKline had a responsibility to tell them. Patients trust drug companies with their health and their lives and GlaxoSmithKline abused that trust," Baucus said. "We will continue watching closely and working with the FDA to make sure patients and doctors are aware of the risks associated with Avandia and all drugs so they can make safe and informed decisions when choosing their medicines."

The committee report explores when the Avandia manufacturer, GlaxoSmithKline, became aware of heart attack risks associated with the drug, whether the company sufficiently warned patients and the FDA of the dangers, and steps the company apparently took to create doubt regarding negative findings about the drug.

The report was developed over the last two years by committee investigators who reviewed more than 250,000 pages of documents provided by GlaxoSmithKline, the FDA, and several research institutes. Committee investigators also conducted numerous interviews and

phone calls with GlaxoSmithKline, the FDA and anonymous whistleblowers. The report can be found at finance.senate.gov.

Baucus and Grassley directed the report over concerns that Avandia and other high-profile drugs such as Vioxx put public safety at risk because the FDA has been too cozy with drug makers and has been regularly outmaneuvered by companies that have a financial interest in downplaying or under-exploring potential safety risks. In 2007, Congress enacted legislation giving the FDA some new tools to better protect patients from harm caused by drugs that are brought to market without sufficient safety oversight or consumer warnings. However, the legislation did not fix a fundamental problem at the FDA -- the imbalance between the office responsible for monitoring the safety of drugs after approval and the office that puts drugs on the market in the first place.

The FDA has overlooked or overridden safety concerns cited by its own officials, as appears to be the case with the ongoing Avandia study. The text of the Baucus-Grassley letter to the FDA on the Avandia study follows here.

February 18, 2010

The Honorable Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
White Oak Building 1
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Hamburg:

As senior members of the United States Senate and Chairman and Ranking Member of the Committee on Finance (Committee), we have a duty under the Constitution to conduct oversight into the actions of executive branch agencies, including the Food and Drug Administration (FDA). In this capacity, we must ensure that FDA properly fulfill their mission to advance the public's welfare, safeguard the nation's drug supply, and protect patients participating in clinical trials.

We recently released a report raising concerns about Avandia, a diabetes drug made by GlaxoSmithKline (GSK). We began this inquiry after the *New England Journal of Medicine* published a study in May 2007 warning of the possible cardiovascular risk of Avandia.

Our report was based on a review of hundreds of thousands of pages of internal GSK documents and concluded:

> The totality of evidence suggests that GSK was aware of the possible cardiac risks associated with Avandia years before such evidence became public.… Based on this knowledge, GSK had a duty to sufficiently warn patients and the FDA of its concerns in a timely manner. Instead, GSK executives intimidated independent physicians, focused on

strategies to minimize findings that Avandia may increase cardiovascular risk, and sought ways to downplay findings that the rival drug ACTOS (pioglitazone) might reduce cardiovascular risk.

In 2007, the FDA asked GSK to perform a cardiovascular safety trial, called TIDE (Thiazolidinedione Intervention With Vitamin D Evaluation), to compare Avandia to other diabetes treatments such as ACTOS (piolglitazone). According to clinicaltrials.gov, the TIDE trial is currently recruiting patients. [ATTACHMENT A]

In response to several document requests made to the FDA, we received and reviewed an analysis conducted by two FDA safety officials. It is our understanding that this analysis, conducted in October 2008, reviewed all available studies comparing rosiglitazone (Avandia) to pioglitazone (ACTOS). The analysis by these FDA officials raise some alarms. For instance, they wrote:

> [T]here is no evidence that rosiglitazone confers any unique health benefits over pioglitazone while there is strong evidence that rosiglitazone confers an increased risk of [heart attacks] and heart failure compared to pioglitazone. [ATTACHMENT B]

Even more alarming, they concluded that "any proposed head-to-head trial of rosiglitazone vs. pioglitazone would be unethical and exploitative."

Two days after releasing this analysis, one of these same safety officers reviewed the protocol for the TIDE trial. This safety officer wrote that because of cardiovascular concerns with Avandia "the safety of the study itself cannot be assured, and is not acceptable." [Attachment C]

After reading these documents, we would like to know what steps the FDA has taken to protect patients in the TIDE trial, and why this trial is allowed to continue. We would also like to know if the Office for Human Research Protection (OHRP) was notified about the safety concerns of the TIDE trial identified by the FDA. Further, we were alarmed to learn that the warnings from these safety officers do not appear to be addressed in the consent form that was handed out to patients that were enrolled in the study. [Attachment D]

We look forward to hearing from you by no later than March 4, 2010.

Sincerely,

Max Baucus
Chairman

Chuck Grassley
Ranking Member