United States Senate
Committee on Finance

Sen. Chuck Grassley · Iowa
Ranking Member

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Grassley asks FDA to account for its response to scientific dissent on safety of Avandia

WASHINGTON — Sen. Chuck Grassley has asked the head of the Food and Drug Administration to respond to allegations that a senior agency scientist was reprimanded for formally agreeing with a recommendation that the diabetes drug Avandia needed a box warning for congestive heart failure and stronger warnings about its possible negative effects on eyesight.

"The Avandia case has opened a new round of questions about the way the FDA monitors drug risks and decides whether to let the public know about emerging risks," Grassley said. "It's another demonstration of the FDA letting the office that's responsible for putting drugs on the market also call all the shots regarding the post-market surveillance of drugs, despite the expertise that's contained within the FDA's office that is responsible for post-market surveillance. For the sake of public safety, I hope to see Congress revisit my legislation on post-market authority."

Grassley has been conducting active oversight of the Food and Drug Administration and sought administrative and legislative reforms to improve the post-market surveillance of pharmaceuticals. He won Senate approval to double civil monetary penalties levied against drug makers who are knowingly out of compliance with FDA directives during the Senate's recent consideration of legislation to revitalize the drug-safety agency. He also won strong support and fell just one vote short of winning passage for his initiative to make the FDA office that monitors and assesses drugs after they're on the market an equal partner on post-market questions with the FDA office that initially approves drugs for public use.

The text of the letter that Grassley sent to the FDA Commissioner about the new allegations follows here.

June 4, 2007

Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration

5600 Fishers Lane
Rockville, MD 20857

Dear Commissioner von Eschenbach:

Recently, the Committee on Finance (Committee) initiated an inquiry into the diabetes drug Avandia. During the course of that inquiry, employees of the Food and Drug Administration (FDA/Agency) were invited to contact the Committee directly and/or to provide relevant information regarding Avandia.

In response, the Committee received a memorandum dated February 22, 2006. That memorandum was prepared by a very seasoned safety evaluator in the Division of Drug Risk Evaluation (DDRE), which lies within the Office of Surveillance and Epidemiology (OSE). These offices are responsible for conducting post-marketing surveillance of drugs that are being sold to the American public.

DDRE made several recommendations in that memorandum on Avandia. First, the DDRE safety evaluator recommended that Avandia's manufacturer include macular edema as a "serious adverse event" on its label. Macular edema is a condition that involves swelling of the retina. This condition can cause serious problems, including blindness.

Second, the DDRE safety evaluator recommended that congestive heart failure (CHF) be highlighted in a "box warning" in accordance with FDA regulations. Specifically the memorandum quoted FDA regulation 21 CFR 201.57 that provides in pertinent part that "…special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box…." CHF is a condition where fluid builds up in the lungs causing severe shortness of breath and potential death. It requires immediate attention.

The fact that the FDA has yet to act on DDRE's recommendation regarding CHF is of course troubling. But another allegation has come to the Committee's attention that is simply unconscionable. It has been alleged by multiple sources, both in and out of the FDA, that the Deputy Director of the Division of DDRE was reprimanded verbally for signing off on the memorandum. According to these sources, the Deputy Director was allegedly reprimanded because she and the Office of New Drugs (OND) did not agree that a "box warning" was needed. More specifically, it was reported to me that two high level supervisors in OND reprimanded the DDRE Director who, in turn, reprimanded the Deputy Director of DDRE. Why? Because she signed off on a "box warning" recommendation based upon the available evidence reviewed by a DDRE safety officer. I guess the Deputy Director of DDRE was supposed to check with OND before signing off on that recommendation. I also was informed that the DDRE Deputy Director was advised that she would no longer be able to "sign off" on any matters related to Avandia in the future. The DDRE Deputy Director was further advised that, in the future, she could no longer sign off on any recommendations for major regulatory actions, like box warnings, without first checking with the DDRE Director. I understand that this is a new requirement for the Deputy Director of DDRE.

Commissioner von Eschenbach, I hope you recognize what is wrong with this picture. I also sincerely hope that this is not standard practice within the FDA. Post-marketing surveillance is critical to the health of this nation. Individuals in the offices responsible for post-marketing surveillance should be allowed to provide to the FDA, including OND, an "independent opinion" based on the best available evidence. Those FDA employees dedicated to post-marketing surveillance at the FDA should be able to express their opinions in writing and independently without fear of retaliation, reprimand, or reprisal. I hope that you agree and will take appropriate action to correct this situation.

Sincerely,

Charles E. Grassley
Ranking Member
Committee on Finance