Congress of the United States

Washington, DC 20515

April 30, 2007

CONFIDENTIAL

Fax Delivery

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane, Room 15-47
Rockville, MD 20857

Dear Dr. von Eschenbach:

Pursuant to Rules X and XI of the Rules of the United States House of Representatives, the Committee on Energy and Commerce and the Committee on Oversight and Government Reform are jointly conducting oversight of the Food and Drug Administration (FDA) with regard to post-marketing drug safety. In the matter that is the subject of these requests, we are also joined by Senator Chuck Grassley, Ranking Senator on the Committee on Finance that has primary jurisdiction for the Medicare and Medicaid programs in the United States Senate.

Two recent large clinical trials suggested an excess of heart attacks for patients taking rosiglitazone (Avandia), a diabetes drug used by millions of Americans.[1] FDA staff briefed the staff of both House Committees on the safety of rosiglitazone on March 16, 2007.[2] We are now writing to request a further briefing relevant to our oversight efforts.

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[1] The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, *Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial.* Lancet. (Sept. 23, 2006); Kahn SE et al, *Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy.* New England Journal of Medicine, (Dec. 7, 2006). In the DREAM trial, the nonsignificant hazard ratio for myocardial infarctions is 1.66 for patients on rosiglitazone as compared to patients on placebo; in the ADOPT trial, the nonsignificant hazard ratio for myocardial infarctions is roughly 1.31 for patients on rosiglitazone as compared to patients on either glyburide or metformin.

[2] Staff-level briefing by FDA Center for Drug Evaluation and Research to the Committee on Oversight and Government Reform and the Committee on Energy and Commerce (Mar. 16, 2007).

According to FDA staff, your agency is currently reviewing pooled clinical trial data from GlaxoSmithKline on 14,000 patients, received from the company for a proposed prior approval label change. These data reveal a statistically significant 40 percent increase in heart attacks for patients on rosiglitazone.[3] If these company-produced data are correct, tens of thousands of excess heart attacks may have occurred in the six months since FDA began examining these data.[4]

We support FDA's need to complete a rigorous, impartial, and scientific review of these data and the implications for those tens of thousands of Americans who take this medication daily. It appears, given the magnitude of the potential post-marketing safety signal, time may be of the essence.

As soon as a decision is made, we request an additional staff-level briefing on agency actions with regard to this issue. We also request that, at a minimum, the following additional key agency staff be included in the briefing: John Jenkins, Director of the Office of New Drugs; and consulting staff from the Office of Surveillance and Epidemiology, the primary medical reviewer and the primary statistician. In addition, we ask that all documents and materials that are directly or indirectly related to this matter be preserved. Finally, if no decision is made by May 15, 2007, we expect an explanation from you regarding the reasons for the delay.

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[3] Staff-level briefing by FDA Center for Drug Evaluation and Research to the Committee on Oversight and Government Reform and the Committee on Energy and Commerce (Mar. 16, 2007).

[4] Centers for Disease Control, *National Diabetes Surveillance System- Number of adults with diabetes by diabetes medication status, United States, 1997-2003* (online at http://www.cdc.gov/diabetes/statistics/meduse/fig1.htm) (Accessed Mar. 27, 2007); GlaxoSmithKline, Annual report 2006: A human race (online at http://www.gsk.com/investors/reps06/annual-report-2006.pdf) (Accessed Mar. 27, 2007); Staff-level briefing by FDA Center for Drug Evaluation and Research to the Committee on Oversight and Government Reform and the Committee on Energy and Commerce (Mar. 16, 2007); Jaffe JR et al, *Reassessment of cardiovascular risk in diabetes,* Current Opinion in Lipidology (2006); Haffner SM et al, *Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction,* New England Medical Journal (Jul. 23, 1998). About 9.5 million Americans take oral diabetic medication. Avandia accounts for about 37 percent of the U.S. market. Reviews of the literature show that the annual incidence of MI for diabetics is between 1 percent and 8 percent. Assuming an annual risk of MI of 1 percent, a hazard ratio of 1.4 would mean 11,600 excess heart attacks every 12 months.

If you have any questions regarding this request, please have your staff contact Stephen Cha, the House Committee on Oversight and Government Reform staff, at (202) 225-5056, David Nelson, the House Committee on Energy and Commerce staff, at (202) 226-2424, or Angela Choy, the Senate Committee on Finance, at (202) 224-4515.

Sincerely,

John D. Dingell, Chairman
House Committee on Energy
and Commerce

Henry A. Waxman, Chairman
Committee on Oversight and
Government Reform

Chuck Grassley, Ranking Member
Senate Committee on Finance