Statement of Rep. Henry A. Waxman
Chairman, Committee on Oversight and Government Reform
Hearing on FDA's Role in Evaluation of Avandia's Safety
June 6, 2007

Today, we are holding a hearing about an important medication that is being used by a million Americans to control their diabetes.

Diabetes is a terrible disease. Diabetics are unable to control their blood sugar. High blood sugar affects nearly every part of the body and can cause blindness, kidney failure, heart attack, and stroke. Heart attacks and strokes caused by high blood sugar levels end up killing two out of every three diabetics.

Diabetes can't be cured. But with proper medical attention and effective drugs, it can be controlled and the devastating consequences of diabetes can be delayed or even prevented. Endocrinologists, who specialize in the treatment of diabetes, believe that drugs that lower blood sugar levels are especially important to prevent the long-term complications of this disease.

Avandia was approved in 1999 because of clinical evidence that it effectively lowers the blood sugar levels in diabetics. Trials conducted since then confirm that Avandia is indeed effective in lowering blood sugar levels. That is why it has been so widely prescribed by doctors across the nation.

Avandia, however, is a sophisticated and complicated drug. It works at the gene level and has multiple effects on the body. For instance, it may increase weight and cholesterol. That is why from the outset, concerns have also been raised about whether Avandia could increase the risk of heart attacks.

I have struggled to find the right tone for today's hearing. Diabetes is a serious illness and Avandia is an effective medication for lowering blood sugar. Sounding a false alarm about the dangers of the drug has the potential to cause serious harm to patients.

On the other hand, there have been repeated warnings — from the day of approval forward — about the potential cardiac risks associated with Avandia. And these should not be ignored.

It is not Congress' role to adjudicate these medical issues. But it is our role to ensure that the Food and Drug Administration is taking these concerns seriously and providing doctors and patients with the guidance they need to make informed decisions.

And that is why I am holding this hearing today. Although Avandia has been on the market for eight years and has been used by millions of Americans, the post-market studies have not been done to say conclusively whether Avandia increases or decreases the risk of heart attacks. That's a major failure of our system. And it is what is causing so much confusion and worry among the patients who are taking Avandia today.

Avandia was approved on May 25, 1999. The primary medical reviewer at FDA recommended approval of the drug because clinical trials showed it to be effective at reducing blood sugar. That was justified and appropriate.

The medical reviewer also noticed that the clinical data raised questions about Avandia's effect on the heart. I would like to introduce the findings of the medical reviewer into the record and read an excerpt. The excerpt is technical — and long — but it reveals how our system is supposed to work:

> Whether [Avandia] favorably affects the natural history of type 2 diabetes is open to question. Long term improvement in HbA1c [a measure of blood sugar] should decrease the risk of retinopathy [eye problems], nephropathy [kidney problems] and neuropathy [nerve problems]. However, the increase in body weight and undesirable effects on serum lipids [cholesterol] is cause for concern. Heart disease due to atherosclerosis is a major cause of morbidity and mortality in patients with type 2 diabetes, and it cannot be assumed that treatment with [Avandia] will decrease the risk.

Because of his concern about the potential for "deleterious long term effects on the heart," the medical reviewer recommended that "a postmarketing study to address these concerns needs to be a condition of approval."

The medical reviewer did everything right. He recognized that Avandia held great promise because of its impact on blood sugars. And he recognized that there were questions about its side effects that could be answered conclusively only through a properly designed post-market trial.

Unfortunately, at that point FDA dropped the ball.

FDA and the drug manufacturer did agree upon a post-market study called ADOPT. But it was designed to show whether Avandia provided long-term control of blood sugar levels, not to assess whether Avandia increases the risk of heart attacks. ADOPT did show that Avandia is an excellent drug for keeping blood sugar under control, but it did not answer the medical reviewer's questions about heart risks.

FDA did receive several warnings about a potential link between Avandia and heart attacks. In March 2000, Dr. John Buse, who will testify on the second panel today, wrote FDA to request

"cardiovascular safety trials in high-risk populations." In February 2003, the World Health Organization issued a warning of the potential cardiac risks associated with drugs like Avandia. A year later, a review in the New England Journal of Medicine stated that "data about the effects of TZDs [drugs like Avandia] on cardiovascular disease are urgently needed."

Then in October 2005, the drug's manufacturer, GlaxoSmithKline, informed FDA that an internal company analysis showed that Avandia may be associated with an increased risk of "myocardial ischemia," a medical term that includes heart attacks. The drug manufacturer gave FDA this analysis 11 months later, along with a second study the company sponsored that did not show increased risk.

Yet despite the FDA medical reviewer's recommendation, despite additional warnings by outside experts, despite the millions of patients who rely on Avandia to control their blood sugar, and despite the potential risks involved, FDA never required the manufacturer to conduct a thorough post-market study of Avandia's heart risks.

In fact, it took the publication of an article last month in the *New England Journal of Medicine* to spur the agency to public action.

European regulators were not so negligent. Over six years ago, they required GlaxoSmithKline to initiate a study called RECORD, which is designed to assess cardiovascular risks. The company published partial results from this study yesterday. Unfortunately, as we will hear from the experts on our second panel, the results to date are inconclusive and RECORD does not appear to be large enough to answer the key questions about Avandia's cardiac risks.

Many people watching this hearing today will be looking for answers about whether Avandia is safe. I understand and share their desire for answers, but because of the lack of data, there may be no definitive conclusions.

By examining Avandia, however, we can learn a lot about the drug approval and post-market surveillance process. Avandia is a case study of the need for reform of the nation's drug safety laws.

As a member of Congress, I'm not qualified to judge whether the risks of Avandia outweigh its benefits. But I do know that the millions of diabetics who have taken Avandia have not been well served by our regulatory system. Doctors and their patients should be able to turn to FDA for guidance about the safety of the drugs they take. But in the case of Avandia, FDA did not insist upon the data it needs to answer their questions definitively.

Legislation has passed the Senate and is pending in the House that would give FDA new powers to require post-market studies of drugs like Avandia. This hearing will show why these reforms are so urgently needed. FDA needs the will, the resources, and the authority to be a more effective watchdog of drug safety.

I look forward to the testimony we will receive and thank all of the witnesses for being here today.