Committee on Oversight and Government Reform
U.S. House of Representatives
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Mr. Chairman, Congressman Davis, members of the Committee, it is an honor to be called to testify before this committee. I would like to make two introductory points as a matter of disclosure.

First, this statement and my testimony do not reflect the opinions or policies of my employer, the University of North Carolina (UNC) School of Medicine, or of the American Diabetes Association (ADA), a voluntary heath agency for which I serve as an officer.

Second, my experience with the glitazone class of insulin-sensitizing anti-diabetic agents is deep and my potential conflicts of interest in this regard are broad. Briefly, between 1992 and 2005 I participated in thirteen pharmaceutical company sponsored studies involving five glitazones including Avandia, Actos and Rezulin. Furthermore, I have been a consultant and a speaker for the manufacturers of these agents. I have worked with more than 20 other companies and conducted over 70 industry-sponsored studies in 15 years as an academic clinical researcher.

Since approximately 2000, all work with companies for whom I participate in clinical trials is under contract with UNC and provides no direct financial benefit to me. They do support the operation of the UNC Diabetes Care Center which I direct. Payments from companies for whom I do not participate in clinical trials and which do not have contract with UNC are donated to various charities. I benefit personally from honoraria from universities, health care systems and continuing medical education providers. I do not consult with financial services companies or market research firms. I do continue to struggle with how to best manage my conflicts of interest with help from a personal attorney, UNC, the ADA and the NIH. I have done no work for the manufacturers of Avandia or Actos for two to three years.

With my remaining time I would like to provide background on the issues that committee staff indicated were of interest to the Committee, specifically how I came to have concerns regarding Avandia in 1999 and my opinions today. .

In June of 1999, I was invited to make several presentations at national scientific meetings. For more than one, I was specifically asked to address the clinical benefits and risks of the glitazones. At least one was sponsored by the manufacturer of Actos. As a fairly junior member of the academic community, I was quite anxious about having to provide insights to hundreds of colleagues including senior scientists and clinicians at multiple presentations. In preparing for those sessions, I pored over every published paper as well as slides from the

FDA Advisory Panel presentations on Rezulin, Actos and Avandia. I was struck that there were consistent differences with regard to cholesterol changes among these agents. My impression was that Avandia had a potentially negative effect on LDL, so-called "bad cholesterol". Because of that, it occurred to me to try to examine whether there was any signal of cardiovascular risk. There was a trend toward increases in serious cardiovascular events and cardiovascular deaths with Avandia as compared to active comparators. Neither was statistically significant. I could not find evidence for such trends with Rezulin and Actos.

I recognized that this was potentially an explosive issue and went to rather extreme ends to make sure that I was not making an error including sharing the results and the slides I was going to present with research scientists from SmithKline Beecham (SKB), the manufacturer of Avandia. Those discussions were cordial and helpful.

Couched with many caveats, I presented the issues outlined at least twice in June of 1999. In the week that ensued, there were a number of phone calls in this regard from SKB. During these calls, it was mentioned on two occasions that there were some in the company who felt that my actions were scurrilous enough to attempt to hold me liable for a loss in market capitalization. The chairman of my department told me that out of respect for a long-standing academic colleague who now had a senior position at SKB, he had agreed to discuss with me the presentations that I had made and how they had been characterized. In the end I offered to help the company with further studies and signed a clarifying statement drafted by SKB which was to be used to with the investment community.

In March of 2000, I was aware that there were ongoing discussions with the Food and Drug Administration (FDA) regarding the safety of Rezulin. I was concerned about the safety of Actos (because there were so few people studied in trials at that point), Avandia (as outlined above) and Rezulin (liver toxicity). I was also impressed that the glitazones had revolutionized the treatment of diabetes. The combination of insulin and glitazones to this day is the most powerful glucose lowering therapy available. My concern was that the entire glitazone class was in danger if Rezulin was withdrawn from the market without robustly understanding the safety of the newer agents. At that time, about half the patients with diabetes in my practice were still inadequately controlled. What I needed was more ways to treat diabetes, not fewer. In a letter to the FDA commissioner, I did repeat the observations that I had made in 1999 and called for both greater enforcement of marketing regulations and additional trials.

By their very nature, the analyses that I made in 1999 and the much more sophisticated analysis by Dr. Nissen are only useful to generate questions, not to produce answers. Today, the most important issue is how patients and doctors should think about Avandia. From 1999 until today, I believe that switching patients from Avandia to another diabetes drug when their blood sugar, blood

pressure and cholesterol values are well controlled is likely to pose a greater risk to patient safety than continuing Avandia. I remain concerned that it will be years before the results of an appropriately powered cardiovascular outcomes study with Avandia is likely to provide an answer to the questions raised.

To be fair, there is no currently available treatment for elevated blood sugar with proven benefits to reduce the risk of heart attack. Arguably, Actos comes closest to meeting that standard, but it does technically fall short.

If there is a lesson from the events of the last weeks and years, perhaps it is that upon filing a New Drug Application, pharmaceutical manufacturers should make every effort to develop an adequately-powered independently-executed study that examines clinically meaningful endpoints such as heart attack or loss of vision. In parallel with regulatory approval, such a study should be reviewed with attention to design, oversight, funding plan and timeline, recognizing that such studies are very expensive and will take many years to complete. Direct to consumer advertising and medical marketing should be constrained until such studies are completed.

Again, these are my opinions and not those of UNC or of the ADA. Thank you for your attention.