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FDA'S ROLE IN THE EVALUATION OF AVANDIA'S SAFETY

HEARING

BEFORE THE

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

FIRST SESSION

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FDA'S ROLE IN THE EVALUATION OF AVANDIA'S SAFETY

WEDNESDAY, JUNE 6, 2007

HOUSE OF REPRESENTATIVES,
COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM,
Washington, DC.

The committee met, pursuant to notice, at 10 a.m. in room 2154, Rayburn House Office Building, Hon. Henry A. Waxman (chairman of the committee) presiding.

Present: Representatives Waxman, Towns, Cummings, Kucinich, Davis of Illinois, Tierney, Clay, Watson, Yarmuth, Cooper, Hodes, Sarbanes, Davis of Virginia, Shays, Cannon, Issa, McHenry, Foxx, and Sali.

Staff present: Phil Barnett, staff director and chief counsel; Kristen Amerling, general counsel; Karen Nelson, health policy director; Karen Lightfoot, communications director and senior policy advisor; Andy Schneider, chief health counsel; Sarah Despres, senior health counsel; Molly Gulland, assistant communications director; Steve Cha, professional staff member; Earley Green, chief clerk; Teresa Coufal, deputy clerk; Caren Auchman, press assistant; Zhongrui "JR" Deng, chief information officer; Leneal Scott, information systems manager; Rachel Sher, counsel; William Ragland and Kerry Gutknecht, staff assistants; David Marin, minority staff director; Larry Halloran, minority deputy staff director; Jennifer Safavian, minority chief counsel for oversight and investigations; Keith Ausbrook, minority general counsel; Ellen Brown, minority legislative director and senior policy counsel; Anne Marie Turner, minority counsel; Victoria Proctor and Susie Schulte, minority senior professional staff members; John Cuaderes, minority senior investigator and policy advisor; Patrick Lyden, minority parliamentarian and member services coordinator; Brian McNicoll, minority communications director; and Benjamin Chance, minority clerk.

Chairman WAXMAN. The meeting of the committee will come to order.

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 stroke 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 con-

sequences 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 been raised about whether Avandia could increase the risk of heart attacks.

I have struggled with the right tone for today's hearings. 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 a 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 assure that the Federal Food and Drug Administration is taking these concerns seriously and providing doctors and patients with the guidance they need to make informed decisions.

That is why we are holding this hearing today. Although Avandia has been marketed for 8 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 is a major failure of our system, and that 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, and the quote I want to read is: "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 would decrease the risk."

Well, because of this concern about the potential for "deleterious long-term effects on the heart," the medical reviewer recommended that "a post-marketing 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 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 on 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 of 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 manufacturer GlaxoSmithKline informed FDA that an internal company analysis showed that Avandia may be associated with increased risk of myocardial ischemia, a medical term that includes heart attacks. The drug manufacturer gave the FDA this analysis 11 months later, along with a second study the company sponsored that did not show increased risks.

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 6 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. It was not designed to be completed until 2009.

While many people watching this hearing today will be looking for answers about whether Avandia is safe, and 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 our drug safety laws.

As a Member of Congress, I am 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 consider 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 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 I want to thank all of the witnesses for being here today.

I want to now call upon the ranking Republican member of the committee, Mr. Davis, for his statement.

[The prepared statement of Chairman Henry A. Waxman follows:]

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.

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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.

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

Mr. DAVIS OF VIRGINIA. Thank you, Mr. Chairman, and good morning.

Once again, this committee meets to consider serious questions about how the Food and Drug Administration and drug makers monitor the long-term safety of approved pharmaceutical products. In 2004 and 2005, we led an extensive bipartisan investigation into the pain reliever Vioxx, confronting many of the same questions we face today.

How effective are programs by the FDA and industry to gather timely and useful data on lingering safety concerns about approved products? When those safety concerns emerge, how should preliminary, often anecdotal information be used by regulators, clinicians and patients? And how do we strike the correct balance between speedy approval of life-saving or life-enhancing therapies that patients want and the much slower process of amassing statistically valid data sets on long-term health outcomes?

Today's hearing was prompted by recent warnings the diabetes medication Avandia, manufactured by GlaxoSmithKline, may increase the risk of cardiovascular disease in some patients, patients already uniquely vulnerable to heart problems. An admittedly limited meta-analysis of disparate research findings suggests that increase may be substantial. But other studies point to little, if any, measurable increase in heart risks.

So patients and doctors are left with conflicting or incomplete information upon which to base delicate judgments about the net benefits of various treatment options.

But this hearing, as the chairman notes, is not about one product. At least, it shouldn't be. It is about the effectiveness of the overall drug approval and the monitoring process. As the chairman's memo to Members cautioned, this hearing is not about whether Avandia makes patients healthier or harms them. We are not here to substitute our judgment for that of scientists and regulators still evaluating clinical safety data.

But we are here to ask whether current post-marketing surveillance programs and protocols are both robust and sensitive enough to detect emerging evidence of deleterious health effects and how that evidence informs regulatory research and treatment decisions.

Taken by almost 1 million Americans today, Avandia was approved in 1999 because it lowers harmful blood sugar levels in patients suffering type 2 diabetes. Managing type 2 diabetes by lowering blood sugar can decrease the patient's chance of having diabetes-related problems later in life, such as kidney failure, heart disease, stroke and limb amputation.

But the so-called surrogate endpoint of reduced blood glucose is only an indirect measure of the drug's overall impact on health. Questions about the extent of any increase cardiovascular risk posed by Avandia were raised 8 years ago. So the FDA required Glaxo to compare the safety and effectiveness of Avandia with other oral anti-diabetes medicines. In 2000, the company initiated another large, long-term clinical trial to look specifically at cardiovascular outcomes in people with diabetes using Avandia to manage the disease.

So far, results from that study have not shown increased health risks at levels suggested by the meta-analysis that would require

discontinuation of the research for safety reasons. Nevertheless, last year, based on data from a study involving patients with existing congestive heart failure, the FDA required a labeling change for the drug to include a new warning about a potential increase in heart attacks and heart-related chest pain in some individuals.

The FDA will convene an advisory committee as early as next month to review this matter. That committee's findings should provide health care providers and patients with a better understanding of any cardiovascular risks involved with the use of Avandia.

It is not clear if the advisory committee will also look at the entire class of oral anti-diabetes medications that operate like Avandia. Perhaps FDA can answer that question today.

This muddled post-marketing picture is not unique. A recent New England Journal of Medicine editorial called the FDA approach to post-approval or Phase 4 research "desultory," because during the period from 1998 through 2003, only about a quarter of the required Phase 4 trials were completed. And as of September 30, 2006, a total of 899 Phase 4 studies remain pending. As a result, the safety profile of some drugs, particularly those approved using surrogate endpoints, can remain incomplete for years.

Most Americans believe once the FDA approves a drug, it carries the medical equivalent of the Good Housekeeping seal of approval and can be used with little or no risk. But the process of developing, marketing, regulating, prescribing and using modern pharmaceuticals involves some, at times considerable risk, at every stage. Those risks have to be acknowledged frankly and managed responsibly.

Adverse event surveillance and research have to be sensitive enough to detect potential safety problems but discrete enough to distinguish between well-publicized anecdotes and scientific evidence. Otherwise, public confidence in both the FDA and the pharmaceutical industry will be undermined by conflicting data and allegations no one is protecting the long-term welfare of patients.

I look forward to hearing from our panels of expert witnesses today on how we can strengthen FDA approval and post-marketing surveillance systems. I would ask unanimous consent that the statement of Dr. Brian Strom, the chairman of biostatistics and epidemiology and director of the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania be included in the official hearing record.

Chairman WAXMAN. Without objection, that will be the record.

[The information referred to follows:]

STATEMENTS FOR THE HEARING RECORD OF
BRIAN L. STROM, M.D., M.P.H.
Chair and Professor of Biostatistics and Epidemiology,
Professor of Medicine, Professor of Pharmacology
University of Pennsylvania School of Medicine
COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM
UNITED STATES HOUSE OF REPRESENTATIVES
JUNE 7, 2007

Mr. Chairman and Members of the Committee:

Thank you for inviting my testimony on the important question of the safety of Avandia, and the implications of this episode for national drug safety policy.

As introduction, I am George S. Pepper Professor of Public Health and Preventive Medicine, founding Chair and Professor of Biostatistics and Epidemiology, Professor of Medicine, Professor of Pharmacology, founding Director of the Center for Clinical Epidemiology and Biostatistics, founding Director of the Graduate Group in Epidemiology and Biostatistics, and Associate Vice Dean, all at the University of Pennsylvania School of Medicine. I am also Associate Vice President for Strategic Integration of the University of Pennsylvania Health System. My curriculum vitae is attached. I have spent my career investigating questions of drug safety. During the last few years, I have received funding from the Agency for Healthcare Research and Quality, the National Institutes of Health, the Pennsylvania Department of Health, Pfizer Inc., and Takeda Pharmaceuticals North America, Inc.; served on the Board of Medco Health Solutions, Inc.; received support for a pharmacoepidemiology training program from Amgen Inc., Berlex, Inc., Merck Company Foundation, Novartis Farmaceutica, SA, Wyeth Consumer Healthcare, Wyeth Pharmaceuticals Inc., and Pfizer Pharmaceuticals Inc.; served as a consultant to Abbott Laboratories, Aetna Health Management, LLC (Aetna Inc.), American College of Neuropsychopharmacology, AstraZeneca LP (AstraZeneca), Berlex, Inc., Biogen Idec Inc., Blue Cross Blue Shield Association, Bristol-Myers Squibb Company, Centocor Research & Development, Inc., Cephalon, Inc., CV Therapeutics, Inc., Cygnus Corporation, Inc., Daiichi Sankyo, Inc., Roche Laboratories, Inc. (Hoffman-LaRoche, Inc.), Oscient Pharmaceuticals Corporation, SmithKline Beecham Corporation (GlaxoSmithKline), Johnson & Johnson Services Inc., Lilly Research Laboratories (Eli Lilly and Company), Institute of Medicine of the National Academies, Novartis Pharmaceuticals Corporation, Pfizer Inc., Sanofi Pasteur Inc., Integrated Therapeutics Group, Inc. (Schering-Plough), Shire Development Inc., TAP Pharmaceutical Products, Inc., Warner-Lambert Company, and Wyeth Pharmaceuticals Inc., and served as an expert witness for law firms representing the Bayer Corporation, and plaintiffs suing pharmaceutical companies.

I will begin by discussing the scientific issues of Avandia safety regarding myocardial infarction, followed by the policy implications, and then provide some conclusions.

SCIENTIFIC ISSUES

Nissen Paper and Its Issues

As the committee is well aware, this latest "drug safety crisis" began with the publication of a paper by Nissen and Wolski, pre-released on the website of *The New England Journal of Medicine*, along with an accompanying editorial (1, 2). The design of the study raises a number of important issues. I will discuss each in turn.

Meta-analysis is an inherently weak and controversial design. The study used the technique of meta-analysis, a well recognized and potentially useful but sometimes controversial study design (3). It uses statistical techniques to add together diverse studies, on the assumption that they give a single answer, attempting to synthesize the studies statistically. However, it is widely acknowledged that it is far preferable to perform a single study with sufficient sample size to answer the question properly.

Most of the trials included were not peer reviewed. Most meta-analyses investigate published studies only. Indeed, meta-analyses normally struggle with the question of whether only selective information is available because of unpublished studies that are not available. In this meta-analysis, in great contrast, most of the studies included were unpublished. While this avoids the issue of publication bias, it raises other important issues, in that the underlying studies in this meta-analysis were never subjected to the usual criteria of scientific peer review. This leaves uncertain the quality of the underlying information.

Six trials were omitted because they did not report any myocardial infarctions or deaths. Most meta-analyses are performed to evaluate the effectiveness of a drug or other exposure. In the Avandia situation, of course, the meta-analysis was conducted to evaluate drug safety. When measuring drug effectiveness, normally all patients have an outcome. When measuring drug safety, in contrast, most patients fortunately do not have the outcome of concern. However, meta-analytic techniques are not equipped to deal with studies with zero outcomes. This necessitated the omission of six studies from the analysis. However, in a study of drug safety, zero outcomes is very meaningful, i.e., it defines the ultimate safety. The omission of such studies is likely to exaggerate any observed difference between the treatment group and control group.

There are marked differences among the studies, yet they are all being combined as if one would expect the same answer. Inherent in the technique of meta-analysis is the assumption that the studies are all giving the same answer. Yet, these studies are extremely different from one another, with different patient populations, and even different comparison groups. Some of the studies compared Avandia to placebo, while others compared Avandia to various other antidiabetic drugs. ***The largest study, by far, considered in the meta-analysis did not even include patients with diabetes***. Combining all of these studies into a single analysis is quite questionable.

These studies were not designed to study myocardial infarction; therefore, absent adjudication, we do not know if the cases of "myocardial infarction" truly had myocardial infarctions. It is conventional in a clinical trial to spend considerable effort to validate whether the people with the outcome in question truly had the outcome. Often, on more detailed exploration, it turns out they did not. This is certainly the case with studies of myocardial infarction, as this term is used liberally, often in patients who do not truly have it. Alternatively, cases of myocardial infarction could easily be missed, if this was not the purpose of the study. Thus, this makes the outcomes in such studies very difficult to interpret, at best.

The absence of patient-level data led to incorrect analyses, which did not adjust for duration of follow-up. The ideal meta-analysis obtains the actual data of the original studies, so that individual patients can be identified and analyzed accordingly. In this scenario, duration of patient follow-up can be adjusted for. If a patient is followed for three months, s/he has three times the risk of a patient followed for one month, independent of any exposure. It is critical that this be dealt with. The authors did not have individual-level data, but only study-level data. Accordingly, they could not apply such analyses, and the statistic used was the odds ratio rather than the hazard ratio, which should have been calculated. Further, to adjust for this, the authors restricted their meta-analysis to studies where the two treatment arms had the same duration of treatment. It is not clear how many studies were omitted in the process, and how this would have affected the results.

Borderline statistically significant findings. In this context, the authors' findings were only borderline statistically significant. The odds ratio for myocardial infarction had a p value of 0.03, while the odds ratio for death from cardiovascular causes had a p value of 0.06. These are very close to the conventional scientific cutoff of 0.05. This means that the findings of this meta-analysis could possibly be due to random error. Given then all of the problems listed above, it is easily conceivable that correction of such problems could have resulted in the association here disappearing entirely. Alternatively, of course, correcting these could result in the association getting stronger. One simply cannot know.

Other Data Are Available with Different Results

The nature of science is that one looks at all available data before making a decision. At the time of the release of this study, the FDA had access to two other studies, which have now been released publicly as well. The first is the RECORD study, a large clinical trial of the kind that needs to be mounted to answer this question definitively. The results are as yet preliminary, and underpowered (4). However, they do not support this concern. The second is a very large epidemiologic study including about 30,000 Avandia users (5). Thus, there is considerable statistical power. No increased risk was seen with Avandia. Of course, like all scientific studies, these are not perfect either. RECORD is as of yet, at least, underpowered, since we are presented only with an interim analysis. Other valid criticisms have been pointed out as well (6). The epidemiologic study is, inherently, non-experimental. The authors went through extreme efforts to make the groups as similar as possible. However, one cannot exclude systematic differences between the study groups, absent randomization. Once again, the only way to address this question definitively is a large, single, randomized trial. However, it is clear that these other two studies do not confirm the marginal findings of the Nissen paper.

Synthesis

In summary, it is clear that the Nissen meta-analysis was a very weak study. It has many problems, most of which were identified, described, and discussed by the authors. This is not a question of science conducted ignorantly, but conducted quickly. It is clear that the study raises an important question. However, it is exceedingly far from providing an answer to that question. Indeed, this is a question that had been raised well before this paper was published. The two other studies available so far do not support this finding, although they too are not definitive. The best way to address such a question is a large outcomes-oriented randomized clinical trial, and one is underway, i.e., RECORD. Ultimately, the hypothesis identified in the Nissen paper may indeed be proven to be correct, but it may not be.

Is there a proper long-term therapeutic role for this drug? To date, the available data regarding myocardial infarction are not substantially changed from the data available at the time of drug approval. We do not yet know the eventual answer about whether this drug should be used. A large outcomes study was needed at the time the drug was marketed. One is now underway. Premature regulatory action should not be taken in the absence of scientific knowledge. Indeed, while it is not clear whether the drug causes this side effect, it is clear that toxicity results from removing patients from drugs they are doing well on, and switching patients to new drugs. It would be most unfortunate if this overreaction also led to the compromise of the definitive study, RECORD, as then we would never have the answer.

POLICY IMPLICATIONS

Congress and the Public Need to Understand That No Drugs Are Safe

It is critically important that Congress and the public understand that no drugs are safe. This includes prescription drugs, over-the-counter drugs, and also nutritional supplements. Drugs are given to interfere with the body's systems. Thus, if they are effective, they will have side effects. In the case of prescription and over-the-counter drugs, we know that the drugs have benefits, felt by regulators to outweigh the inevitable risks. It does not mean these risks are absent. Indeed, it is ironic that we, as a society, panic over rare adverse effects from drugs known to have a beneficial effect, yet allow on the market nutritional supplements that also may have toxic effects, and have never been proven to have any beneficial effect whatsoever. It is critically important that the issues raised by Avandia be looked at in proper perspective.

Congress and the Public Need to Understand That the Discovery of a New Adverse Reaction After Marketing is Not Intrinsic Evidence of Someone's Failure

As a society, we study drugs after they are marketed in, generally, 2000 to 3000 patients. This means that adverse reactions that occur once per 100 patients will be known at the time of marketing. In contrast, adverse reactions that occur once per 1000 patients, or less commonly, will not be known as of the time of marketing. This is an intrinsic part of our drug approval process. The discovery of a rare adverse event after a drug is marketed does not mean that somebody necessarily failed in their job. To the contrary: someone succeeded, as the adverse event was detected. I worry more about all the safety problems we do not detect. To be more certain of drug safety at the time of marketing would not mean extending studies to 4000 or 5000 patients, but to 20,000 to 30,000 patients, or even 200,000 to 300,000 patients. These numbers simply are not attainable prior to marketing. Further, even if they were, such a requirement would dramatically delay access to good drugs to many patients who need them. It does mean, however, that considerable information will continue to emerge after a drug is marketed, and it behooves us to expedite this when is the drug is marketed.

The Risk/Benefit Balance of a Drug Continues to Evolve After Marketing

It also means that when the drug is first marketed, physicians, patients, and society need to take into account in making a risk/benefit judgment, the substantial probability of as yet unknown adverse reactions. To me, this argues to limit the marketing of a drug in its first years on the market

to those patients who truly need it, and to collect as much information as possible on their experiences, so that all can learn about uncommon adverse effects as soon as possible.

There Is a Critical Need for Outcomes Studies to Be Performed After Marketing

Many drugs are approved using studies that investigate the true purpose of giving the drug, e.g., drugs given for symptom relief. Other drugs, however, are given to achieve long-term outcomes that cannot practically be investigated prior to marketing. For these, we commonly investigate surrogate outcomes, expecting that the efficacy of the drugs on the surrogate outcomes will approximate their efficacy on true outcomes. In most cases this is borne out to be true. For example, anti-hypertensive drugs were approved for marketing on the basis of their ability to lower blood pressure, and many studies have since shown the many positive effects of these drugs on cardiovascular disease, stroke, etc. As another example, statins were approved for the market on the basis of their ability to lower cholesterol, and subsequent studies have clearly shown the long-term improvement of cardiovascular outcomes associated with their use. This is not always guaranteed, however. It is critically important that drugs approved on the basis of surrogate outcomes be accompanied by large-scale outcome studies conducted as soon as possible at the time of marketing so that this assumption can be tested.

There Is a Critical Need for Comparative Effectiveness Studies to Be Performed After Marketing

By law, drugs are approved on the basis of their safety and efficacy, i.e., do they work for a given indication and is their risk worth this benefit? This requires, with rare exceptions, studies comparing drugs to placebo, rather than studies comparing drugs to each other. Indeed, for good scientific reasons, this is generally a preferable approach, since it is then in the sponsor's interest to perform the best study possible to identify a difference from placebo, as opposed to conducting a sloppy study that will fail to identify a difference from an active drug. This approach is also often logical, since patients who respond to one drug in a class do not necessarily respond to other drugs in the class. Thus, some choice is of use. Nevertheless, it is a critical clinical question to identify the relative safety and efficacy of a drug, in comparison to others available for the same indication. This remains to be performed after marketing and, indeed, is rarely forthcoming.

There Is a Critical Need for Observational Studies to Be Performed After Marketing

In addition to the host of safety questions that often remain, and later emerge, at the time of drug marketing, pre-marketing trials are generally conducted in a select, artificial population, i.e., patients willing to be enrolled in clinical trials. It is critically important to find out what the true effects of a drug are when used in the general population, without the artificial protections and selections inherent in a clinical trial. This, along with the inevitable safety questions that emerge, demand use of epidemiologic, non-experimental study designs after drugs are marketed.

FDA's Credibility Is Critical to Protecting the Public's Health

If there is a plane crash and a small number of people die, we mobilize an expert organization to evaluate why this occurred, trust the results we obtain, and learn from the experience in order to prevent the next plane crash. In many ways, the FDA serves that role for society. Indeed, it receives hundreds of signals of possible adverse reactions each year, similar to

those that emerged from the Nissen paper. Its job is to evaluate those signals, decide whether more information is needed, and decide whether regulatory action is to be taken. When such a question is asked publicly, the public must be able to turn to the FDA to provide an answer. Poorly placed panic and accusations that hurt the FDA's credibility do not help the public's health, but rather harm it.

It Is Imperative That FDA Be Markedly Strengthened and Resourced to Address Such Issues Properly

The US drug safety system is indeed flawed, and should be changed (7). The problem, however, is not the actions of individuals or the FDA, but Congress. Congress has not seen fit to create a system that is rational. Right now, we have crying needs for studies conducted after drug marketing. Yet, the FDA does not have the regulatory authority to require such data, does not have enforcement authority if the data are not provided, and our pharmaceutical manufacturers are given no incentive whatsoever to provide it; quite the contrary. It seems hypocritical for Congress to criticize the FDA when it is doing the best it can with the limited authority and resources it was provided by Congress. I have previously published in the *Journal of the American Medical Association* a proposal for a drug safety system that makes more sense (7), and I will briefly summarize it here.

Conditional approval. First, when a drug is initially approved, it should enter a period of conditional approval. During this time, marketing, especially direct-to-consumer marketing, should be restricted. Conditional approval would be removed only when sufficient numbers of individuals have been investigated to ensure the detection of rare side effects and to answer all drug safety questions that emerged pre-marketing or thereafter. This way, drug use immediately after marketing would be restricted to those who truly need the drug, in whom the risk/benefit balance in the face of uncertainty is more favorable. In addition, sponsors would have an incentive to gather safety information quickly, instead of delaying such efforts.

Empowered FDA. Second, we need an empowered Food and Drug Administration. The FDA needs an increased ability to regulate drugs after marketing so that it can, for example, require post-marketing studies and labeling changes, rather than these studies and labeling changes being subject to negotiation. The FDA also needs markedly increased resources to conduct and fund more post-marketing safety studies. The Institute of Medicine's report on drug safety estimates that 10 safety signals per year could be evaluated extramurally at an annual cost of between $10 million and $60 million (8). Perhaps we need an additional $50 million, or maybe an additional $150 million, depending on how much safety the public seeks. However, these sums are trivial in comparison to the $188.5 billion that was spent on prescription drugs in the United States in 2004 and the $11.9 billion on pharmaceutical advertising in the same year (9). In contrast, the FDA's current extramural epidemiology contracts program has a budget of less than $1 million per year, to investigate <u>all</u> drugs (9). This is preposterous.

A complementary nongovernmental organization or organizations. Third, I would propose the need for a complementary nongovernmental organization or organizations for performing non-regulatory tasks that are not now, nor should be, the mission of the Food and Drug Administration. Among such tasks are attempts to change prescribers' use of drugs, including old drugs; performing post-mortem examinations in the event of drug "disasters"; developing new methods for doing such studies better; training new scientists in this field; and other such non-regulatory tasks. This body

should probably be a nongovernmental organization since many of these tasks are academic in nature. This is a possible role for the Centers for Education and Research in Therapeutics (10), the Institute of Medicine, or other existing or future organizations.

CLOSING

In closing, I am once again grateful to the Committee for being willing to hear my proposals. In my view, an exaggerated response to the recent Nissen paper is misguided. Ultimately, this study may be proven to be correct, but it may not be. This is simply a signal, and only better science will determine whether the signal is real. The FDA gets perhaps hundreds of these signals per year, and it is its job to sort through them and determine when the signal is real. To date, at least, the two available studies, flawed but probably better, do not confirm this finding.

However, this whole episode does have important policy implications. It is critically important that Congress and the public have a better perspective on the true nature of risks from pharmaceutical products. Drugs are not without risk, and the risk/benefit balance of a drug changes during its lifecycle. Thus, there is an enormous need for additional information to be obtained about the effects of a drug after drugs are marketed. We need to create a system that provides pharmaceutical manufacturers with incentives to provide this information, rather than disincentives. Only in this way will the information be obtained more quickly. Further, we need to dramatically empower and markedly increase the resources of the Food and Drug Administration, rather than ridicule and criticize the FDA. The public needs to be able to rely on the FDA as a neutral, scientific, credible source of information and unbiased judgment when these questions arise, as they will do with increased frequency. Only in this way will the pharmaceutical manufacturers be forced to provide the information that must be provided to the public.

I call on Congress to make use of the opportunity of this public misunderstanding to make significant changes in the FDA, strengthening it in the process.

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Mr. DAVIS OF VIRGINIA. Thank you.

[The prepared statement of Hon. Tom Davis follows:]

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Statement of Rep. Tom Davis
Ranking Republican Member
Committee on Oversight and Government Reform
"FDA's Role in the Evaluation of Avandia's Safety"
June 6, 2007

Good Morning. Once again, this Committee meets to consider serious questions about how the Food and Drug Administration and drug makers monitor the long-term safety of approved pharmaceutical products. In 2004 and 2005, Republicans led an extensive, bipartisan investigation into the pain reliever Vioxx, confronting many of the same questions we face today: How effective are programs by the FDA and industry to gather timely and useful data on lingering safety concerns about approved products? When those safety concerns emerge, how should preliminary, often anecdotal, information be used by regulators, clinicians and patients? And, how do we strike the correct balance between speedy approval of life-saving or life-enhancing therapies that patients want and the much slower process of amassing statistically valid data sets on long-term health outcomes?

Today's hearing was prompted by recent warnings the diabetes medication, Avandia, manufactured by GlaxoSmithKline, may increase the risk of cardio-vascular disease in some patients – patients already uniquely vulnerable to heart problems. An admittedly limited "meta-analysis" of disparate research findings suggests that increase may be substantial. Other studies point to little if any measurable increase in heart risk. So patients and their doctors are left with conflicting or incomplete information upon which to base delicate judgments about the net benefits of various treatment options.

But this hearing is not about one *product*. At least it shouldn't be. It's about the effectiveness of the overall drug approval and monitoring *process*. As the Chairman's memo to Members cautioned, "this hearing is *not* about whether Avandia makes patients healthier or harms them." We are not here to substitute our judgment for that of scientists and regulators still evaluating clinical safety data. But we are here to ask whether current post-marketing surveillance programs and protocols are both robust and sensitive enough to detect emerging evidence of deleterious health effects, and how that evidence informs regulatory, research and treatment decisions.

Taken by almost one million Americans today, Avandia was approved in 1999 because it lowers harmful blood sugar levels in patients suffering type-2 diabetes. Managing type-2 diabetes by lowering blood sugar can decrease the patient's chance of having diabetes-related problems later in life, such as kidney failure, heart disease, stroke, and limb amputation. But the so-called "surrogate endpoint" of reduced blood glucose is only an indirect measure of the drug's overall impact on health. And questions about the extent of any increased cardio-vascular risk posed by Avandia were raised eight years ago. So the FDA required Glaxo to compare the safety and effectiveness of Avandia with other oral anti-diabetes medicines. In 2000, the company initiated another large long-term clinical trial to look specifically at cardiovascular outcomes in people with diabetes using Avandia to manage the disease.

So far, results from that study have not shown increased health risks, at levels suggested by the meta-analysis, that would require discontinuation of the research for safety reasons. Nevertheless, last year, based on data from a study involving patients with existing congestive heart failure, the FDA required a labeling change for the drug to include a new warning about a potential increase in heart attacks and heart-related chest pain in some individuals. The FDA will convene an advisory committee as early as next month to review this matter. That committee's findings should provide healthcare providers and patients with a better understanding of any cardiovascular risks involved with the use of Avandia. It is not yet clear if the advisory committee will also look at the entire class of oral anti-diabetes medications that operate like Avandia. Perhaps FDA can answer that question today.

This muddled post-marketing picture is not unique. A recent *New England Journal of Medicine* editorial called the FDA approach to post-approval, or phase 4, research "desultory" because "[d]uring the period from 1998 through 2003, only about a quarter of the required phase 4 trials were completed, and as of September 30, 2006, a total of 899 phase 4 studies remain pending." As a result, the safety profile of some drugs, particularly those approved using surrogate endpoints, can remain incomplete for years.

Most Americans believe once the FDA approves a drug, it carries the medical equivalent of the Good Housekeeping Seal of Approval, and can be used with little or no risk. But the process of developing, marketing, regulating, prescribing and using modern pharmaceuticals involves some, at times considerable, risk at every stage. Those risks have to be acknowledged frankly and managed responsibly. Adverse event surveillance and research have to be sensitive enough to detect potential safety problems, but discrete enough to distinguish between well-publicized anecdotes and scientific evidence. Otherwise, public confidence in both the FDA and the pharmaceutical industry will be undermined by conflicting data and allegations no one is protecting the long-term welfare of patients.

I look forward to hearing from our panels of expert witnesses today on how we can strengthen FDA drug approval and post-marketing surveillance systems.

Chairman WAXMAN. We have a number of witnesses to present testimony to us today. So we did not invite Members to give opening statements. Of course, all of the Members' opening statements that they wish to submit will be made part of the record.

But we do have a request from Congressman Towns and I do want to recognize him. In doing so, I will invite any other Member who wants to make a very brief statement to do so. But do recognize the fact that we will keep it brief, and you may submit a fuller statement for the record.

Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman. I thank you for calling this hearing on patient safety.

As you know, diabetes and heart disease occur in the African American population at a rate disproportionate to the general population. That is also true of Hispanic Americans. Death rates for strokes are about 25 percent higher for African American males and about 20 percent higher for African American women. African Americans develop high blood pressure at an early age, and heart disease death rates are 1.5 times higher and 1.8 times greater for fatal strokes.

Yet, despite the disproportionately higher mortality and morbidity of cardiovascular disease, Latinos and African Americans are significantly less likely than Whites to undergo treatment for their conditions, and less likely to receive the most advanced cardiac procedures. Despite having the same insurance status and disease severity rates, diabetes rates are also significantly higher for African Americans and Hispanic Americans. These are also not one at a time conditions. If you have one, there is a greater likelihood that you may have them together.

The published higher death rates from the May 16th New England Journal of Medicine study is of course what brings us here today. However, Mr. Chairman, while I am certainly concerned about the possibility or the potential higher level of risk for cardiovascular causes that has been associated in this single study of Avandia, I am more concerned with the likelihood of the low levels of participation of African Americans and other people of color in the clinical trials associated with Avandia.

I am certainly aware of the large number of clinical trials associated with it. However, I am particularly concerned that the findings have not had sufficient data to make a determination as to the effects of this drug on African Americans and Hispanics, whether they associate Avandia with the higher levels of risk for death from cardiovascular causes or not.

While we are not here today, Mr. Chairman, to discuss the reauthorization of the Prescription Drug User Fee Act, a number of us serve on the Committee on Oversight and the Committee on Energy and Commerce, as you and I do. I am here today to make sure that both the Food and Drug Administration and the pharmaceutical and medical devices industry takes the expansion of the numbers of African Americans and Hispanic Americans in drug and medical devices studies seriously.

I am therefore proposing in the PDUFA reauthorization a more verifiable alternative for minorities than the pediatric exclusion and an office of diverse population within the Office of the FDA

Commissioner that will have the authority and responsibility of increasing the numbers of racially and ethnically diverse populations within the FDA.

Mr. Chairman, I believe that we need to get to the bottom of whether or not there is associated risk with Avandia. However, that risk should have scientific evidence that applies to ethnically and racially diverse communities, as well as the general population.

And on that note, I yield back, Mr. Chairman, and thank you for the special consideration.

Chairman WAXMAN. Thank you, Mr. Towns.

Does any other Member wish to make an opening statement? Mr. Issa.

Mr. ISSA. Thank you, Mr. Chairman. I will be brief.

But I think it is important, first of all, I would like to thank you for your opening statement. I think it helped balance perhaps what started off very much as imbalance in this hearing. I am concerned today that we not tread too closely toward the hypocrisy that I believe this hearing begins to look like.

Just a few months ago, this committee held a hearing in which the Bush administration was accused of politicizing science, of censoring and editing research and politicizing science is exactly what we could be doing here today. This is not global warming, this is in fact, though, an ongoing investigation on a current drug early in the questioning period. I believe that the anecdotal evidence that came out from the New England Journal of Medicine, which we now understand included some consulting to the majority members of this committee, is in fact a very dangerous pattern.

A few weeks ago, the New England Journal of Medicine questioned something. We now hold a hearing on that drug and consistent with that drug. As the chairman said, rightfully, and I appreciate his saying it, none of us here is qualified to evaluate this drug. As a matter of fact, none of the people speaking before us today, without a vast group of people not present, is capable of evaluating the safety and side effects of this drug. It is in fact the FDA and science's community responsibility to get all the research in, and in fact then to go through that as a panel, not as one individual speaking before this committee.

I appreciate that this is the Committee on Oversight and Government Reform. If we are doing oversight, I believe that it is OK to look at something if it is a clear and present danger. That is not the case here. This drug is very much still effective and on the market for patients today and should not be artificially called into question as to its safety or side effects as a result of anecdotal information presented here.

Vioxx, Celebrex and other drugs certainly have gone through a much more exhaustive study and could be just as easily used to show the need for reform and in fact, as an oversight agency, to look at past failures. I believe that we are treading very close to exactly the hypocrisy that this committee can easily be drawn into, politicizing science while saying that we don't want to politicize science. So I appreciate the chairman's opening remarks. Hopefully that has set a tenor for not only what is being said by the witnesses today, but in fact for our questions, that we not allow this

to be about one drug or one limited study, and that we try to stay toward the settled science, toward the settled cases of the FDA in our oversight and potential reforms.

I thank the chairman for his opening statement, because hopefully it brought us a little closer—and the ranking member—a little closer toward the correct reason for this committee to hold these types of hearings. I yield back and thank the chairman.

Chairman WAXMAN. Mr. Issa, I am pleased you attacked the hypocrisy that you admitted did not exist. I don't know if the New England Journal of Medicine would resent being categorized as a magazine that simply puts together a bunch of anecdotes, but I certainly resent the statement that there was any kind of consultation between the people that wrote the article in the New England Journal of Medicine and the majority of this committee. It is just absolutely not true.

Mr. ISSA. Mr. Chairman, the author of the study published in the New England Journal of Medicine admitted to the Wall Street Journal that he had talked to people on the Hill while preparing his analysis. Yet the FDA says that no one has consulted them. So in fact, I believe that this is dangerously close to that question of politicizing science. And like I say, I appreciate the fact that your opening statement was balanced. But we have to look at the underlying premise of bringing a hearing on a drug 3 weeks after an article comes out and the author of that article admits that he's been talking to people on the Hill.

This is one of those times in which I want to make sure that this is not an attack on the practice of a particular company, or a chilling effect on companies, but rather, legitimate oversight and legitimate effort to find reform. I appreciate the chairman's effort to try to lead at that direction. I wanted to make sure that I supported him in pushing this hearing in that correct direction.

Chairman WAXMAN. I thank you for your explanation of your conclusion. And it will stand for all to review. And I appreciate your statements.

Any other Member wish to make an opening statement? Yes, Mr. Davis.

Mr. DAVIS OF ILLINOIS. Thank you, Mr. Chairman. I do not have a written statement, but I do want to, as a member of the committee, thank you for calling the hearing. And also as a person who has been diagnosed as a type 2 diabetic, I want to emphasize the particular personal interest that I have in this hearing. I agree with the conclusion in your opening statement that I hope that we will move toward, and we do in fact need a stronger and more resourceful Food and Drug Administration, so that they have not only the authority but also the resources that are needed to do extensive research and oversight to try and assure that the pharmaceutical drugs that we use for medical treatment are as safe as humanly possible.

So again, I thank you for calling the hearing and look forward to hearing the witnesses.

Chairman WAXMAN. Thank you very much, Mr. Davis.

Any other Member wish to make a very brief statement? Ms. Foxx.

Ms. FOXX. Thank you, Mr. Chairman. I appreciate it very much.

My background is as a social scientist. I worked for many years in medical research. So in reading the material about today's hearing, I tried to bring back some of my experiences of some time ago. And I wanted to get a definition of the term "meta-analysis." I think that it is really important that in this hearing we keep in mind what a meta-analysis is.

The purpose of it is to raise questions but not to draw a conclusion. Let me read you a definition from Taber's Cyclopedic Medical Dictionary. It says, "Meta-analysis, a statistical procedure for combining data from a number of studies and investigations in order to analyze the therapeutic effectiveness of specific treatments"—and this is the really important part—"and plan future studies."

The meta-analysis does not actually do research. It does not gather the data that is so important to gather when drug companies are searching for the effectiveness of the drugs they're working with. So I think it's extremely important that we keep in mind what a meta-analysis is.

Now, Mr. Chairman, on May 21st, Dr. Nissen's study was published by the New England Journal of Medicine, along with a Journal editorial encouraging physicians to stop prescribing the drug and encouraging the FDA to take regulatory action. Then there were alarming headlines pronouncing an increased risk of death for anyone taking this drug.

According to a very interesting article entitled Political Defibrillator, published in the May 28, 2007 issue of Biocentury, a journal providing analysis for the biotechnical community, soon after the release of Dr. Nissen's study, some of my congressional colleagues in the House and Senate issued statements to the press suggesting that they knew ahead of time about this study. Included among the press releases, there was an apparent attempt to manufacture a scandal, including the statement that "Both the drug company and the FDA have some major explaining to do about what they knew about Avandia, when they knew it and why they didn't take immediate action to protect patients." These statements were made with disregard for the limits of this study and the impact that these statements and actions could have on public safety or the reputation of the company involved.

Let me read the opening paragraph of the Biocentury piece: "The circumstances surrounding the publication by the New England Journal of Medicine of a meta-analysis of safety data from studies of Avandia and an accompanying commentary suggesting that FDA critics on Capitol Hill have collaborated with whistleblowers in the agency and pharmaceutical industry critics and academia to create a controversy over Avandia's safety in order to advance a political agenda." According to this article, even though Members of the Senate and House and their staffs were apparently aware of this study and that it was going to be published, the author never notified the FDA. Yet the FDA is the one agency that holds the key to action if this study in fact reveals data about an immediate threat to the public.

The British medical journal, the Lancet, published May 23, 2007, took issue with how this was handled, stating that "To avoid unnecessary panic among patients, a calmer and more considered ap-

proach to the safety of rosiglitazone is needed. Alarmist headlines and confident declarations help nobody."

Mr. Chairman, while there is no need to manufacture a scandal here, it appears that there may already be one that needs investigating, at least by the press. I would like to see the press determine what Members of Congress and their staff knew about this study, when they knew it and whether there was a coordinated effort among the author, disgruntled FDA staff and staff at the New England Journal of Medicine to develop and publish this study in a way that would create a sensation in the press and maximum embarrassment for the FDA.

My husband is diabetic. So I am very interested in this disease and very interested in our finding treatments for it. It is a very pernicious disease and one of the most expensive in our country.

However, we serve no purpose by scaring people about drugs. And I have no dog in this fight, as they say. I am not here as an apologist for Glaxo, but I think we should be very careful when we talk about scientific issues and make sure that we have a balanced approach to this. Thank you, Mr. Chairman.

Chairman WAXMAN. The gentlelady's time has concluded.

I would like to get to the witnesses. Does any Member feel compelled to say anything further? Yes, the gentleman from Massachusetts.

Mr. LYNCH. Thank you, Mr. Chairman, and I will be brief.

I just wanted to address a couple of things. First of all, there has been the allegation that this study was anecdotal. I just want to point to the editorial itself and the reports and the concerns that have been cited by the doctors. They were based on 40 different studies, and I think they are very thoughtful.

Second, I agree with the sentiment, although I am not sure it is shared, that this shouldn't be dragged down into some type of partisan politics issue. However, I think when you begin the hearing by criticizing the New England Journal of Medicine because of something that has been published there, which is, I think, a very thoughtful view, it is just one view, but very thoughtful, but to impugn their character that it is somehow in league politically to take down a drug company, I think you immediately drag down the debate to that level. I would just caution against it.

The second comment I want to address is the idea that somehow folks that come to the Oversight Committee because of an issue of genuine concern have done so for political purposes and not for legitimate reasons has not been proven here, and should not be suggested. This is where people should come. It should not be circumstantial evidence to the disingenuousness of people who come to this committee that they have come to us with an issue. This is the Oversight Committee. This is where they should be coming. And we should have the intelligence and the balance here to just let the evidence be presented and not suggest that it is being done for a disingenuous reason and then have it presented in that context.

This is a tremendously important issue. My family has diabetes, I know thousands and thousands of families that are dealing with this problem. We should approach this as adults. And at the end of the day, it may prove that the concern was elevated. It may

prove that the concern was understated, but we should receive the evidence in an open and honest discussion. That is the way we should have it, and I yield back.

Chairman WAXMAN. The gentleman's time has expired. We will now go to our witnesses.

Mr. SALI. Mr. Chairman, may I make a brief statement?

Chairman WAXMAN. The gentleman is recognized for a brief statement.

Mr. SALI. Mr. Chairman, it appears to me, in hearing the opening statements and kind of thinking through this, that the real concern is that there may be a side effect from this drug. And we don't know if that side effect is present based on this meta-study, that it may be a side effect.

I also understand that, according to the FDA, no approved diabetes drug has ever shown any kind of reduction in macrovascular risk, the kinds of risk that may exist here today. So I guess in the testimony, I am hoping that it becomes clear, No. 1, whether we can really say that the side effect does exist from this drug, and if it doesn't, then I think our job of oversight may be done at that point.

Second, even if it does exist, does it exist in such a significant number of cases that we know about that we can say the FDA is off track and this committee, with its oversight capability, should intervene?

Finally, Mr. Chairman, I think the question is, knowing that there is a side effect, is it appropriate for doctors to prescribe it anyway? There are plenty of drugs that have known side effects. If patients are better off if this drug is prescribed, perhaps it will change prescribing patterns for physicians that are involved. But if there is a known side effect, if everybody takes that into account in making the decision whether to take the drug, prescribe the drug, are the people better off who can take this drug by prescription? And if they are, again, this committee has no business in providing oversight.

[The prepared statement of Hon. Bill Sali follows:]

Statement of Mr. Sali of Idaho
House Committee on Oversight and Government Reform
Full Committee Hearing on "FDA's Role in the Evaluation of Avandia's Safety."
June 6, 2007

MR. CHAIRMAN, the issue before this Committee today demands a delicate balance – that balance between making important quality-of-life improving, and even life- saving medication available to millions of Americans, on the one hand and, on the other, ensuring that the approved prescription drugs have been vetted adequately for effectiveness and safety. That balance is one that admittedly is difficult, and ongoing oversight by Congress is an important part of ensuring that the FDA is carrying out its statutory obligations.

Mr. Chairman, I am troubled, however, by today's hearing. While reaction to Dr. Nissen's meta-analysis published May 21, 2007 is probative, today's hearing seems a rather excessive overreaction to it. On the date the meta-study was published, this Committee sent out invitations to many of the witnesses here today, requesting testimony focused on Dr. Nissen's study. The timing invites a certain curiosity.

Dr. Nissen's study, by its own admission, is inconclusive, raising questions regarding cardiovascular risks associated with Avandia. Dr. Nissen's study is not a study that in and of itself reaches a conclusion on the safety of Avandia. In fact, since Avandia was approved, various safety measures have been in place. Throughout the post-approval testing of the drug, an independent data safety monitoring board has been overseeing the studies, and has, based on the data accumulated throughout the study, continued to allow the study to go

forward. As yet another example of the post-approval involvement, the FDA issued a cautionary advisory warning of potential safety issues on the day Dr. Nissan's study was released.

As I have stated, Mr. Chairman, I believe that appropriate testing for prescription drugs is essential. But I am concerned with the haste with which this particular hearing has been convened.

More than 20 million people in the United States have diabetes, with 1.3 million new cases of diabetes diagnosed each year. For those millions of Americans who have diabetes, drugs in the same class with Avandia can mean an improvement in the quality of their lives not otherwise available.

While approval of prescription drugs should only be given when appropriate, in order to completely assess the long term affects of any drug, testing would literally take decades. Surrogate endpoints are used by the FDA as a basis for the approval of drugs in order to allow drugs to be available to patients sooner. The shorter time in the approval process allows patience access to life changing, and even life saving drugs in a timely manner.

It is also important that this Committee not engage in hasty and imprudent – and, dare I say, politically motivated - conduct, but rather approach the balance presented by this subject mater deliberately and judiciously. I look forward to hearing the testimony presented today.

Thank you Mr. Chairman, and with that I yield back.

Chairman WAXMAN. Well, perhaps we can get some answers to those questions from the scientists.

I would like to welcome our first witnesses. Dr. von Eschenbach is the current Commissioner of the Food and Drug Administration. He is the former head of the National Cancer Institute and is a renowned cancer specialist. We are delighted to have you here to testify.

Accompanying Dr. von Eschenbach is Dr. Dal Pan, who is the head of the Office and Surveillance and Epidemiology at the Food and Drug Administration. And Dr. Jenkins is the head of the Office of New Drugs at FDA. We want to welcome each of you to our hearing today. We are looking forward to your views on some of these scientific and regulatory questions that Members have on their minds.

It is the practice of this committee to ask all witnesses to take an oath. I would like to ask you to rise.

[Witnesses sworn.]

Chairman WAXMAN. Thank you very much. The record will indicate that each of the witnesses answered in the affirmative. Dr. von Eschenbach, why don't we start with you?

We ordinarily ask witnesses to be limited to 5 minutes in their oral presentation. Your full statement will be part of the record. We will run the clock, if you need a little bit more time, we will certainly provide it to you.

STATEMENT OF ANDREW C. VON ESCHENBACH, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY JOHN K. JENKINS, M.D., DIRECTOR, OFFICE OF NEW DRUGS, FOOD AND DRUG ADMINISTRATION; AND GERALD DAL PAN, M.D., OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY, FOOD AND DRUG ADMINISTRATION

Dr. VON ESCHENBACH. Thank you very much, Mr. Chairman and Ranking Member Davis and members of the committee. I really want to express our appreciation for allowing us to appear before you today.

My written testimony provides important details about the scientific facts and many post-marketing trials that are involved in FDA's ongoing multi-faceted regulation of the diabetes drug rosiglitazone, perhaps better known as Avandia. Rather than recount those details, I would like to focus my oral statement on the process used at FDA to do the right thing for patients by making decisions using a comprehensive, multidisciplinary approach that incorporates all the data available and addresses the best interest of all patients affected by that decision.

With me are two senior and expert FDA colleagues: Dr. John Jenkins, the Director of the Office of New Drugs; and Dr. Gerald Dal Pan, the Director of the Office of Surveillance and Epidemiology, formerly the Office of Drug Safety. Both of these offices are part of FDA's Center for Drug Evaluation and Research. Their presence this morning is important regarding the FDA's decision-making process, because they represent the close interaction between the FDA office that reviews marketing applications for new drugs and the office that monitors their safety profile.

We are here as partners, reflecting the management and the professionals at the FDA who are dedicated to collaborating even more closely, not simply to approve products, disapprove them or defer decisions, but rather, to do the right thing, so that our actions will both promote and protect the health of Americans.

Mr. Chairman, I know that you called this hearing because of your deep concern for the welfare of Americans, a motivation that transcends politics and that is shared by every member of this committee. I know you and Members of Congress want and even demand that the FDA do its utmost to protect and promote the health of all Americans, including those millions of Americans affected by diabetes, and the hundreds of thousands that are perhaps using the drug Avandia.

Let me be clear at the outset. Our focus in the decisions FDA has made and will make on Avandia is to serve an approximate 18 to 20 million Americans who are at risk of blindness, kidney failure, limb amputation and death from diabetes. We will carry out that mission by thoughtfully weighing the potential effect of FDA's actions on the entire patient and on all patients. It is our goal to not just make the right decision about a drug like Avandia; but more importantly, to always do the right thing for patients.

How do we do the right thing? First, by doing it as a team that embraces the diversity of all points of view and weighs all points of view to arrive at an FDA decision. Second, by using decision standards that are science-based, drawing upon all the scientific data that bears on an issue and by demanding of ourselves and others rigor, precision and accuracy in the analysis of that data. Because our decision that weighs both the benefits and the risks of a drug will affect not one or a few, but often millions of lives.

Third, by committing to a standard of excellence that requires us to constantly improve the processes by which we make decisions. Since I arrived at FDA, we have specifically addressed process improvement as it relates to decisions regarding drug safety. We have completed or are rapidly putting in place more than 40 drug safety initiatives that are in keeping with the recommendations of the Institute of Medicine report that we commissioned.

A few recent examples of process improvement are the fact that we have issued a guidance on communicating drug safety information, announced the creation of a risk communications advisory committee, proposed tougher procedures for membership on FDA advisory committees, and our critical path initiative promises to provide the modern tools needed to improve the predictability of the processes by which products are discovered, developed and monitored after delivery to patients.

We have acknowledged that increasing demands and the complexity of the products we regulate requires increasing resources. We are grateful for the administration's proposals and the congressional consideration given to the additional resources in fiscal year 2007 and those being considered for 2008.

Among the many needs, we must especially use these resources to build a more robust FDA infrastructure of information technology to obtain and analyze all the data required for timely and accurate decisions. We need to focus on product safety throughout the entire life cycle of the product, including stronger post-market

surveillance and pharmaco-vigilance. In fact, a robust pharmaco-vigilance system supported through a public-private arrangement such as an institute or a foundation could provide considerable benefit and would be most welcome as part of the congressional consideration of pending FDA legislation.

In closing, Mr. Chairman, let me emphasize that as we deal with drug safety, we encourage those with an interest to bring to us comments, ideas and data from all sources. FDA is committed to appropriate scientific dialog and discussion about the making of decisions. And in the end, we must always be true to our mission to both protect and promote the health of all Americans.

Mr. Chairman and members of the committee, thank you for your time, your interest and your commitment to this mission. My colleagues and I would be pleased now to answer any questions.

[The prepared statement of Dr. von Eschenbach follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

ANDREW C. von ESCHENBACH, M.D.
COMMISSIONER OF FOOD AND DRUGS

FOOD AND DRUG ADMINISTRATION

BEFORE THE

COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM

UNITED STATES HOUSE OF REPRESENTATIVES

June 6, 2007

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Andrew von Eschenbach, M.D., Commissioner of Food and Drugs at the United States Food and Drug Administration (FDA or the Agency). We appreciate the opportunity to participate in this hearing regarding FDA's assessment of the safety of rosiglitazone maleate (marketed as Avandia, Avandamet, and Avandaryl), a drug approved to improve glycemic control in patients with type 2 diabetes.

I would like to frame my testimony this morning by placing it in the context of the very important and complex societal challenge of providing abundant and timely information to patients and health care professionals, while at the same time making regulatory decisions that affect the availability and use of life-saving or health-enhancing interventions.

I. DRUG SAFETY: A RISK-TO-BENEFIT BALANCE

FDA has a strong record on issues of safety and remains the world's gold standard for drug regulation. In reflecting on the concept of drug safety, it is important to remember that no drug is absolutely safe and to recognize that sometimes information about the safety of a drug emerge after the drug is on the market. FDA approves a drug only after a sponsor demonstrates that the drug's benefits outweigh its risks for a specific population and a specific indication, and shows that the drug meets the statutory standard for safety and effectiveness. Because of practical limitations on how many patients can be studied for any given drug, the full array of potential risks does not necessarily always emerge during the mandatory clinical

trials conducted before approval. Indeed, serious adverse effects may occasionally emerge after approval through post-marketing clinical trials or through spontaneous reporting of adverse events or both.

FDA's role as a public health agency is to protect and promote the nation's health by assuring that patients and health care providers have access to safe and effective drugs along with accurate benefit and risk information to make informed choices. The issue of how to identify and, when possible, limit adverse reactions is challenging. How to weigh the impact of reported adverse reactions against known benefits of the products for individual patients and the public health is multifaceted and complex, involving scientific as well as public policy issues. As described below, FDA has approached the issues associated with the diabetes drug, rosiglitazone, mindful of our important role as a public health agency, and the need to make the best regulatory decisions we can for health care providers and patients.

II. ROSIGLITAZONE AND THE TREATMENT OF TYPE 2 DIABETES

As a science-based regulatory agency, FDA bases its regulatory decisions on sound science. More than that, FDA's decisions must result from a comprehensive, rigorous, disciplined analysis of all the science and data that bear on the evidence. This is precisely the process that FDA followed with regard to rosiglitazone, and I would like to outline that process for you.

FDA approved Avandia in 1999 for treatment of Type 2 diabetes, a serious and life threatening disease that affects about 18 to 20 million Americans. Diabetes is a leading cause

of blindness, kidney failure, and limb amputation, and a major contributor to coronary heart disease.

Since the approval of rosiglitazone in 1999, numerous clinical studies have examined how well rosiglitazone works relative to other diabetes drugs individually and in combination. These studies, described in more detail below, have also shed new light on some of the safety concerns associated with this product. Since the drug was approved, FDA has been monitoring several heart-related adverse events (e.g., fluid retention, edema, and congestive heart failure [CHF]) based on signals seen in these controlled clinical trials and from post-marketing reports.

FDA has updated the product's labeling on several occasions to reflect these new data. In April 2006, the labeling for Avandia was updated to include new data in the WARNINGS section about a potential increase in heart attacks and heart-related chest pain in some patients. This change was based on the results of a controlled clinical trial in patients with existing CHF. In the study, diabetic patients with known, mild CHF were randomized to receive either placebo or rosiglitazone. A higher number of heart attacks or angina was observed in patients treated with rosiglitazone compared to those treated with placebo. The difference was not statistically significant, but we considered the information to be clinically important, and it was therefore included in labeling.

In August 2006, the manufacturer of Avandia, GlaxoSmithKline (GSK or the company), provided FDA with a pooled analysis (meta-analysis) of 42 separate double-blinded,

randomized, controlled clinical trials to assess the efficacy of rosiglitazone for treatment of type 2 diabetes compared to either placebo or other anti-diabetic therapies in patients with type 2 diabetes. At the same time, the company also provided a population-based database study discussed below. The pooled analysis and the population-based database study presented inconsistent data with regard to the potential cardiovascular risk of rosiglitazone. Since then, results of other long-term controlled clinical studies have been published or unpublished results have been made available to FDA. In looking at all the studies to date related to the potential contribution of rosiglitazone to increasing the risk of heart attack, the data are inconsistent and conclusions are not clear.

III. COMMUNICATING ABOUT POSSIBLE RISKS FROM MEDICAL PRODUCTS

FDA is committed to early communication of emerging information about the safety of medical products. But any communication must be responsible and measured, taking into account the impact that the message will have on patients and practitioners alike, to encourage good heath care choices, and help avoid bad ones.

The issues of whether using the diabetes drug rosiglitazone increases the risk of heart attacks, and how and what information should be communicated in the face of inconsistent evidence, illustrate the inherent tensions between early communication of emerging safety information and waiting to communicate information until after a comprehensive scientific assessment is completed and a regulatory decision is made. There are consequences in communicating safety concerns when FDA's safety assessment is still underway and before it has decided what, if any, regulatory action is appropriate. In light of a signal of concern in a diabetes

drug like rosiglitazone, patients may choose to unilaterally discontinue their treatment, despite advice from FDA and other medical experts not to do so. Discontinuation of any anti-diabetic therapy can result in loss of control of blood sugar, which carries risks of its own, including increased infections and blurred vision. Also, switching to another diabetes therapy does not necessarily ensure similar glycemic control for that individual patient. Moreover, other anti-diabetic drugs have their own specific safety concerns.

Let me describe FDA's public communication about the data submitted related to risk for heart attacks. FDA did not publicly discuss the data submitted by GSK at the time it was submitted in August 2006, because the data from the pooled analysis and the population based study were inconsistent and we began a comprehensive internal re-analysis of those data. On May 21, 2007, FDA issued a safety alert that addressed potential safety issues stemming from the pooled analysis of previously completed controlled clinical trials demonstrating a potentially significant increase in the risk of heart attack and heart-related deaths in patients taking this drug. Also, the FDA alert noted that other published and unpublished data from long-term controlled clinical trials of the drug did not show this type of risk and, in fact, provide inconsistent evidence about the risk of ischemic cardiovascular events in patients taking rosiglitazone. We urged patients to consult with their health care providers about this information as they evaluated their treatment options. Also, on May 21, 2007, another meta-analysis of rosiglitazone studies, conducted by Dr. Stephen Nissen, was published in the New England Journal of Medicine (NEJM). FDA was not aware of Dr. Nissen's study methods or findings until the date of the publication. Dr. Nissen's analysis was based on data from 42 controlled clinical trials (though this is the same number of studies as in the GSK pooled

analysis, many-- but not all-- of the studies were the same). Despite the differences in the studies, the conclusions of Dr. Nissen and GSK about the estimated risk of cardiac ischemia from their respective studies were similar.

On May 23, 2007, consistent with recommendations made by senior FDA staff at an internal regulatory briefing held in April 2007, FDA issued letters to the manufacturers of Avandia and pioglitazone, (marketed as Actos) another drug in the same therapeutic class, requesting that the product labeling include a boxed warning to more prominently address the risks of congestive heart failure associated with the use of these drugs in certain patients. Although this issue is already prominent in the WARNINGS section for both drugs, FDA decided to make this request because, despite the existing warnings, these drugs were being prescribed to patients with significant heart failure. FDA will work diligently with both companies to accomplish these revisions.

On May 29, 2007, FDA held a Stakeholder Meeting to discuss the recent safety alert for rosiglitazone. Because we wanted to make sure that the nuanced message about rosiglitazone is both clearly articulated and reaches the right audience, we invited over forty organizations representing patients, health care professionals, and government agencies to participate.

In addition, FDA maintains current information about rosiglitazone for patients and health care professionals on its website. The posted information reflects FDA's current analysis of available data concerning this drug and does not mean that FDA has concluded there is a

causal relationship between the drug product and the emerging drug safety issue, nor does it mean that FDA is advising health care professionals to discontinue prescribing the product.

IV. NEXT STEPS

Even before Dr. Nissen's meta-analysis was made public, FDA was planning to convene an Advisory Committee meeting to allow a public discussion of the available data on rosiglitazone and to seek input from our expert advisors on how to interpret the large, and often inconsistent dataset. The Agency has decided to convene the Advisory Committee in the near future because we have serious concerns that patients on Avandia and their health care providers are confused about the safety of this drug as a result of media reports surrounding the recent NEJM publication. At a public Advisory Committee meeting, experts with specialties in diabetes and heart disease will review the entire set of data that FDA has received from the sponsor. FDA will ask the Committee to make recommendations and give the Agency guidance on additional regulatory action that could be taken.

V. BACKGROUND INFORMATION AND DATA

Evaluating the benefits and risks of all drug products is a dynamic process—and FDA's ongoing evaluation of rosiglitazone is no exception. FDA has received and is continuing to receive data from several different clinical studies of rosiglitazone for treatment of type 2 diabetes. These studies vary with respect to the study design (e.g., pooled analysis, meta-

analysis, individual randomized controlled clinical trial, and observational epidemiological study), patient populations enrolled, treatment groups, and length of patient follow-up.

Among the relevant studies we are aware of are two large, long-term clinical outcome studies (RECORD and BARI-2D) that are underway and nearing completion of patient follow up. Both of these studies may yield valuable information on rosiglitazone. In addition, two completed long-term studies have recently been published, DREAM (a study conducted by academic investigators, not GSK) and ADOPT (a Post-marketing Commitment study conducted by GSK). Both of these have published results. Their data are in the process of being analyzed in detail by FDA (ADOPT) or being obtained to allow this (DREAM). We are working to analyze, as quickly as possible, valuable data from these studies in order to better understand the risks and benefits of rosiglitazone. Following are summaries of the studies and data.

A. Clinical Trial Data - Pooled Analysis of 42 Studies

As previously noted, in August 2006, GSK, the manufacturer of Avandia provided FDA with a pooled analysis (meta-analysis) of 42 separate double-blinded, randomized controlled clinical trials to assess the efficacy of rosiglitazone for treatment of type 2 diabetes compared to either placebo or other anti-diabetic therapies in patients with type 2 diabetes. The combined studies included 8,604 patients on rosiglitazone and 5,633 patients randomized to a variety of alternative therapeutic regimens, including placebo. In general, these studies had differing primary efficacy endpoints; they were not designed to thoroughly investigate cardiovascular safety. Treatment groups varied and included rosiglitazone alone or in

combination with insulin, sulfonylureas, and/or metformin. The comparator arms were varied and included placebo alone or as an add-on treatment to other anti-diabetic agents, and other active anti-diabetic treatment regimens. The combined patient population was diverse, including patients with average duration of diabetes ranging from 5 to 13 years as well as patients with significant risk factors for cardiovascular disease (e.g., history of myocardial infarction, bypass surgery, stroke, peripheral vascular disease, and New York Heart Association Class 1 and 2 heart failure). All but four studies were six months in duration or less.

In this pooled analysis as submitted by GSK, the overall incidence of myocardial ischemia in rosiglitazone-treated subjects relative to the comparators was 1.99 percent vs. 1.51 percent with a hazard ratio of 1.31 (95 percent CI 1.01-1.70). This risk equates to a more than 30 percent excess risk of myocardial ischemic events in rosiglitazone-treated patients. (This means that if this risk estimate were accurate and a patient's risk of having a heart attack in a given year were 2 percent, taking rosiglitazone would increase that risk to 2.6 percent. It does not mean that diabetics taking the drug have a 30 percent risk of having a heart attack). These data, if confirmed, would be of significant concern because patients with diabetes are already at an increased risk of heart disease. FDA scientists identified several substantial concerns with the methodology used by GSK in conducting their pooled analysis. GSK performed an analysis that pooled data on patients from 42 clinical trials of rosiglitazone administered as monotherapy and in combination with sulfonylureas, metformin and insulin and compared pooled results across these treatment groups. GSK pooled analysis assigned patients to exposure groups and in doing so did not maintain the randomized comparison of

treatment differences within each of the 42 studies and did not preserve the study identity for each patient as the unit of analysis. This approach is not the generally accepted way to meta-analyze many independent randomized studies and the consequence of their pooled approach was comparisons that are potentially biased and not interpretable. Given the potential importance of the finding of excess risk of ischemic cardiovascular events, FDA decided to undertake its own meta-analysis to more fully evaluate this safety signal and is working diligently to complete this very complex analysis in the next few weeks.

B. Balanced Cohort Study of Coronary Heart Disease Outcomes in Patients Receiving Anti-diabetic Agents

The Balanced Cohort Study is an observational study of 33,363 patients using a medical and pharmacy claims database (the population-based study noted above) that was conducted by GSK and submitted to FDA at the same time as the meta-analysis described above. Propensity matching was used to match risk factors for cardiovascular disease and other considerations for patients initiating therapy. About 90 percent of the patients had no history of cardiovascular disease. The composite cardiovascular endpoint for the study was hospitalizations for myocardial infarction and coronary revascularization. Patients included in this study began treatment with rosiglitazone between the years 2000 and 2004. The treatment groups were monotherapy with rosiglitazone, metformin, or sulfonylurea; oral dual therapy (two-drug) combinations, and combinations that also included insulin. Follow-up was 1.2 years. The incidence of the composite cardiovascular endpoint was 1.75 events per 100 patient-years for the rosiglitazone-containing regimens and 1.76 events per 100 patient-years for other treatments (hazard ratio 0.93; 95 percent CI 0.80-1.10). These findings are inconsistent with the results of GSK's meta-analysis in that they do not show an increased risk

of adverse cardiovascular outcomes in patients taking rosiglitazone compared to other therapies.

As submitted last August, then, GSK provided FDA with two studies (August 2006 meta-analysis study and Balanced Cohort Study) examining a large number of patients with divergent results. These results made it even more imperative that FDA examine all these data carefully and independently of the sponsor.

C. A Diabetes Outcomes Progression Trial (ADOPT)

ADOPT, a Phase IV Post-marketing Commitment study, is a randomized, double-blind study of 4,351 patients that compared rosiglitazone, metformin, or glyburide monotherapy on the improvement of and maintenance of glycemic control in patients newly diagnosed with type 2 diabetes. Patients with diagnosed cardiovascular disease were excluded. Median follow-up was four years. The myocardial ischemic event hazard ratios were: rosiglitazone vs. metformin- 0.96 (95 percent CI 0.66, 1.38); rosiglitazone vs. glyburide- 1.16 (95 percent CI 0.78, 1.73); and metformin vs. glyburide- 1.22 (95 percent CI 0.082, 1.80). The results of the ADOPT trial have been published (*New England Journal of Medicine* 355;23 pg 2427-2443 December 7, 2006). These data do not support an increased ischemic risk of rosiglitazone relative to metformin or glyburide. It is important to note that metformin is recommended by many treatment guidelines as the first line therapy for type 2 diabetes and has been shown in other long-term studies to lower cardiovascular risk. The final study report was submitted to FDA in February 2007 and is currently under review.

D. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) Study

The DREAM study is a placebo-controlled, randomized, double-blind clinical trial in pre-diabetic patients designed to determine if the use of early treatment with medication could forestall the development of overt type 2 diabetes. The study was conducted in nearly 5,300 patients who were randomized to either rosiglitazone or placebo and were followed up for a mean duration of three years. The study also was intended to examine whether rosiglitazone and/or ramipril delayed onset of overt type 2 diabetes. Therefore, the trial used a factorial design, with patients randomized to any of four treatment arms: placebo; rosiglitazone; ramipril; or rosiglitazone with ramipril. This study, as reported in The Lancet, showed an effect of rosiglitazone in delaying the development of type 2 diabetes (not found with ramipril) in these pre-diabetic patients. Also, the published report noted an increased risk of cardiovascular ischemic events (30 percent) in patients treated with rosiglitazone (e.g. the rosiglitazone plus placebo and rosiglitazone plus ramipril arms). This risk was not statistically significant. It should be mentioned that the overall death rate for rosiglitazone was lower than with placebo, but that too was not statistically significant.

The DREAM study was conducted by scientists from McMaster University; GSK only recently obtained the database from McMaster for further analysis. In a recent meeting with FDA, GSK shared an analysis of the data broken out by the four individual arms of the study, data that were not reported in the published manuscript. These data showed that for rosiglitazone alone versus placebo there was no increased risk of myocardial infarction, stroke, or cardiovascular death. FDA has not yet received the DREAM study data so we

cannot independently evaluate these data at this time. FDA expects that GSK will submit the DREAM study data to FDA for more complete review in the near future.

E. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) Study

The RECORD study is a large, ongoing, randomized, open-label trial evaluating cardiovascular outcomes in patients treated with rosiglitazone as add-on therapy to either metformin or sulfonylurea in comparison to add-on therapy with metformin and a sulfonylurea (patients already receiving metformin were randomized to receive add-on rosiglitazone or sulfonylurea and patients already receiving sulfonylurea were randomized to receive add-on rosiglitazone or metformin). The RECORD study is being conducted by GSK as a post-marketing commitment to the European Medicines Evaluation Agency. RECORD was designed as a non-inferiority safety study of rosiglitazone vs. combined controls with a primary endpoint of cardiovascular death and hospitalization (including congestive heart failure). Although the study is not blinded (patients and doctors know which medicine the patients are randomized to take) unlike other studies of rosiglitazone, RECORD's cardiac events are being adjudicated in a blinded fashion to treatment assignment by a Cardiovascular Endpoints Committee.

Over 300 study centers in 25 countries in Europe are involved in the conduct of this study with each center attempting to enroll 10 to 20 patients. This non-IND study (done outside the United States and without input to the protocol or study design by FDA) started in 2001 and completed enrollment in 2003, with over 4400 patients enrolled and proposed to be followed

for 5 years. The study is still ongoing with the last patient expected to reach the targeted duration of follow-up in late 2008. The study has regularly been monitored by a data monitoring committee aware of the apparent elevation in cardiovascular ischemic risk indicated by the pooled analysis, but the Committee has not called for the study to be stopped. Further, FDA has been allowed to see the results of a recent interim safety analysis and these interim data will be taken into account in FDA's considerations and actions. However, to preserve the study integrity, FDA is not explicitly commenting on these analyses.

F. Bypass Angioplasty Revascularization Investigation in Type 2 Diabetics (BARI 2D)

BARI 2D trial is a multi-center study being conducted by the National Institutes for Health that uses a 2x2 factorial design, with 2800 patients being assigned at random to initial elective coronary artery revascularization with aggressive medical therapy or aggressive medical therapy alone, and simultaneously being assigned at random to an insulin provided or insulin sensitizing strategy of glycemic control. This latter group includes a large number of patients on rosiglitazone. FDA has not been involved actively in this study, but we do know the investigators are aware of the GSK pooled analysis and that the study has not been stopped in any interim analysis by the data monitoring committee.

G. Most Recent Meta-Analysis

As noted above, on May 21, 2007, the NEJM published another meta-analysis of rosiglitazone studies. This makes, to date, a total of three pooled or meta-analyses of rosiglitazone and the risk of ischemic cardiovascular outcomes: the one conducted by GSK, FDA's ongoing re-analysis of GSK's data, and the newly published study by

Dr. Stephen Nissen. Dr. Nissen's analysis was based on data from 42 controlled clinical trials (though this is the same number of studies as in the GSK meta-analysis many but not all, of the studies were the same). Despite their differences, conclusions of Nissen and GSK about the estimated risk of cardiac ischemia from the respective studies were similar.

Even though the GSK and Nissen analyses had similar conclusions, FDA's continuing re-analysis of GSK's data is important. The Nissen analysis was based on study-level data, while FDA's re-analysis of the GSK data is based on more detailed patient-level data. Patient-level data provide the opportunity to look more closely at how studies were conducted and better assess which diabetes patients may be at particular risk of any adverse event associated with rosiglitazone. Such data will far better inform health care providers and patients in selecting appropriate therapies. Also, it will allow for a more careful interpretation of the meta-analysis findings in light of data from the other large, individual trials (described above) whose data are emerging.

In light of the recent public attention to NEJM's publication, many have raised questions about the role of meta-analyses in FDA's regulatory decision-making. A meta-analysis is the process or technique of synthesizing research results by using various statistical methods to retrieve, select, and combine results from previous separate but related studies which on their own are not large enough to examine a particular question. Meta-analyses are often informative, but have important limitations. They are complicated to conduct. Deciding the best methods of combining data, which studies to combine, and similar decisions can be

controversial. FDA has historically been cautious in the use of meta-analyses in support of regulatory decisions.

We at FDA are committed to examining all data available in answering the challenging scientific and clinical questions before us about rosiglitazone. We are continuing our own meta-analysis using rigorous statistical procedures. We will evaluate the results of that analysis along with the data from other sources, including the long-term controlled clinical trials described above and the large observational study, before reaching a conclusion about the potential for an increased risk for ischemic cardiovascular events in patients treated with rosiglitazone.

CONCLUSION

FDA's mission is to promote and protect the public health. A major component of that mission is to ensure that the American public has access to safe and effective medical products. We base decisions to approve a drug or to keep it on the market if new safety findings surface, on a careful balancing of risk and benefit, as well as consideration of the tools we have to help minimize the risks to patients from a drug's use. This multifaceted and complex decision process involves weighing both scientific and public health issues. We will continue to work diligently to assess all available data on rosiglitazone. As always, we value input from Congress, the public, and the medical community as we develop and refine these drug safety initiatives.

As I have emphasized in this statement, FDA remains committed to the thorough, timely assessment of the information needed to reach conclusions about both the benefits and risks of rosiglitazone and other drugs for diabetic patients. As a public health agency, we must evaluate the safety of medical products on the basis of how they affect the entire patient. We do not have the luxury of focusing on one organ or on one organ system.

Mr. Chairman, in this case, we wanted people not only to be aware of the potential risk, but also to understand that the evidence – not only according to FDA's best judgment but in the view of other experts as well – remains inconclusive. That means FDA is not at present justified in taking additional regulatory action or recommending that patients stop using it. We wanted patients to be aware of this developing situation and to consult with their physicians if they had concerns. It would be counterproductive indeed if patients stopped taking rosiglitazone to avoid a small and potential increased heart risk, only to incur a much greater risk from their underlying diabetes. We will, of course, revisit this position as additional data become available and are analyzed.

Thank you for the opportunity to testify before the Committee today. I am happy to respond to questions.

Chairman WAXMAN. Thank you very much, Dr. von Eschenbach.

We are going to start with 10 minutes on each side. I want to thank you very much for your testimony. You are very distinguished scientists and I know that you have a job at FDA that you are trying to see through and relying on good science and recognizing the public interest. Of course, I have been a strong supporter of the FDA, because I think the American public expects the FDA to make sure that drugs that are available to them are safe and effective, not just at the time they are approved, but throughout the time the drug is available and going to be used. And that information is to be based on science, not rumors, not anecdotes, not demagoguery, but science.

The issue with Avandia, like so many other drugs, it was approved without the full knowledge of all the impacts it might have. This is not unusual, because many drugs need to be watched carefully after they are approved. But there has been a pressure at FDA to get drugs approved as quickly as possible. In fact, we even have user fees that can help FDA have more resources to get those drugs approved.

The question that I am looking at is the post-marketing surveillance of this drug as it reflects post-marketing surveillance of other drugs. This particular drug was approved in 1999. And your reviewer at the FDA did, as I mentioned in my opening statement, exactly what he should do. He looked at the effectiveness, whether it lowers blood sugar, and he found that there was enough clinical evidence to show that it did.

But he was concerned about the possibility of increased heart attacks, strokes, because of some evidence that he saw in the data, and suggested that there be a post-marketing surveillance of that issue. So in 1999, we had this opportunity for FDA to make sure that the post-marketing study was being done.

But it wasn't done. And then later, in 2000 and 2003, you mention in your statement, you welcome the input from those who have concerns, well, FDA got input from people who had concerns. Dr. Buse wrote to FDA to express his concern about Avandia's potential cardiovascular risks. And he urged the FDA to conduct a cardiovascular safety trial on high risk populations. It is still not being done.

In February 2003, the World Health Organization issued a warning of potential cardiac risks associated with Avandia's class of drugs. And this was another opportunity for FDA to insist that a post-market study be done by the manufacturer on this potential danger, and nothing was done. Not until we got this report in the New England Journal of Medicine has there been this great concern expressed in the public, which I must state to you, I had nothing to do with, nor did any member of my staff have anything to do with, nor would the distinguished journal welcome us to get involved in their scientific evaluations.

So there are a number of missed opportunities. What happened? Wy didn't FDA insist on the post-marketing surveillance to look at the risk for heart attacks and strokes?

Dr. VON ESCHENBACH. Thank you, Mr. Chairman. First of all, I would like to echo your important emphasis on the fact that we are in fact looking at these issues from the point of view of the total

life cycle of product. We are building in much more opportunity to assure the safety of these drugs, even before they are allowed to be applied to patients in the general population.

We are doing that in the most efficient and effective way we can, so that it is more rapid, so that we can get these life-saving and life-enhancing drugs to people. But that rapidity does not mean it is reckless. We are applying the rigor and precision and discipline in the internal processes, and also recognizing, as you pointed out, that once that drug goes out into a much larger population, no clinical study or trial could ever give us all the information we need. So we are engaged in rigorous post-market surveillance.

With regard to this drug, there were post-marketing studies being conducted. FDA continued to be engaged in acquiring, analyzing and assessing data coming in with regard to the experience that was being developed with Avandia and these large populations, both here and in Europe, and did in fact take regulatory action. I would like to ask Dr. Jenkins——

Chairman WAXMAN. Before you talk about the regulatory action, did you ask for and did you get a study on the potential side effects dealing with the heart, as was recommended by so many others that I mentioned. Did you actually tell the manufacturer to do the study so you could have a definitive study?

Dr. VON ESCHENBACH. I am going to let Dr. Jenkins talk about the approval and what was involved, and Dr. Dal Pan describe the post-market assessment.

Chairman WAXMAN. I am more interested in the post-market. Because the approvals seem to be reasonable. You have enough evidence. The reviewer saw the studies, said, this drug merits approval from what we have seen so far. But raised a concern about the possible heart attack problem. And he recommended that there be a followup post-market review.

Dr. Dal Pan, why wasn't one done? Which of you——

Dr. VON ESCHENBACH. This is on the approval, Dr. Jenkins.

Dr. JENKINS. Thank you, Mr. Chairman. Let me try and address that point.

I was the senior member of the review team that reviewed Avandia back in 1999. I actually signed the approval letter for Avandia in 1999. And the approval did have a phase 4 commitment for a long-term, 4-year safety and efficacy study titled ADOPT, which was designed to look at the long-term efficacy of the drug, but also long-term safety and specifically reading from our post-marketing commitment Web site, we talked about long-term safety, including hepatic effects, cardiovascular and hematologic effects, changes in body weight and serum lipids.

So the medical officer that you are describing who, in his review called for the study, this is the same study that he was calling for that we actually got as a post-marketing commitment.

Chairman WAXMAN. Did the study, the ADOPT study look at the specific concerns about potential heart attack? I know you requested it. But in my understanding, the ADOPT study only confirmed that the drug was effective in lowering blood sugar.

Dr. JENKINS. At the time we approved Avandia, there were quite a number of different questions we had that we were looking for answers for. One of them was about its long-term efficacy in com-

parison to other drugs. There were concerns about its hepatic safety, because the previous member of this class had proven to have a liver toxicity signal. There were also concerns about congestive heart failure and edema.

Chairman WAXMAN. Did the study give you the answers you needed on the question of the safety matters that involved the larger population using the drug? Did we have the answers from that study that we can now cite as showing us, on this specific issue of cardiac problems, that we now know the risks?

Dr. JENKINS. The study was not specifically designed to be a study to evaluate myocardial infarction or heart attack in and of itself. It was designed to look at cardiovascular outcomes. We now have the data from that study. It was published last fall, it is currently under review by FDA——

Chairman WAXMAN. You are talking about ADOPT?

Dr. JENKINS. ADOPT. It provided a lot of very valuable information about the cardiovascular safety of Avandia, as well as its liver safety, its effectiveness in long-term use. So I think it was a very useful study.

Chairman WAXMAN. And when was that study concluded?

Dr. JENKINS. I can't give you the exact date when it was concluded. It was published last fall and it was submitted to the FDA as a final study report earlier this year. It is currently under a complete review by the FDA.

Chairman WAXMAN. Did it show that there were more heart attacks?

Dr. JENKINS. The overall data did not seem to suggest that there was a difference between Avandia and Metformin, another commonly used drug, or a sulfonylurea, I think it was glyburide, in that study.

Chairman WAXMAN. So you didn't have any reason as a result of that study to think anything more needed to be done?

Dr. JENKINS. We only got the final study report of ADOPT earlier this year. It is still under review. We have not completed our review of that study. The results I am describing are what are in the published article from last fall.

Chairman WAXMAN. The company says that they have the study RECORD. They weren't told to do that study by the FDA, but by the Europeans.

Dr. JENKINS. Right.

Chairman WAXMAN. And they cited some preliminary data from that study which was specifically on the cardiac problems. And they said, well, this shows that it is not a problem. But some of the critics say, well, it wasn't a big enough population covered in that study.

Why did they do a second study if ADOPT resolved this issue?

Dr. JENKINS. The RECORD study was requested as a post-marketing commitment by the European regulatory agency when they approved the drug shortly after we did. So it was designed to address different questions. As I said, at the time of approval, there were multiple questions that could be answered by different studies. They chose to try to address a cardiovascular outcome study. Those data just recently became available and are under review at

FDA. As you know, they were just published online in the New England Journal of Medicine yesterday.

Chairman WAXMAN. My time is up, but I would submit to you, Dr. Jenkins and Dr. von Eschenbach, that the study, ADOPT, did not have a sample big enough, from what I understand, of the cardiac issues. It was not conclusive on that question. Even accepting what you had to say, it took 8 years before you got that study. And there had been enough warning signs that this is a problem, even before the New England Journal of Medicine article finally came out with their report.

You had a number of instances where FDA's intention should have been to ask for a genuine study looking at this specific issue. Because after all, heart attacks and strokes are one of the leading causes of death for people with diabetes. We want to know if this drug is reducing the risk or increasing the risk. That is an issue that I don't think we fully resolved, or do you believe we resolved?

Dr. JENKINS. If I could respond to that, we did ask for a study to look at the long-term safety of Avandia. And we have the results of that study under review. The Europeans asked for a different study. We now have an interim analysis from that study.

There were several different issues related to the cardiac effects of Avandia that were of interest in 1999 and 2000 when those studies were designed, including congestive heart failure. So you are probably correct that the RECORD study doesn't look like it is going to be adequately powered for the endpoint of myocardial infarction or heart attack alone. That was not the primary concern in 2000 when the study was designed.

Chairman WAXMAN. But there are others who have raised that concern.

Dr. JENKINS. We do have very valuable information coming to bear on this question.

Chairman WAXMAN. Dr. Dal Pan, you reviewed this ADOPT study, and other studies post-market?

Dr. DAL PAN. Right.

Chairman WAXMAN. Do you think we have concluded this issue as a result of this ADOPT study?

Dr. DAL PAN. I don't think we have come to a conclusion as a result of this or any study. I think we are still looking at all the data. We are looking at exactly how the study was designed, conducted, taking apart the data, if you would. We are also doing that for RECORD. We are taking a careful look at how the study was designed, what it can and can't answer. We only have data that is essentially what we have in the online publication from the New England Journal about RECORD. We don't have the data sets or anything like that to look at it more thoroughly. But we are looking at the design and the end term analysis results.

Chairman WAXMAN. Thank you.

Mr. Davis.

Mr. DAVIS OF VIRGINIA. Thank you. I want to thank you all for your time.

There is controversy in the medical community about the use of surrogate endpoints because drugs approved on this basis are not required to demonstrate actual clinical benefit. Is that correct?

Dr. VON ESCHENBACH. The expectation is that we look at a clinical endpoint that will reflect the favorable outcome of survival, the improvement.

Mr. DAVIS OF VIRGINIA. But we don't test for survival, we just look at the endpoint and assume the rest, basically.

Dr. VON ESCHENBACH. Correct.

Mr. DAVIS OF VIRGINIA. Some argue that the Avandia was approved on a surrogate endpoint, and while the drug is clearly efficacious, the health benefits haven't been demonstrated for exactly that reason. If you were to sit through the whole process it could take years to get any kind of approval.

Dr. VON ESCHENBACH. That is correct. It was also approved in the context of the overall experience with diabetes, both type 1 and type 2, where it is recognized that control of blood sugar is an extremely important part of care, resulting then in the ability to reduce the complications and problems that then would reduce the risk of death and——

Mr. DAVIS OF VIRGINIA. I guess my question is, what effect would abandoning glycemic control as an endpoint have on the approval process for a diabetes drug?

Dr. VON ESCHENBACH. If we were to eliminate that and go to a model that said we could not make a decision about a drug until we had absolute outcomes with regard to death, you would be looking at studies that would have to go on for decades, 25, 30 years perhaps, before you would get an answer.

Mr. DAVIS OF VIRGINIA. So if you went to that to get a diabetes drug approved, if the outcome trials were needed pre-approval, you are talking decades?

Dr. VON ESCHENBACH. There would literally be millions of people or hundreds of thousands of people dying in the interim until we got that answer.

Mr. DAVIS OF VIRGINIA. Some in the medical community have been critical in recent weeks that Dr. Nissen's study was rushed to publication, and created unnecessary confusion and concern among diabetics. How has the meta-analysis published in May in the New England Journal of Medicine contributed to our understanding of the balance of risks and benefits of Avandia?

Dr. VON ESCHENBACH. We view the publication of this meta-analysis, along with all of the other pieces and data of information that we had, both from other meta-analyses as well as data and information from controlled clinical trials. So we welcome the additional contribution, recognizing that like other meta-analyses, there are limitations of these kinds of studies. That is factored in, obviously, to the weight we apply to a meta-analysis.

But the important point is, it was one piece of information in a large portfolio of data and information that we, the FDA, have available to us upon which to make ultimate decisions about the right thing.

Mr. DAVIS OF VIRGINIA. In fact, the editorial itself notes the study has a number of weaknesses, only summary trial level data rather than patient level data were available. So it was not possible to conduct time to event analyses or to evaluate the time course of risks. And they note in this setting the possibility that

the findings were due to chance cannot be excluded. So the meta-analysis could be basically irrelevant.

Dr. VON ESCHENBACH. As you are very well pointing out, there are limitations to any study. There are particular limitations to a meta-analysis. We took the opportunity to recognize this, along with other information, were clues in any kind of detective game. But we had to look at all the clues, all the information, all the data from all sources.

Mr. DAVIS OF VIRGINIA. Now, you had done your own meta-analysis, am I right on that?

Dr. VON ESCHENBACH. That is correct.

Mr. DAVIS OF VIRGINIA. Prior to this article?

Dr. DAL PAN. Dr. Dal Pan can speak specifically to our analysis on that, Mr. Davis.

Mr. DAVIS OF VIRGINIA. That is what I am interested in.

Dr. DAL PAN. So in August 2006, the company submitted what was called a pool of clinical trial analysis, essentially a meta-analysis. That was one of two studies they submitted. They also submitted a large observational epidemiologic study. The pooled clinical trial analysis, the meta-analysis, suggested a risk of heart attacks, let's call it, while the observational study did not suggest that risk. So one of our challenges was to try to reconcile this apparent difference.

As part of that, we looked into both of these studies and we realized that there were some methods that the company used that we didn't think were the best methods, given the data they had. We had the data and our statisticians have recently completed their own meta-analysis of the data.

Mr. DAVIS OF VIRGINIA. And what have your statisticians concluded?

Dr. DAL PAN. The statisticians came up with a numerical finding that is similar to the company's and similar to Dr. Nissen's, approximately a relative risk of 1.4. Now, the job of the FDA at this point is to look at those data in, how can I put it, in a more granular level, to look to see if there are sub-groups of patients who may be at particular risk, to analyze the data more to see what's contributing to that, and also to put it in the context of all the other data we have. So that is an ongoing process.

Mr. DAVIS OF VIRGINIA. So you haven't reached any conclusions yet, is that fair to say?

Dr. DAL PAN. No, the agency hasn't reached a conclusion on this.

Mr. DAVIS OF VIRGINIA. Would you say even with your setting, looking at both of them, that the findings could be due to chance?

Dr. DAL PAN. I think that is a question more for a statistician. I think that from someone who is interested in drug safety, I always have to consider that possibility, but I have to actually look at what the data are telling me as well about the numerical evidence of risk.

Mr. DAVIS OF VIRGINIA. Your testimony also mentioned that FDA is going to convene an advisory committee in the near future. When do you plan to convene the panel?

Dr. VON ESCHENBACH. The advisory committee meeting is now scheduled for July 30th. It is the end of July, it has been published in the Federal Register.

Mr. DAVIS OF VIRGINIA. Are they going to look strictly at Avandia, or is it going to examine other drugs in its class?

Dr. DAL PAN. The focus will be on Avandia. But because of the nature of the studies, we are going to be looking at other oral agents to treat diabetes. They are all involved in the same studies.

Mr. DAVIS OF VIRGINIA. People get very confused when this stuff gets out in the media and it gets very unfiltered. Some others in the medical community have argued that too many warnings on a drug label can lead to as much harm as too few warnings, because it leads to the under-use or the under-prescribing of effective drugs to treat certain conditions. How does FDA reach an appropriate balance between caution about safety and unnecessary concern?

Dr. VON ESCHENBACH. Mr. Davis, I think you are making an extremely important point that I tried to emphasize in my oral statement. Our challenge, first of all, is to take the data associated with this particular drug, which is in fact very voluminous, very complex and very complicated, come to an analysis and an understanding of what has it told us about this specific drug as it relates to its complications. Also, what has it told us about drugs that may be very similar to it.

Second, then take that information and put it in the context of what should be our appropriate action, what is the right thing to do for patients. If we have to in that regard weigh the benefit of what would occur if we continued to use this drug under certain circumstances and provide information to patients and doctors, or if we were to withdraw this drug and everything else like it, what would that mean to patients who were now deprived of an important therapy to control their diabetes, and what would the alternatives be and what were the complications of those alternatives, for example, if they had to go on insulin.

So we, the FDA, are not looking at one slice or one piece in isolation.

Mr. DAVIS OF VIRGINIA. You are looking at the big picture.

Dr. VON ESCHENBACH. We are looking at every piece and putting it together into a comprehensive decision of what the right thing to do is for patients.

Mr. DAVIS OF VIRGINIA. Have similar drugs also been subject to meta-analysis by either you or anyone else? And if so, what have they found?

Dr. JENKINS. We have requested that the manufacturer of the other drug in this class, pioglitazone, which is marketed as Actos, perform a similar meta-analysis of their short-term studies. Other than that, I am not aware if there have been other published meta-analyses for the other drugs. Gerald may know.

Dr. DAL PAN. I am not aware of published meta-analyses for diabetes drugs.

Mr. DAVIS OF VIRGINIA. Could you give me a scientific reason why you might have that cause and effect that the Nissen report, their meta-analysis brought up? Why the cause and effect would be a higher risk of heart attacks?

Dr. DAL PAN. I am sorry, I don't really understand the question.

Mr. DAVIS OF VIRGINIA. We understand what the meta-analysis and the article in the New England Journal of Medicine said. Can you give me a scientific reason why you would get that conclusion

with higher incidence of heart attack, given your understanding of the drug?

Dr. DAL PAN. I think that is what the meta-analysis does, it is a technique to bring together smaller trials, which each individually——

Mr. DAVIS OF VIRGINIA. Well, it shows the results, but I am asking, not the results, I am asking then what is the reason? Why does this happen?

Dr. VON ESCHENBACH. One of the things I think your question is pointing out, Mr. Davis, is the need for us to understand more about the mechanisms of these drugs.

Mr. DAVIS OF VIRGINIA. That is what I am trying to get at. I am a lawyer.

Dr. VON ESCHENBACH. And as we know more about the mechanisms, as well as observe the effects that they are having on patients, then we will be in a much better position to make decisions about safety.

Mr. DAVIS OF VIRGINIA. So you don't know at this point, in other words?

Dr. VON ESCHENBACH. No, in fact, one might suggest it is a little paradoxical. You might conclude that the effect on microvasculature would be to have improved it, rather than to predispose to infarction.

Mr. DAVIS OF VIRGINIA. I have one last question. In your testimony, you say that the FDA approves a drug only after a sponsor demonstrates that drug's benefits outweigh its risks for a specific population and a specific indication and it shows that the drug meets the statutory standard for safety and effectiveness. Does the FDA still believe that Avandia continues to meet those statutory standards?

Dr. VON ESCHENBACH. We are in the midst of an analysis as we speak, and we have not arrived at a conclusion regarding that final decision. Up to this point in time, we clearly have believed that it was an important part of the armamentarium. We have issued changes in the label to provide appropriate warnings, as we had the data to support it. And we will continue to do that. And if the data changes or alters after our decision after this current analysis that we are in the midst of, we will take appropriate action.

Mr. DAVIS OF VIRGINIA. I guess my question is, it meets the standards until you conclude otherwise, basically?

Dr. VON ESCHENBACH. Correct.

Chairman WAXMAN. Thank you, Mr. Davis.

Mr. Davis.

Mr. DAVIS OF ILLINOIS. Thank you very much, Mr. Chairman. Dr. von Eschenbach, it is good to see you again. I want to thank you for being here and thank you for your testimony.

On May 21st, the Food and Drug Administration issued a safety alert on Avandia. Could you tell us, as close to possible, exactly what that means?

Dr. VON ESCHENBACH. I am going to let Dr. Jenkins and Dr. Dal Pan speak specifically to that.

Dr. JENKINS. Mr. Davis, the intent of the announcement from the FDA was to communicate to physicians and patients and other health care providers about the status of the information, so they

could be aware of the findings from the meta-analysis, aware of other data that FDA was reviewing from other trials that we have talked about a bit already this morning, as well as to give advice to physicians and patients about how we felt they should respond to this new information.

We particularly wanted to make sure that patients got the message that they should not stop taking the drug precipitously. If they had concerns, they should speak with their doctor. Because going off of a drug for diabetes without careful attention can lead to your diabetes being out of control, which has its own health risks.

Mr. DAVIS OF ILLINOIS. The Food and Drug Administration, of course, knew prior to this article and prior to the issuance of this information that there were potential side effects for the use of the drug, is that correct?

Dr. JENKINS. Yes.

Mr. DAVIS OF ILLINOIS. What has the Food and Drug Administration done, if anything, to help make the general public more aware of these side effects?

Dr. JENKINS. The primary vehicle by which we communicate about the risks and benefits of drugs is through the approved labeling for the product. And we have made numerous changes to the Avandia labeling over the years since it has been approved to reflect emerging information and new information about the risks. When we make those changes to the labeling, we share those through a system we have with many stakeholder groups and public patient groups, professional societies, so that they are aware of the changes. They are often communicated to the physicians through letters from the company and through the promotional materials.

So those are the primary vehicles that we have utilized for Avandia.

Dr. VON ESCHENBACH. Mr. Davis, also, if you will allow me, this is an extremely important issue for the FDA in the future, in terms of our continuous improvement of how we communicate both to professionals and most importantly, to patients and to patients of a diverse population. We are approaching that, first of all, to learn more about how to do that even better. And we have issued guidances with regard to communicating drug safety information.

We now have put in place a risk communications advisory committee to help us learn how to do that. We are paying particular attention to the vehicles we use, including our Web site, and we are engaged in a major overhaul of the FDA Web site and the initial project. And that overhaul is to address the part of our Web site that is prepared for consumers, for patients, so that they can come to the FDA and get information in a form that is understandable and useful to them as they need to make informed decisions about their health care, but to do that in the context of a relationship with their physician.

Mr. DAVIS OF ILLINOIS. Are we of the opinion that this causes physicians now to know anything that they did not already know? If I am a physician and I have studied and I have paid close attention to what I prescribe and what I do, would I learn anything from this that I didn't already know?

Dr. VON ESCHENBACH. What we hopefully have done, and even going back to April 2006, when we added a warning in the labeling of Avandia, is that as doctors are caring for patients and they are looking at those patients with diabetes who they believe are at greater risk of cardiovascular problems or already have an underlying cardiovascular history, that they will be able to make much better informed decisions about whether this drug or some alternative drug is the most appropriate treatment for that specific patient.

So it arms them with more information and more awareness to make patient by patient decisions.

Mr. DAVIS OF ILLINOIS. I know that my time is about to expire, Mr. Chairman. Let me just ask this one question, following up on the opening statement of Representative Towns. Is there anything that the Food and Drug Administration can do to help assure that there is greater diversity in the clinical trials that are often used to determine the viability of pharmaceutical drugs? We all know that when it comes to African Americans and some other population groups, there is a paucity, it is very difficult to have data that actually reflects the impact on this particular population group.

Dr. VON ESCHENBACH. Absolutely, Mr. Davis. And we are approaching that from a number of perspectives. One, as you are well aware from our previous conversations, even our relationship with NIH and continuing to find ways to encourage participation of minority and under-served populations in clinical trials, so that we can learn about that in specific.

Also, we have been reaching out at the FDA as a part of our overarching diversity initiative. I have had meetings with the National Medical Association leadership specifically to address the issue of how can we get representation, especially from the African American community in this situation, in the FDA as part of our advisory process, as part of our committee structure, so that there is the richness of their representation as we go about the process of our regulatory activity.

So we are coming at it from both ends of that spectrum, the leadership that is required, the involvement at the FDA level, and then promoting opportunities at the clinical trials level, so that we learn, understand and can serve those populations more appropriately.

Mr. DAVIS OF ILLINOIS. Thank you very much, and thank you, Mr. Chairman.

Chairman WAXMAN. Thank you, Mr. Davis.

Mr. Issa.

Mr. ISSA. Thank you, Mr. Chairman.

Dr. von Eschenbach, I am going to try and summarize what I think I heard. You don't know whether or not there are any, in this class of drugs or in this particular one drug, if there are any side effects that essentially say, we will help you with your blood sugar, but we may hurt your heart? That is what I heard, particularly from Dr. Dal Pan.

Dr. VON ESCHENBACH. What we have tried to communicate, Mr. Issa, is the fact that we have had signals and indications about this drug. As those signals and indications have had the adequate sci-

entific data in support of a conclusion, we have made that conclusion and taken steps to inform the public and physicians about what we have known.

For example, the warning——

Mr. ISSA. My time is limited. My summary is the one that I wanted the question answered on. Basically, you are saying here today that, and I used the word anecdotal, and maybe that is not perfect, but Dr. Nissen in his upcoming testimony is going to say that there were several small and medium size clinical trials that are insufficient to answer a scientific question. He is going to observe that this group already has a high risk of heart disease, and that in fact, his own study, which he published, which caused this hearing to be rushed here today 3 weeks later, is not in fact based on sufficient study to reach—it looks like my time is coming and going, Mr. Chairman.

Dr. VON ESCHENBACH. I apologize. I misunderstood your question. You are correct in the sense that we are in the midst of making that decision right now. Up to this point in time, we have not had sufficient data of a nature that we could rely upon to draw that conclusion. But we are assessing that as we speak, and we are taking that to an advisory committee at the end of July.

Mr. ISSA. Then let me change my line of questioning. If it is insufficient and premature for us to be having this hearing on this drug and this line of drugs, which I think it is, I think this is not settled science, you are certainly not here to tell us it is, then let's go through—I don't have a family history of diabetes, but I do have a family history of heart disease. So I just want to go through real quickly my understanding of a little bit of the history of heart disease, so that something that is much more settled you can comment on.

When you were in medical school, or maybe before, they used to open somebody's chest and sprinkle talc in there in hopes that it would promote growth of arteries and veins and so on. And that was the best medical science they had at the time. This is not a pharmaceutical, per se, there was no prescription there. But that is what they did, because that was the best they could do. And looking back, it undoubtedly killed more than it saved, because of the risk of opening somebody's chest. Is that right? Is that fair to say?

Dr. VON ESCHENBACH. That is a fair assessment.

Mr. ISSA. OK. And then we went through a long period of time of yanking out one vein and putting it into another part in hopes that patching in a new one was going to take care of it. And we thought we were doing better, but now the studies show that in at least some categories of patients, they are more likely to die on the table or as a result of it later than they are to be saved or get a longer quality of life. And having had my father go through that and then die, I am acutely aware of it.

Now, in my own district, it is no longer Guidant Pharmaceutical, but Guidant was a major manufacturer of stents. So I have had the coated/uncoated stent question going on and on and on. And it appears as though you approved, in good faith, both coated and uncoated stents and in both cases felt they were going to do certain things. And now that the studies are in, at least on certain ones,

historically, some of them simply are not going to do a very good job for a long period of time, and you would be better off not having them than having them. Isn't that correct?

Dr. VON ESCHENBACH. Right.

Mr. ISSA. So isn't the pattern and the likely future, based on that past, I am just using that anecdotally myself, based on that past, you are going to always be in a position in which you have to face allowing a drug which shows promise, and then in fact recognizing that in the long run, maybe 15, 20 years later, the alternative to paralysis by analysis is that you go forward with drugs that have promise, as this one does, that show in clinical trials it does one thing good.

And then unfortunately, over a long period of time, you may find out, as a matter of fact, about the time it is an obsolete drug and there is another one, you may find out that on balance, you wouldn't have done it if you knew everything that you can only know 10 years later. Isn't that right?

Dr. VON ESCHENBACH. That is absolutely correct.

Mr. ISSA. OK. So when I am looking at this hearing today, because I am a dedicated member of this Committee on Oversight and Government Reform, I am seeing two things. One is, from an oversight standpoint, we shouldn't be second guessing your science, even though I just went through that sort of in the case of heart disease, that we have to accept that as long as your function—just a moment, Mr. Chairman—as long as your functional system is as good as science and minds can be, that we have to accept that those risks are going to be part of the process, and that 10 years from now, a number of drugs or a number of procedures that are common today will no longer be common because of what we learned over time.

Thank you, Mr. Chairman. I yield back.

Chairman WAXMAN. Thank you, Mr. Issa. I am sorry the system is not working, but we gave you the time.

Before I recognize the next Member, just to clarify something that Members ought to be aware of, Dr. von Eschenbach, before a drug is approved, you can demand any test from the manufacturer that you think is pertinent to safety and effectiveness, isn't that true?

Dr. VON ESCHENBACH. Correct. Dr. Jenkins may want to comment on that.

Chairman WAXMAN. Well, it is just yes or no. Do you have the power to say, we need more information on this or we need more information on that?

Dr. VON ESCHENBACH. That is true.

Chairman WAXMAN. Give us a test on it.

Dr. JENKINS. The statute says all tests reasonably applicable.

Mr. ISSA. Mr. Chairman, point of privilege. Whose time are you speaking on?

Chairman WAXMAN. If the gentleman would permit, I just think we ought to have this clarification.

Now, after the drug is approved, can FDA demand that a test be done on anything related to efficacy or safety, or do they have to negotiate it with the company to get the company to do it?

Dr. JENKINS. Mr. Chairman, there are certain places where we do have the authority to require studies after approval. In other places the studies are negotiated agreements between us and the manufacturer.

Chairman WAXMAN. And this particular drug, and I am sure it is true of a lot of others, for the approval, there was a strong recommendation that the test be done on heart attack risks. Could you have demanded such a test be done?

Dr. JENKINS. At the time of approval, we did in fact have a post-marketing commitment for the long-term safety study to address the medical concerns.

Chairman WAXMAN. What if those commitments aren't kept? Could you demand they be kept?

Dr. JENKINS. Well, we certainly monitor those comments and expect them to be kept. They are written commitments to the agency and we expect them to be honored. In this case, the company did do the study in a timely manner and reported it to us earlier this year.

Dr. VON ESCHENBACH. I think the point that perhaps we should emphasize, Mr. Chairman, is that if we by virtue of the absence of that data believe that drug should no longer be available to patients in terms of our ability to assure and protect them and in promoting the public health, we can require that drug to be withdrawn.

Chairman WAXMAN. Right. Some people call that a very strong nuclear option. But that is your option at that point. I did want to clarify that issue of the FDA law.

Mr. Tierney, you are next.

Mr. TIERNEY. Thank you, Mr. Chairman. It is exactly the line of questioning I wanted to proceed on, Doctors, if I could. Your FDA physician, originally, the one who looked at the original application, were concerned about adverse effects on the heart. As I understand it, he was concerned about bad cholesterol increases and increases in weight, and concluded that a post-approval study of cardiac effects should be a condition of approval. Am I right so far?

Dr. JENKINS. That is what the medical officer recommended, and that is what we implemented with the ADOPT post-marketing commitment.

Mr. TIERNEY. Your approval letter stated that?

Dr. JENKINS. Yes.

Mr. TIERNEY. That it wanted a study after approval looking at cardiovascular risks?

Dr. JENKINS. Well, the approval letter said what I said earlier. It asked for a 4-year long-term safety and efficacy study including looking at cardiovascular and hematologic events, the liver events.

Mr. TIERNEY. Right. So including the safety and the cardiovascular events on that.

Dr. JENKINS. Yes.

Mr. TIERNEY. Now, GlaxoSmithKline in their ADOPT study didn't really do that. What they did on the ADOPT study was they looked at the control, whether or not it controlled elevated blood sugar.

Dr. JENKINS. The primary endpoint for the ADOPT study was an efficacy endpoint comparing how well rosiglitazone compared to

two other commonly used medications. But they also did specifically collect information and submit and analyze information about safety of the liver, the heart and other aspects, yes.

Mr. TIERNEY. People tell us, and I think you will agree, that the study was too small, really, to get at heart risk, and it also had no independent panel to even look at the heart-related matters, right?

Dr. JENKINS. The study was never designed to be a specific study for heart attack at the time it was designed in 1999.

Mr. TIERNEY. All right. So let me bring you back to your FDA physician who had the original application. He was concerned about heart attack.

Dr. JENKINS. He was concerned about various heart effects.

Mr. TIERNEY. Including heart attack, right?

Dr. JENKINS. Including heart attack, but also including congestive heart failure.

Mr. TIERNEY. So we didn't have in the ADOPT study enough information to really give us an answer on heart attacks on that. And I guess my question is, with the stakes being so high, and if in fact Dr. Nissen is correct in his analysis of 30 to 40 percent increase in heart attack possible from this, we could have a serious health problem here.

So why didn't we have a clinical test or the data designed on a post-marketing study? The FDA as I understand it did not insist on the particularity of that, on whether we got the heart attacks, but afterwards, you don't have the power to do a post-study except in very isolated incidents, if I am correct. So Dr. von Eschenbach, do you believe the FDA ought to have the authority to require more specific and better post-approval tests?

Dr. VON ESCHENBACH. I think the point that Dr. Jenkins was making was that the concern at the time was with regard to toxicity across a number of organs. With the issue of the heart, concerns because of the nature of the drug would be more around the idea of heart failure. Those things were included in the study.

Mr. TIERNEY. I am sorry, you are telling me now that you think your FDA, the original doctor was concerned with heart failure but not heart attack?

Dr. VON ESCHENBACH. I think he was concerned about cardiac events. But what we know about these drugs would make you think that would be more likely heart failure, fluid accumulation and edema that could put stress on the heart.

Mr. TIERNEY. I guess I am having trouble with that. Because the impression that we had clearly from the physician was that he was concerned about heart attack, long range, as a result of bad cholesterol increase, and the increase in weight. You are saying that is not the case, he was just worried about a little bit of heart trouble?

Dr. VON ESCHENBACH. I can't speak specifically to that particular individual's concerns. I am raising a general concern that in retrospect, now that we have the data that we are discussing today, this issue of heart attacks, as in different or separate from heart failure, is an important area that needs to be explored, and a concern. That is apparent to us now. I don't know that it was as obvious to everyone back in 1999.

Mr. TIERNEY. Doctor, do you support legislation that would give you and your agency the authority to require post-market studies?

Dr. VON ESCHENBACH. As I have indicated, Congressman, I believe very strongly that we have to be engaged in post-market surveillance and pharmaco-vigilance. There is legislation that is underway that is addressing those specific issues. I am looking forward to working with you on that.

Mr. TIERNEY. So it would be, I am trying not to be impolite, but it is a very straightforward question. Do you support legislation that would give your agency the authority to require post-market studies?

Dr. VON ESCHENBACH. I would look forward to discussing that legislation in an effort to get us to a point where we will be able to get opportunities to collect appropriate data in the appropriate way. And the complexity of that——

Mr. TIERNEY. Well, wouldn't the post-market studies, wouldn't that do it?

Dr. VON ESCHENBACH. A post-market study is an extremely important tool. The information technologies are extremely important tools.

Mr. TIERNEY. So if it is an extremely important tool, would you not support legislation that would give you that extremely important tool?

Dr. VON ESCHENBACH. I am in support of legislation that would give us the resources to be able to have those tools and be able to implement them. [Laughter.]

Mr. TIERNEY. You know, I am going to take that as a yes, because what the hell, why not. [Laughter.]

I would understand the drug companies running us around the rosie like that, but I am not sure I understand your reluctance to be direct on that. It is your job to protect public health.

Dr. VON ESCHENBACH. It is legislation that is currently in process.

Mr. TIERNEY. I know, I filed it.

Dr. VON ESCHENBACH. I know, and I am engaged—we are engaged in providing technical assistance in that legislation. I look forward to continuing to participate in that process.

Mr. TIERNEY. So I can look forward to your assistance in writing legislation that will give your agency the authority to require post-market studies? [Laughter.]

And I would be happy to sit down and talk about that with you.

Dr. VON ESCHENBACH. I will look forward to that, sir.

Mr. TIERNEY. Good. Thank you. Thank you, Mr. Chairman.

Chairman WAXMAN. Thank you. Your time is up, even though the light is still green.

Ms. Foxx. Thank you, Mr. Chairman.

I have a fairly brief comment and my colleague may want to use the remainder of my time.

Commissioner, your written testimony states that while meta-analyses are often informative, they have important limitations. And FDA has been historically cautious in the use of meta-analyses in support of regulatory decisions. To your knowledge, has the FDA ever acted solely on the basis of a meta-analysis?

Dr. VON ESCHENBACH. Congresswoman, I am going to ask the two experts on either side. In terms of ever having acted on it, I quite frankly cannot answer that factually right now.

Dr. JENKINS. Yes, I can provide some insight to that. We are very cautious about the use of meta-analysis to demonstrate the efficacy of a drug. So I am not aware that we have ever used a meta-analysis to form the basis of showing a drug is effective.

We do consider pooled analyses of studies or meta-analyses, as they are sometimes called, when we are looking at safety data. In fact, that is one of the primary ways we look at safety data in an application, is we pool it all together. Because any one study is usually not adequate to provide us with the information.

We did recently make a regulatory decision about a drug called Zelnorm that was primarily based on a safety signal that was derived from a pooled analysis of their clinical trials, where the evidence of the risk of a heart effect was very large, and we thought it was so convincing that it was actionable to recommend that drug come off the market.

Ms. FOXX. Thank you, Mr. Chairman. I yield back the remainder of my time to my colleague, Mr. McHenry, if I may, Mr. Chairman.

Mr. MCHENRY. Thank you, Mr. Chairman, and I thank my colleague from North Carolina.

There was a stakeholder meeting on May 29th, regarding the safety alert on Avandia. Who participated in that meeting and what was the outcome?

Dr. JENKINS. Dr. von Eschenbach participated in that meeting, I participated in that meeting, several others from the center, including the center director. We invited, I think over 40 stakeholder organizations, professional societies, patient groups, etc. I think approximately somewhere in the teens were the number of groups that were actually represented. Some were in the room with us, some were on the phone.

Mr. MCHENRY. What was the outcome?

Dr. JENKINS. We had a discussion to help them understand where we were in our analysis of the data, the scope of the large number of trials that we were evaluating to try to come to our decision about Avandia. They expressed their interest in assisting us in better communicating this information to patients in particular parts of society that may not get access to the information through the usual pathway.

So it was a discussion and an information sharing meeting, not an action meeting per se.

Dr. VON ESCHENBACH. And if I may, Congressman, just from the perspective of the Commissioner, I believe very strongly in the need for FDA to be open, transparent and proactive in our communications. One of the things we wanted to accomplish in this meeting was to address with stakeholders, especially patient groups, the FDA's ongoing investment commitment and involvement in coming to a scientific conclusion and answer, and then whatever action that deemed appropriate.

In the meantime, to also have them understand that communicating, to prematurely and abruptly stop this medication, where patients might choose to do that on their own, could lead to other serious problems if their diabetes was uncontrolled, and to always

re-emphasize the need for these decisions to be made in a doctor-patient relationship. It was an important part of our communication strategy.

Mr. MCHENRY. And a final question to you, Dr. von Eschenbach. What do you think the implications are of elevating a safety review office within FDA? What do you think those implications are? And could that possibly offset the balance of benefits to patients and life-saving medications?

Dr. VON ESCHENBACH. I think we need, as you see from the two gentlemen on either side of me, the diversity of focus within the FDA that looks at these issues from different perspectives, but does it in an integrated and coordinated way. And more and more, science is moving us in the direction that information data, scientific data is telling us both about the effectiveness of a drug and the safety or adverse events associated with that drug simultaneously.

Mr. MCHENRY. So rather than stovepiping it, it would be integrated?

Dr. VON ESCHENBACH. It would be, in my opinion, moving into the modern era, that would be more destructive than constructive to what we want as an ultimate outcome. I look for greater integration rather than separation.

Chairman WAXMAN. The gentlelady's time has expired. Mr. Tierney, you are recognized next. Not Mr. Tierney, Mr. Lynch.

Mr. LYNCH. Thank you, Mr. Chairman.

I want to thank the witnesses for coming before this committee and helping us with our work. I would like to ask about the warning labels connected with Avandia. Dr. von Eschenbach, in your written testimony you said that in April 2006, the labeling for Avandia was updated to include new data in the warnings section about potential increases in heart attacks and heart-related chest pain in some patients. You also told USA Today with regard to the risk for heart attacks that "About a year ago, we began warning the public about possible risks in Avandia's labeling."

Again, Dr. von Eschenbach, perhaps you can assist the committee right now. There is a Physicians' Desk Reference being provided to you, which as you know contains all the updated labels for prescription drugs. A new version of the 3,500 page book is printed each year. We have actually flagged the section for Avandia for your convenience.

Now, can you tell me and can you tell the committee where the risk for heart attack warning is in the text of the label? Because I read it, and I actually had a couple of physicians read it and they couldn't tell me either. I remember the earlier statement you had about the warnings of heart attacks and chest pain. If you could just tell me in the text there, I couldn't find it.

Dr. VON ESCHENBACH. Congressman, we are looking at that as you are questioning us. But I would in the meantime emphasize the point you are making. As a physician, I recognize the inadequacy of the portrayal of this kind of information. And in fact, earlier this year, the Food and Drug Administration initiated a revision of the label in terms of our ability to provide the meaningful, important information that a physician and patient needs to get to

immediately at the front end of this process, so that it would be easily available to any physician who had to find it.

At the same time, we are moving toward an electronic label that would not depend upon the publication of desk references, but would be immediately available in real time electronically, so that when we make a change, it isn't a delay in another publication of a hard copy, but something that would be available in real time.

Mr. LYNCH. Have you found it, Doctor? Because even after I read through it and read the applicable text, I couldn't define the——

Dr. VON ESCHENBACH. I draw your attention to page 1,387 and 1,388. There is a section, warnings, cardiac failure and other cardiac events.

Mr. LYNCH. OK, can you just read the language that is supposed to warn me about a heart attack? That is what I am interested in.

Dr. VON ESCHENBACH. Placebo v. Avandia ischemic adverse effects, myocardial infarction, 2 percent with regard to placebo, 5 percent with regard to Avandia.

Mr. LYNCH. Is that in the table or is that—where is that?

Dr. VON ESCHENBACH. It is in the table in this drug label.

Mr. LYNCH. That is it?

Dr. VON ESCHENBACH. There is a whole section on cardiac failure and cardiac events.

Mr. LYNCH. That study of that table is for a couple of hundred people, 2 non-Avandia and 5 in Avandia. I mean, you are not seriously telling me that is it?

Dr. VON ESCHENBACH. Actually, the power—well, the point is——

Mr. LYNCH. Doctor——

Dr. VON ESCHENBACH [continuing]. At page 1387 there is a long section on contraindications and warnings, cardiac failure and cardiac events. I drew your attention specifically to the cardiac——

Mr. LYNCH. Cardiac events is not heart attack, though. Congestive heart failure is something gradual, over time. I am asking you where the—I understand infarction, that comes in under, it is in four point type, it is one line in a table. You are not seriously suggesting that is the warning?

Dr. VON ESCHENBACH. I am going to ask Dr. Jenkins to describe, perhaps better than I am able to do right now to you, Congressman, about this information.

Dr. JENKINS. This language was added in April 2006. It specifically refers to a study that was done in patients with pre-existing congestive heart failure to look primarily at the function of the heart, how well did the heart function——

Mr. LYNCH. Was it——

Dr. JENKINS. Let me please finish. As an outcome of that study, when we reviewed it, we noticed that there was an imbalance in the events for heart attack and heart-related chest pain, but they were not conclusive, because as you pointed out, the study was small. So we put the study in the labeling as a warning. And it says, "Although in treatment a difference in change from baseline of ejection fractions was observed, more cardiovascular adverse events were observed with Avandia treatment compared to placebo during the 52 week study. See Table 7." Table 7 is the table that Dr. von Eschenbach just pointed to where it shows ischemic adverse events, myocardial infarction——

Mr. LYNCH. My time is limited. You are repeating what the doctor already said.

Look, all I am saying is that, you cannot be serious about locating the warning in a label referred to, four point type, it is this small, in an adjacent table to the warning. And the warning, the study that you selected, you have thousands and thousands and thousands of people who have gone through these various studies. You select a very small portion of them and you are warning people who have been in on insulin or who have had heart failure.

What about the millions of other people who are diabetic and have not been on insulin and who have not experienced heart failure, congestive heart failure? What about all those folks?

I read the label, the warning, and it talks about just those two groups. Then it refers to another, very obscure reference in a table. I mean, this is really absurd. This is ridiculous, what you are saying is a warning. If I wanted to hide something, I would do this.

Chairman WAXMAN. Mr. Lynch, your time has expired.

Mr. LYNCH. Thank you, Mr. Chairman.

Dr. VON ESCHENBACH. Mr. Chairman?

Chairman WAXMAN. Yes, Dr. von Eschenbach.

Dr. VON ESCHENBACH. I fully appreciate the concerns and the criticisms of what we have used for decades in the practice of medicine, the Physicians' Desk Reference. But the type size with regard to this warning is absolutely no different than the type size in any of the other drugs on the other 3,500 pages in this book. It is not an intent to sequester or hide. It is just the vehicle that we have to work with.

Chairman WAXMAN. Thank you. Mr. Cannon.

Mr. CANNON. Thank you, Mr. Chairman. We had a lot of pictures clicking there, but I am not sure the record is going to reflect the size of the book that you were just holding up, Dr. von Eschenbach. That is the kind of thing you could have stood on the parapet of a castle and thrown on the attacking enemy and crushed their heads, it is so big. [Laughter.]

This questioning, I think, really reflects the underlying problem of the complexity of how we deal with drugs that deal with the human body in complex ways and how we identify what the issues are and therefore, deal with them through the FDA. I appreciate the chairman's holding this hearing.

We had earlier some discussions among Members about the role of the New England Journal of Medicine. I think one of the points that was missed there is that the New England Journal of Medicine, this enormously important journal, has an editorial position that they would like to see the FDA change the nature of the way we do business in America. That is acceptable. That is a great debate.

My concern is the sensationalization of the process that scares people when we have a problem with drugs. Virtually all drugs are going to be helpful, but they will also have sidebar problems. Now, Dr. von Eschenbach, you and I have spoken personally on these issues. You know that I am committed to change and improvement in the FDA. We have also spoken in public hearings and said pretty much the same thing. And we recognized opportunities, but I am concerned about how do we go from here to there. In other words,

I think doing basion studies instead of double blind studies is an important step that we need to take. But we have to do it in the context of procedures that work.

Here, what we have is some alarmism that is extraordinarily important to many people who are suffering from a disease that is difficult and for whom this drug is helpful.

Taken together, these results, although based on very small numbers of events, certainly raise a signal of concern. Now, signal is, I think, a term of art in the system here, which means, we ought to look at it. There is something that we ought to be looking at. So it raises a signal of concern and indicates the need for more reliable information about—I can't say this name, I will call it the drug at hand, rosiglitazone. Pardon me. [Laughter.]

It is not the one we use when we are asking the pharmacist about it.

But the FDA physicians and patients can reasonably weight the results of record, a phase 3 trial designed specifically to study cardiovascular outcomes. Until the results of record are in, it would be premature to over-interpret a meta-analysis that the authors and the New England Journal of Medicine editorialists all acknowledge contains important weaknesses. To avoid unnecessary panic among patients, a calmer and more considered approach to the safety of Avandia is—that is not what they say here, but I will call it Avandia—is needed. Alarmist headlines and confident declarations help nobody.

This is not a matter of confidence. This is a matter of what happens to people when they take this drug. Now, the problem here is what I think are called surrogate endpoints, like controlling blood sugar levels with Avandia and other drugs. It takes 10 to 15 years to discover and develop a new medicine. Without such endpoints for evaluating a diabetes medicine, for example, what would the development and approval process, wouldn't it take much longer? And how much longer would it take, if it does? Do you agree with the value of using surrogate endpoints?

Dr. VON ESCHENBACH. Yes, sir, I do. And I also echo your important point about the need for continuous improvement. We are seeing revolutions in science and technology around us that are going to enable FDA to continuously improve, including how we use clinical trials, new clinical trial type designs that will be much more informative. We will also be using many more tools of science and biomarkers and genomics etc. that is going to help us with regard to the ability to use these biomarkers and these intermediate endpoints.

Mr. CANNON. I see my time is about to expire. But let me just ask about this study in particular. The meta-analysis by Dr. Nissen excluded studies in which there were no adverse events. From a layman's point of view, of not including studies where there were no heart attacks or other heart problems, that would seem to skew the results a little. But more specifically with respect to heart attacks, I understand that six studies were not used, because none of the patients had a heart attack. Even more studies, approximately half of the overall available were not used, because there were no deaths. Yet headlines screamed about a 43 percent increased chance of death.

Is that a responsible way to communicate to the public?

Dr. VON ESCHENBACH. We value all data and all input with regard to these issues. This study, like other meta-analyses, has both strengths and weaknesses that have been discussed and pointed out by others. And we use it as an additional piece of information, but not necessarily one upon which decisions in and by themselves would be made.

I will let Dr. Dal Pan speak specifically to how we use data and meta-analyses.

Mr. CANNON. Mr. Chairman, I see my time has expired. But the question I asked is, is it responsible to use this meta-data to create what is essentially a public panic?

Dr. VON ESCHENBACH. I believe that the data was being presented in the Journal as in a contribution and an additional piece of information. We have all done that in our careers in terms of publishing information and data that we believe was a valuable contribution. We leave it then to the entire scientific domain to weigh that, add that, evaluate that in the larger context. I believe that is what was hopefully going to occur here.

Other people reacted, perhaps responded to that information and perhaps created some of the concerns that you are alluding to.

Mr. CANNON. If the Chair would indulge just one followup, there is something different from publishing and awaiting a reaction and publishing and promoting. Would that be different in your mind?

Dr. VON ESCHENBACH. I can't speak to the author's intent. I have not had any conversations with Dr. Nissen.

Mr. CANNON. Mr. Chairman, I see my time has expired and I yield back.

Chairman WAXMAN. The gentleman's time has expired.

Now I would recognize Mr. Yarmuth.

Mr. YARMUTH. Thank you, Mr. Chairman, and I thank Dr. von Eschenbach.

I have a question that relates to the scope of the risk that we are talking about. I think any of us who have watched television commercials and have taken medications and see these percentages have a hard time getting our arms around it. Your staff, when they briefed the committee on this particular situation, indicated that if these numbers are real, this is a big deal. I think that was one of the direct quotes. And you said, these data, if confirmed, would be of significant concern because patients with diabetes are already at an increased risk of heart disease.

I want to understand this study. The GSK data that was presented in August 2006 basically said, and I think you confirmed this, that those numbers indicate that the risk went from approximately 1.5 percent to approximately 2 percent, which was approximately a third increase in the risk.

But that body of data, 13,000 or so cases, included a lot of different combinations of regimens that were being used. As I understand it, some were taking Avandia by itself, some with insulin, some with nothing else. So in fact, am I not correct in saying that for some patients, presumably the conclusion would be that the risk is much higher than the 2 percent, but we don't know, because we didn't have a breakout of those incidents?

Dr. VON ESCHENBACH. There are confidence, what we call confidence intervals around that number, which means there could be a range of lower and slightly higher risk. I will let Dr. Dal Pan speak specifically to those statistical considerations as we are trying to make these decisions.

Dr. DAL PAN. I think what you are asking, Congressman, is, are there patients or combinations of medications that can confer higher risk and could there be some situations where the risk is lower. That is the kind of thing our statistical analysis is focusing on. We are trying to answer those questions and put the answers to those questions into the larger context to make our decision.

Mr. YARMUTH. So you don't know that yet, and you are trying to break it down?

Dr. DAL PAN. Right. Our statistician has finished her review, I haven't finished looking at it extensively. But this is the kind of thing that we are actively engaged in now, yes.

Mr. YARMUTH. But presumably in this case, say a patient who was taking Avandia and insulin, might have a risk of 5 percent of a heart attack as opposed to 2 percent or 1 percent?

Dr. DAL PAN. Right. There are risks that could be higher than the overall summary risks for certain patients.

Mr. YARMUTH. And of course, what we are dealing with is a situation in which if a million people are taking a particular medication, a 0.5 percent increase in risk amounts to 5,000 people who are adversely affected who otherwise wouldn't be. So it does become a significant risk.

Now, at what point would you consider that risk to be of significant peril that some dramatic action needed to be taken, whether it was the nuclear option or advising doctors to immediately take patients off the medication?

Dr. VON ESCHENBACH. Well, you are pointing out, Congressman, an extremely important part of what FDA's role is in this whole process. First of all, it is to absolutely, critically, vigorously assess the scientific data. Do patient individual analyses, for example, the kinds of things you were alluding to. But then put that into a larger context. That brings into play what is the implication of that risk as it relates to the total population of patients with diabetes who might be affected.

Are there other alternatives that would be available to them that would get a benefit and perhaps at less risk? Or if there is no other option available, what risk do we deem is appropriate and under what circumstances? Can we advise doctors and patients to be more selective about who should, who should not get that particular treatment. That becomes an important part of our overall decisionmaking process to that end of both protect and promote the public health.

Mr. YARMUTH. And I am concerned because as we watch television commercials and we talk about warnings, at a certain point the public becomes numb to these things, because they really don't mean anything. But if you told me that if I went to the grocery in my car and I had a 2 percent risk of being in an accident, I might still take the chance. If I had a 10 percent risk of it, I might not drive my car to the grocery.

I am concerned that what information that FDA provides to the public and what we do here as well gives the public adequate explanation of the risks they are taking. Because for those 5,000 people presumably it was a 100 percent risk.

Dr. VON ESCHENBACH. Right. And to your point, we are attempting to do that even better than we have done it, as I indicated to you, the initiatives that we have with regard to risk communication, the vehicles that we use. But your point is extremely well taken. There are issues in which our decision will always be based on the standards of rigorous, scientific analysis, whether it is a drug for hay fever or whether it is a drug for diabetes or for cancer.

However, from the patient's perspective, the risk-benefit ratio is dramatically different, whether you are thinking about taking a drug for sniffles or whether you are taking a drug for terminal cancer for which there is no other option available to you. And that is an important part of this equation that we can't lose sight of.

Chairman WAXMAN. Thank you, Mr. Yarmuth.

Mr. YARMUTH. Thank you, Mr. Chairman.

Chairman WAXMAN. Mr. Hodes.

Mr. MCHENRY. Excuse me, Mr. Chairman? I have not been recognized.

Chairman WAXMAN. I didn't see you. You are recognized for your time.

Mr. MCHENRY. I appreciate it. At this time I would like to yield my time to my colleague from California, Mr. Issa.

Mr. ISSA. I thank you, Mr. McHenry. I just want to followup on two more things. I know you are going to be leaving shortly. Mr. Cannon's question, it sort of prompted my wanting to delve a little further.

If you have the study, the study at hand, the study that led to today's hearing, if you have a study taking out, and maybe this is a statistical question, but it doesn't seem like a complex one, taking out those in which nobody died of heart attack, in which nobody got a heart attack, if you take those out, by definition, you put them back in and the 43 percent becomes lower. We may not know how much lower, but significantly lower, isn't that correct, inevitably?

Dr. DAL PAN. Let me say, none of the three of us here is an expert on the statistics methods of——

Mr. ISSA. No, no, no, wait a second.

Dr. DAL PAN. But there are statistical issues——

Mr. ISSA. But let's—I only took 2 years in statistics in college. It doesn't make me a statistician, but I know that if you leave the zeroes out of a zero through 10 and you are averaging, you are going to get a lower amount if you put the zeroes in, isn't that right?

Dr. DAL PAN. One of the things our statistician is doing is to see if there are techniques that she could use to actually address that issue. I can say conclusively that it would make that risk go away, though.

Mr. ISSA. OK. Do you know of any reason, though, for leaving out those who did not suffer? I mean, other than promoting panic, other than getting people to think that this drug had a higher incidence of heart attack, is there any reason to leave out other groups who took the drug and didn't have heart attacks? Is there any valid

reason that you can think of, without knowing anything more than what we have heard today?

Dr. DAL PAN. I think it is the statistical issue. But then the issue then becomes looking at all the available data to put it together. But I think all these techniques have their statistical basis. And those statistical bases have to be respected to do the study.

Mr. ISSA. Well, maybe I will go back to what we did a couple of weeks ago. We did global warming. I happen to believe in global warming, I have been a promotor of reducing CO_2 emissions. But I am trying to understand, if I only took the days of the year that were cooler and I left out the days that were hotter, I could prove the earth is cooling, not heating. So I am a little shocked that you are not more concerned that a study published not for peer review but in fact published for the public and widely reported on and linked to this hearing today deliberately ignored those other patients who could have brought the number more to zero.

Dr. VON ESCHENBACH. Mr. Issa, I cannot comment on why and how this particular study was done and designed and developed. That is something for the author to comment on. But your point is extremely well taken, that with regard to a meta-analysis, it is well recognized that they are fraught with problems, statistical problems, in terms of how you do them. And in this case, whether you did fixed events or random events, in terms of how you analyze the information and data.

And that points out, whether it is this meta-analysis or any other meta-analysis, the problem and concern about making definitive, explicit decisions with regard to just a meta-analysis. You have to be mindful of the dangers that could involve. And that is why the FDA chose to go much further since we had individual patient data, which the author was not available to him. And we have expanded and used our expertise of our biostatisticians to take this to an appropriate level, which we are in the midst of doing right now.

Mr. ISSA. OK. I am going to yield back to the gentleman. I just want to make sure something gets in the record, though.

The American Enterprise Institute published something that I think says a lot about the author that we are going to hear from in a few minutes. The study's primary author, Cleveland Clinic cardiologist, Steven Nissen, admitted to the Wall Street Journal that he was in touch with Congress while preparing his analysis. Three days after the study was submitted to the New England Journal of Medicine and before it was published, the FDA Commissioner received a letter about Avandia from members of the House Energy and Commerce Committee that seemed to reference the New England Journal of Medicine study. I just want to make sure that is in the record, and I will yield back to the gentleman.

Mr. MCHENRY. I thank my friend from California.

Let me just ask a broader question, I would like you to touch on this. I know your struggles at the FDA to make sure that we have safe drugs on the market, there is a proper balance between patient safety and life-saving medicine. It is an ongoing struggle.

Do you think our regulatory hurdles are too high or just about right, or too low? There is a lot of debate going on right now and I know the chairman is very interested in this issue and actually

wants to increase the regulatory hurdles to get drugs on the market. I would like you all, all three of you, to comment upon this, on whether or not that is appropriate or our regulatory level to get a drug on the market, is about right or too high?

Dr. VON ESCHENBACH. Congressman, I believe that the regulatory levels are appropriate for the individual circumstances in which the regulatory barrier has to be extraordinarily high with regard to this risk and benefit ratio. I have alluded to that, the reasons why that might be the case whether you are dealing with hay fever or whether you are dealing with cancer.

So I think they have to be applicable to the individual situation and circumstance. I think it is important to point out, as I did in my oral testimony, that the world around us is radically changing, rapidly changing. Science and technology, the complexity of the products, the circumstances. We need, at the FDA, to continue to adapt and respond to those changes. The resources that we are looking forward to are designed to specifically enable us to do that and continuously improve.

So I think it is an issue of using the regulatory framework but continuously improving it and improving our ability to apply it. I think the standards are appropriate.

Chairman WAXMAN. The gentleman's time has expired.

Would Dr. Jenkins or Dr. Dal Pan like to respond to the question, or do you agree with Dr. von Eschenbach?

Dr. JENKINS. Congressman, I head the Office of New Drugs that makes these decisions every day. So my staff and I make these decisions every day. It is always a weighing, of balancing the certainty you know about the drug versus the uncertainty of things you don't know about the drug. I think we strike that balance very well and within the framework of the regulations and the statute that have been given to us by Congress to operate in. So I do think we have struck the right balance.

This is clearly a societal, public policy question as far as how much certainty do you need to know about a drug before you approve it, how much uncertainty are you willing to accept at the time of approval. You can never know everything about a drug at time of approval. I think it is a public policy debate about where that standard should be set. I think we adhere to the standard that has been set for us by Congress in the statute.

Chairman WAXMAN. Dr. Dal Pan.

Dr. DAL PAN. Let me just add on to what Dr. Jenkins has stated. There always is this residual uncertainty at a time when a drug is approved. I think for that reason, as Dr. von Eschenbach said, it is important to have a strong post-marketing system as well, to be able to monitor that uncertainty and come up with better understanding of the drug's risks as time goes on.

Chairman WAXMAN. Thank you.

Mr. Hodes.

Mr. HODES. Thank you, Mr. Chairman.

Gentlemen, thank you for your testimony. Much of the focus of this hearing has been on post-market surveillance, what does the FDA do after a drug is approved. I would like to direct your attention to a slightly different question. I am specifically concerned with what the FDA does to ensure the accuracy of the pharma-

ceutical direct to consumer drug ads after the company's drug has gone to market.

I note in Dr. von Eschenbach's written testimony the statement "In April 2006, the labeling for Avandia was updated to include new data in the warning section about a potential increase in heart attacks." That was the language you used, Dr. von Eschenbach.

There was questioning by my colleague Mr. Lynch about warnings. Now, yesterday, in both the New York Times and the Washington Post, GSK, the maker of the drug, took out full-page advertisements about Avandia. In fact, a page and a half in the New York Times, I have it here. I think you have it in front of you. There is a full page which has something on top, and then they have important safety information on the bottom. And then in another half page, there is the patient information.

Now, I am concerned about the gap we seem to have between concern about heart attacks and warnings about heart failure. Because if you are a consumer, plain ordinary guy like me, a heart attack means something very different than heart failure, which happens to be, could be the inability of the heart to pump blood, could be a long-term thing. Heart attack is a rather sudden and specific event.

Now, despite that you say there were label warnings for heart attacks, if I read the language in both the New York Times and the Washington Post, what I see is a warning that says if you have heart problems or heart failure, tell your doctor. Avandia can cause your body to keep extra fluid, which leads to swelling and weight gain. Well, that is a problem. Extra body fluid can make some heart problems worse or lead to heart failure. The word heart attack, which is what consumers understand, does not appear.

Now, GSK has spent $42 million on advertisements to consumers for Avandia. Its revenue has increased 25 percent in recent years. If I am right, and if this doesn't contain the concerns about heart attacks, do you believe that consumers understand this warning by GSK to be a warning that there is an increased risk of heart attacks from Avandia?

Dr. VON ESCHENBACH. No, sir, I do not believe that looking at an ad like this in a newspaper really helps to provide the kind of depth and understanding that you just described. I think that this does not occur by looking at these kinds of ads.

Mr. HODES. So this ad doesn't use the word heart attacks, does it?

Dr. VON ESCHENBACH. I haven't read the complete ad, sir, but I will take your word that it does not.

Mr. HODES. Because I am happy to represent to you with absolute assurance that it doesn't use the word heart attacks.

Dr. VON ESCHENBACH. I will accept that.

Mr. HODES. Now, in that light, if there is concern as we now know about the increased risk of heart attacks, and that is what you talked about in your testimony, that is what has now come out. And yesterday, this company is still not warning consumers about the increased risk of heart attacks.

My question to you, as the regulatory agency, is do you have enough power now to do something about the manufacturers and what they are doing with post-consumer advertising? Do you need

more power? Do you need different power? What needs to be done for you to adequately regulate how the manufacturers are communicating in simple, plain terms that consumers will understand?

Dr. VON ESCHENBACH. As part of the negotiations and discussions with regard to PDUFA IV reauthorization, which is currently in place, we have sought the resources to be able to expand our ability to review, survey and therefore take action against direct to consumer advertising.

Mr. HODES. Sir, with great respect, this reminds me of your answer to my colleague Mr. Tierney's question, when he asked you a direct question, you said, we are looking for more resources. Now, to me, resources means maybe people, maybe it means money. By resources, do you mean some more regulatory power that you currently do not have to interface with the drug manufacturers to make sure that they are doing what they need to do to tell consumers about the risks you are flagging?

Dr. VON ESCHENBACH. I believe right now the most serious concern for me is having adequate numbers of people to be able to monitor and take action against direct to consumer advertising when it is inappropriate. That for me is a major area that needs to be addressed.

The ability to then affect that, if that becomes a problem that requires legislation, is something that, as I indicated, I think we need to address. But I am not prepared at the present time to say that is absolutely the answer that I need in order to fix the concern or problem that is being raised.

Mr. HODES. I am not sure I understand you. If I may just follow-up briefly with one question. Are you telling me you don't have enough people to read this ad and see whether or not the ad adequately, in your expert opinion, warns the consumer of the increased risk of heart attack? Are you telling me you don't have enough people to do that?

Dr. VON ESCHENBACH. Yes, sir. I am telling you that I need more resources to be able to direct to the issue of the FDA's oversight of direct to consumer advertising.

Chairman WAXMAN. The gentleman's time has expired.

Mr. HODES. May I just have one last question, Mr. Chairman? Thank you.

You need more people to read the ad. Fine. Do you have the power that you need to say to the drug manufacturer, fix the ad?

Dr. VON ESCHENBACH. I believe at the present time I do have the ability to get that accomplished and get that done. I would certainly, if that is not adequate, after we have done our appropriate intervention, I would then welcome any legislative action that would require that to be a fix. But at this point in time, I don't believe that is at the core of the problem for me.

Mr. HODES. Thank you very much. Thank you, Mr. Chairman.

Chairman WAXMAN. Thank you, Mr. Hodes.

Ms. Watson.

Ms. WATSON. Thank you so much, and I thank the panelists for indulging us.

I too have the same concern. I myself have diabetes 2. I had a complete health examination before I took my post as Ambassador, no problems. Now I develop diabetes 2 after 2 years. All of a sud-

den, I had a heart murmur, a heart problem. I went to my cardiologist and he examined me, he said, what are you taking. Avandia. He said, get off of it. I myself, no history in the family. I have a history of diabetes, yes. He said, get off of Avandia. There are other options out there.

Now, here is my concern, listening to the testimony. Why has it taken FDA so long to come and say, we need more resources? Why did so much time pass after your approval? And the post-marketing studies seem to me to be a way to reduce the risks that millions of people are under in this country. I heard your response to Representative Hodes, I heard your response to Mr. Tierney.

But I didn't hear a plea to give us that authority. You ought to have heart attack on the label, because that would have been understood. It looked like I was heading toward just that when I went to my physician.

Dr. VON ESCHENBACH. I believe at the core and the heart of the question that you have just placed before me, Congresswoman, is the issue of the fact that we have attempted to provide information that when a doctor is caring for a patient such as yourself, and there seems to be a problem or concern, that is addressed. And it may require a change in your medicine.

Ms. WATSON. Doctor, let me take back my time because I will be out of it in just a second. Would you have anything against putting on the label, there is a high risk of heart attack?

Dr. VON ESCHENBACH. That is precisely what we are engaged in determining as we speak. The comprehensive analysis of all of the data related to heart attack, both from meta-analyses as well as other studies. And the deliberation that will occur at the advisory committee at the end of July will lead us to the answer to that specific question.

Ms. WATSON. All right. Thank you. The stakes are very high.

Dr. VON ESCHENBACH. I agree.

Ms. WATSON. And you represent us who give permission for these drugs to go on the market, and too many people are at risk.

Now, let me shift my questioning. I am an African American. And diabetes is spreading higher among African Americans and now Hispanic Americans than any other group. But I find there are too few of us in the test. So what can you do to be sure that Americans of all ethnicity become part of your test?

Dr. VON ESCHENBACH. I fully support and concur. We are approaching this from one, the perspective of working with, for example, our sister agency, the National Institutes of Health, to be able to promote the participation of more minorities and under-served in the clinical trials themselves. Two, we are approaching this from the perspective of I am engaging, with the National Medical Association and have met with them to lay out specific plans to address that issue, to bring representation from the African American community specifically into the FDA's processes. Participation in committees and the ability for us to address in the appropriate way the way in which the community believes is most appropriate and effective. But to get to the endpoint, we absolutely need to serve patients better by having them participate in these clinical trials.

Ms. WATSON. Thank you for that response. I just want to end up by saying, the American Diabetes Association had to be forced by

a group of us, I represent Los Angeles, to do outreach into these communities. So we had to hold our own outreach informational sessions, ourselves. So we need a whole reform in how we meet and reach Americans of various ethnicities.

Thank you, Mr. Chairman.

Chairman WAXMAN. Thank you very much, Ms. Watson.

Dr. Jenkins, Dr. Dal Pan, Dr. von Eschenbach, thank you very much for your appearance today and your willingness to answer the questions that we had to ask you. We are of course interested in the process used to inform the American public about the efficacy and safety of these drugs. I think your contribution today is helpful to us. We want to of course review this situation in the context of legislation that is pending in both the House and the Senate.

Dr. VON ESCHENBACH. Thank you, Mr. Chairman. On behalf of my colleagues and the entire FDA, let me thank you and the rest of the members of the committee for your consideration and your openness to our perspective. Thank you.

Chairman WAXMAN. Well, I was a little premature in thanking you and expecting that we would move on, because we have another distinguished member of our committee who is eager to ask questions. So I do want to recognize him. Mr. Cummings.

Mr. CUMMINGS. Thank you very much, Mr. Chairman.

Dr. von Eschenbach, I want to ask you about the actions of your press office over the past 2 weeks. On May 21st, the New England Journal of Medicine published an analysis of clinical trial data about Avandia that started a vigorous scientific and medical debate that continues today. The analysis provided a signal that Avandia may be associated with increased risk of heart attack. As you acknowledge in your written testimony, if confirmed, this signal "would be of significant concern, because patients with diabetes are already at an increased risk of heart disease."

You told us in your written testimony how the FDA is committed to "early communication of emerging information about the safety of drugs," stressing that "any communication must be responsible and measured, taking into account the impact that the message will have on patients and practitioners alike to encourage good health care choices and help avoid bad ones." This seems like an appropriate communication strategy.

What I want to know is why it was not followed in the case of Dr. Nissen, the author of the study in the New England Journal article.

Dr. VON ESCHENBACH. I am sorry, Mr. Cummings, could you be more specific about——

Mr. CUMMINGS. On May 24th, just 3 days after the publication of Dr. Nissen's analysis, at least two individuals in the FDA press office forwarded to reporters in the national media and trade press an article from the Web site, heart.org, that contains derogatory comments about Dr. Nissen. Specifically, the article contained accusations from an anonymous commenter to a blog posting in the Wall Street Journal that questioned Dr. Nissen's motives in undertaking and publishing his analysis, implying that he was only interested in hurting companies that did not work with him and the Cleveland Clinic.

The accusations were so baseless that the Web site itself later retracted the comments. It said that the accusations "do not meet the highest standards of journalistic or scientific integrity or credibility." Even worse, one of your press consultants, Douglas Aberfell [phonetically], sent out these articles with bizarre titles. One e-mail title was "What are St. Steven's feet made of? Clay, perhaps?"

Another one read, "Did you ask Nissen if the Pope called yet?" Are you familiar with this? Are you following me so far?

Dr. VON ESCHENBACH. Yes, sir, I understand the point that you are——

Mr. CUMMINGS. I would like to request that a copy of Mr. Aberfell's [phonetically] e-mail be included in the record, Mr. Chairman.

Mr. MCHENRY. Reserving the right to object.

Chairman WAXMAN. The gentleman reserves the right to object.

Mr. MCHENRY. I have not seen the e-mail. I would love to see a copy of the e-mail before I agree that this should be entered into the record.

Chairman WAXMAN. The gentleman will withhold his unanimous consent request and——

Mr. CUMMINGS. Very well.

Well, since I will have to work with what I have, do you believe that these actions represent responsible and measured communication to which your agency is committed?

Dr. VON ESCHENBACH. No, sir.

Mr. CUMMINGS. Let me finish. I am almost finished. Is it really an appropriate use of Federal, Federal taxpayer dollars to use the FDA press office as a vehicle for attacking scientists who raise important signals about potential public health dangers in prestigious scientific journals?

Dr. VON ESCHENBACH. Mr. Cummings, this was not an action on the part of the FDA or the FDA's press office. This was an action of an individual within the FDA. I completely concur with you that it is inappropriate and unacceptable. That individual's supervisor has taken appropriate action with that individual. I would not condone or accept that kind of behavior.

Mr. CUMMINGS. Is that individual still working with the Government?

Dr. VON ESCHENBACH. That individual is still employed by the Government. His action was addressed.

Mr. CUMMINGS. What action was taken?

Dr. VON ESCHENBACH. This action has been addressed by the individual's superior, a letter of reprimand is in his file.

Mr. CUMMINGS. But we are still paying him?

Dr. VON ESCHENBACH. It was an inappropriate and unfortunate action on the part of an individual, and I believe that is being appropriately addressed from a disciplinary point of view.

Mr. CUMMINGS. The medical experts who are appearing before this committee this morning have distinguished professional careers. They and their institutions should be proud of the work they have done. And we as a country should not tolerate efforts by either private or public entities that engage in intimidation and smear campaigns against experts who act in the service of the public.

Thank you very much.

Dr. VON ESCHENBACH. Thank you, Mr. Cummings. Let me reassure you and other members of the committee, there is absolutely no intention nor has there been any action on the part of the FDA to take and behave or participate in any kind of campaign with regard to Nissen. We have welcomed his information and his data as a part of our ongoing assessment and analysis. Although I have never had the opportunity to discuss things with him personally or directly, I would look forward to doing so at any time.

Chairman WAXMAN. Thank you, Mr. Cummings. Another Member seeks recognition, Mr. Shays.

Mr. SHAYS. Thank you, Mr. Chairman. I don't usually seek recognition when I have come so late in the panel and I don't have a question to ask, but I know that Mr. McHenry would like to ask a brief question, so I would yield to him.

Mr. MCHENRY. I thank my colleague.

I would like to followup with you and give you an opportunity to respond to this. With complex scientific research, it is important that a balanced perspective is given on a study that has been released? Is that an important function?

Dr. VON ESCHENBACH. Yes. Yes, it is.

Mr. MCHENRY. Now, an additional followup to this. Is it necessary for the FDA to perhaps, in order to quell overreaction about a release of a study, to provide a balanced perspective on that study?

Dr. VON ESCHENBACH. I believe the FDA must accept information and data from a variety of sources, analyze it appropriately and then take what we believe to be the appropriate action.

Mr. MCHENRY. An additional comment here. After the release of the study, there have been a number of articles written about the failure in the study. Is that something important for consumers to be aware of?

Dr. VON ESCHENBACH. I think it is important for everyone to be aware of balance and where there is legitimate scientific debate, that should be something that people are aware of. There were issues here where, for example, two journals that are each highly reputable had differing perspectives and points of view with regard to this particular study. I think that is an important part of an open and healthy dialog and discussion.

Mr. MCHENRY. Thank you. I yield back.

Mr. SHAYS. I yield back.

Chairman WAXMAN. Thank you very much again. Thank you, gentlemen, for your testimony. We appreciate your being here.

Dr. VON ESCHENBACH. Thank you, sir.

Chairman WAXMAN. We are now pleased to call forward for our second panel Dr. Steven Nissen, who is the chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic, one of the Nation's most respected academic medical centers. He is the immediate past president of the American College of Cardiology. And from 2000 to 2005, Dr. Nissen served as a member of the FDA's cardio-renal advisory panel and chaired the committee during his final year.

Dr. Nissen was the lead author of the May 21, 2007, New England Journal of Medicine article that drew a connection between Avandia and increased cardiac risks.

We have also Dr. Bruce M. Psaty, who is professor of medicine, epidemiology and health services and co-director of the cardiovascular health research unit at the University of Washington. From 2000 to 2006, he was a member of the Institute of Medicine's Committee on the Assessment of the U.S. Drug Safety System. Dr. Psaty was the lead author for the May 21st editorial in the New England Journal of Medicine, commenting on Dr. Nissen's study, and is a lead author of one of the June 5th editorials in the same journal commenting on the newly released RECORD study.

And Dr. John Buse is a professor of medicine at the University of North Carolina School of Medicine in Chapel Hill, NC, where he serves as the chief of the Division of Endocrinology. One of our Nation's most highly respected experts on diabetes care, Dr. Buse is president-elect of the American Diabetes Association. He has received numerous awards and honors, including citation in Best Doctors of America every year since 2001.

Dr. Buse was the first physician in the country to raise concerns about the cardiovascular safety of Avandia in a letter he wrote to the FDA in 2000.

We welcome the three of you. It is the practice of our committee to ask all witnesses to take an oath. I would like you to rise.

[Witnesses sworn.]

Chairman WAXMAN. The record will indicate that each of the witnesses answered in the affirmative.

Dr. Nissen, why don't we start with you. We have your full statements in the record. We would like to ask you to summarize your testimony in around 5 minutes. We have a clock that I hope will work appropriately to let you know. Yellow light means that 1 minute is left, red light means the time is up. We would like to ask you to, when you see the red light, to conclude.

There is a button on the base of the mic. Be sure it is pressed in. We want to hear from you.

Dr. Nissen.

STATEMENTS OF STEVEN NISSEN, M.D., F.A.C.C., CHAIRMAN, DEPARTMENT OF CARDIOVASCULAR MEDICINE, CLEVELAND CLINIC; JOHN B. BUSE, M.D., PH.D., PROFESSOR, UNIVERSITY OF NORTH CAROLINA SCHOOL OF MEDICINE; AND BRUCE M. PSATY, M.D., PH.D., CO-DIRECTOR, CARDIOVASCULAR HEALTH RESEARCH UNIT, PROFESSOR OF MEDICINE, EPIDEMIOLOGY AND HEALTH SERVICES, UNIVERSITY OF WASHINGTON, INVESTIGATOR, CENTER FOR HEALTH STUDIES, GROUP HEALTH, SEATTLE, WA

STATEMENT OF STEVEN NISSEN

Dr. NISSEN. Thank you very much, Mr. Waxman.

My name is Steven E. Nissen, M.D. I am chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic, and the immediate past president of the American College of Cardiology. My testimony does not reflect the views of either the Cleveland Clinic or the ACC.

Before I begin, I want to thank the committee, I want to thank the bipartisan efforts of this committee to look into issues of drug safety and the FDA. This is an extremely important issue. It affects all 300 million Americans, and I applaud you for looking into this. I think it is clearly the right thing to do.

I have been asked to summarize for the committee the sequence of events and the scientific basis for our manuscript describing the potential cardiovascular risks of Avandia. In September 2006, a clinical trial called DREAM was published in the British medical journal, the Lancet. In the study, patients at high risk for developing diabetes were assigned to receive either Avandia or an inactive placebo. Avandia did indeed reduce the incidence of new onset diabetes.

However, the DREAM study also showed a numerical excess of heart-related adverse events, including 15 heart attacks in the Avandia group compared with 9 in the placebo group. The number of heart attacks was too few to reach statistical significance, but they were trending in the wrong direction. This was potentially an important observation, because the reason for giving a drug to prevent diabetes is to reduce the complications of diabetes, the most serious of which is heart disease.

Then in December 2006, a clinical trial known as ADOPT was published in the New England Journal of Medicine. This study was designed to show whether Avandia had a more durable effect at reducing blood sugar than two generic diabetes medications. The study indeed showed a more long-lasting reduction in blood sugar with Avandia, but heart-related complications were also trending in the wrong direction. The heart attack rate was 33 percent greater in Avandia-treated patients, but again, there were too few events to reach statistical significance.

After reviewing DREAM and ADOPT, I was concerned, because these were the only long-term large-scale clinical trials comparing Avandia with other therapies. And both studies showed an excess of heart attacks. When you have several small or medium-size clinical trials that are insufficient to answer a scientific question, the logical next approach is to combine these trials to try to address the issue. This process is known as a meta-analysis.

Using this method, I asked one of my colleagues, a statistician, to combine DREAM and ADOPT. We noted a 40 percent excess of heart attacks, which was not statistically significant, but showed a strong trend in the wrong direction. And it was approaching statistical significance.

This observation was particularly concerning, because heart disease is highly prevalent in diabetics, comprising between 65 and 80 percent of all diabetic deaths. A diabetes drug that may increase the risk of heart disease would represent a potentially important public health concern.

We sought more data to objectively address this scientific question. Eventually we located on the FDA Web site the original group of clinical trials submitted to the agency to support approval of the drug in 1999. There were five clinical trials comparing Avandia to other diabetes drugs or placebo. We again noted that there were more heart-related complications in the Avandia treatment group

in these initial clinical trials. But we still did not have enough clinical trial data to form any reasonable scientific conclusions.

Eventually, in April 2007, we discovered a GlaxoSmithKline Web site that disclosed basic information and summary results for clinical trials conducted by the company. Now we had access to the heart attack and death rates for all relevant 42 Avandia clinical trials completed before or after drug approval. We competed the meta-analysis, which showed a 43 percent excess incidence of heart attack in Avandia-treated patients, which was statistically significant with a p value of 0.03. A p value of 03 means that there is a 97 percent probability that the results of the study are not due to chance alone. We submitted a manuscript reporting our findings to the New England Journal of Medicine, where the manuscript was peer-reviewed and published online on May 21, 2007.

In our manuscript, we were careful to point out the strengths and limitations of our analysis. Because our access to data was limited to publicly available clinical trial data, we could not analyze original patient-level information. In addition, as we pointed out, a meta-analysis is always less convincing than a large, prospective trial designed to answer a specific scientific question. Nonetheless, we thought the findings were sufficiently important to warrant prompt publication and concluded "Until more precise estimates of the cardiovascular risk of this treatment can be delineated in patients with diabetes, patients and providers should carefully consider the potential risks of rosiglitazone in the treatment of type 2 diabetes."

The same 42 trials that we included in our analysis are available to the company and to the FDA. Because both of these organizations have access to raw patient data, they can perform more statistically powerful analyses which can help clarify the extent of risk. GSK has reported the basic results of their own patient-level meta-analysis on their clinical trials Web site, which confirms a statistically significant increase in heart-related complications in patients who received Avandia.

The FDA also recently announced that their own internal analysis of patient-level data confirms an approximately 40 percent excess of heart-related complications. However, neither the GSK nor FDA analyses have been published and it is therefore not possible to directly compare the results for all three of these analyses.

I look forward to discussing these findings and the policy implications with the committee during the course of today's hearing.

[The prepared statement of Dr. Nissen follows:]

Oral Testimony to the House Committee on Oversight and Government Reform

My name is Steven E. Nissen, M.D. I am Chairman of the Department of Cardiovascular Medicine at Cleveland Clinic and the Immediate Past-President of the American College of Cardiology (ACC). My testimony does not reflect the views of either Cleveland Clinic or the ACC.

I have been asked to summarize for the Subcommittee the sequence of events and the scientific basis for our manuscript describing the potential cardiovascular risks of Avandia.

In September 2006, a clinical trial called DREAM was published in the British medical journal, the Lancet. In this study, patients at high risk for developing diabetes were assigned to receive either Avandia or an inactive placebo. Avandia did indeed reduce the incidence of new onset diabetes. However, the DREAM study also showed a numerical excess of heart-related adverse events, including 15 heart attacks in the Avandia group, compared with 9 in the placebo group. The number of heart attacks was too few to reach statistical significance, but they were trending in the wrong direction. This was potentially important observation because the reason for giving a drug to prevent diabetes is to reduce the complications of diabetes, the most serious of which is heart disease.

Then, in December 2006, a clinical trial known as ADOPT was published in the New England Journal of Medicine. This study was designed to show whether Avandia had a more durable effect at reducing blood sugar than two generic diabetes medications. The study showed a more long-lasting reduction in blood sugar with Avandia, but heart-related complications were also trending in the wrong direction. The heart attack rate was 33% greater in the Avandia-treated patients, but again, there were too few events to reach statistical significance.

After reviewing DREAM and ADOPT, I was concerned, because these were the only long-term, large scale clinical trials comparing Avandia with other therapies, and both studies showed an excess of heart attacks.

When you have several small or medium sized clinical trials that are insufficient to answer a scientific question, the logical next approach is to combine these trials to try to address the issue. The process is known as a meta-analysis. Using this method, I asked one of my colleagues, a statistician, to combine DREAM and ADOPT, and we noted a 40% excess of heart attacks, which was not statistically significant, but showed an strong trend in the wrong direction, which was approaching statistical significance. This observation was particularly concerning, because heart disease is highly prevalent in diabetics, comprising between 65% and 80% of all diabetic deaths. A diabetes drug that may increase the risk of heart disease would present a potentially important public health concern.

We sought more data to objectively address this scientific question. Eventually, we located on the FDA website, the original group of clinical trials submitted to the Agency to support approval of the drug in 1999. There were 5 clinical trials comparing Avandia to other diabetes drugs or placebo. We again noted that there were more heart-related complications in the Avandia treatment group in these initial clinical trials. But we still did not have enough clinical trial data to form any reasonable scientific conclusions.

Eventually in late April 2007, we discovered a GlaxoSmithKline website that disclosed basic information and summary results for clinical trials conducted by the company. Now we had access to the heart attack and death rates for all 42 relevant Avandia clinical trials completed before or after drug approval. We completed the meta-analysis, which showed a 43% excess incidence of heart attack in Avandia-treated patients, which was statistically significant with a p value of 0.03. A p value of 0.03 means that there is a 97% probability that the results of the study are not due to chance alone. We submitted a manuscript reporting our findings to the New England Journal of Medicine, where the manuscript was peer-reviewed and published on-line on May 21, 2007.

In our manuscript, we were careful to point out the strengths and limitations of our analysis. Because our access to data was limited to publicly available clinical trial data, we could not analyze original patient-level information. In addition, as we pointed out, a meta-analysis is always less convincing than a large prospective trial designed to answer a specific scientific question. Nonetheless, we thought the findings were sufficiently important to warrant prompt publication and concluded that "Until more precise estimates of the cardiovascular risk of this treatment can be delineated in patients with diabetes, patients and providers should carefully consider the potential risks of rosiglitazone in the treatment of type 2 diabetes."

The same 42 trials that we included in our analysis are available to the company and to the FDA. Because both of these organizations have access to raw patient data, they can perform more statistically powerful analyses, which can help clarify the extent of the risk. GSK has reported the basic results of their own patient-level meta-analysis on their clinical trials website, which confirms a statistically significant increase in heart-related complications in patients who received Avandia. The FDA also recently announced that their own internal analysis of patient-level data confirms an "approximately 40%" excess of heart related complications. However, neither the GSK, nor FDA analyses have been published, and it is therefore not possible to directly compare the results for all three analyses.

I look forward to discussing these findings and the policy implications with the Committee during the course of today's hearings.

Chairman WAXMAN. Thank you, Dr. Nissen.

Dr. Buse.

STATEMENT OF JOHN BUSE

Dr. BUSE. Chairman Waxman, members of the committee, it is really an honor to be called to testify before this committee. Before I tell you what I am really here for, I do want to make two introductory points as a matter of disclosure.

First, this statement and my testimony do not reflect the opinions of my employer, the University of North Carolina School of Medicine, nor the American Diabetes Association, a voluntary health agency for which I serve as an officer.

Second, I have been working in the glitazone class since approximately 1992. I have a number of conflicts of interest in that regard, and I have tried to expand those a bit in my written statement, but I don't want to go through that in detail, because of my time limitations.

So I do want to give some background as to how I got involved in this process. In June 1999, I was invited to give about six presentations at the American Diabetes Association meetings and the Endocrine Society's meetings, and dug around through the same databases with the same materials that Dr. Nissen spoke of earlier.

I was concerned about the potential of cardiovascular safety because of what I perceived to be an increase in cholesterol that was relatively specific to Avandia among the three agents that have been marketed in the United States, Avandia, Actos and Rezulin. Because of that, I looked for signals of cardiovascular safety and found a signal with regard to a comparison between Avandia and so-called active comparators in the initial Avandia data set.

I realized that was a potentially explosive issue, reviewed these data with colleagues and with scientists from SmithKline Beecham, the manufacturer of Avandia. Those discussions were very helpful. Couched with many caveats, in June 1999, on two occasions, I presented this information, including, among many, many things, this potential signal of increased risk of cardiovascular disease.

Subsequent to that, I received a phone call from an employee of SmithKline Beecham, suggesting that people in the company were very upset. I explained to him that I had discussed it with people in the company before. He mentioned that there was a notion that market capitalization of the company had decreased by approximately $4 billion, and that the company, there were people in the company that felt that I might be liable for that.

Similar discussions were held with the chairman of my department. And over the next few days, I made an agreement to sign a statement to be used with the investment community to clarify some of my statements and offered to help with further analysis with regard to this problem.

In March 2000, I was aware of ongoing discussions with the Food and Drug Administration regarding the safety of Rezulin. Because I was concerned about the safety of each of the agents for different reasons, I wanted to make sure that the Food and Drug Administration was careful in considering withdrawing one agent when we didn't have robust safety data with the other agents. So I made the FDA Commissioner aware of the concerns that I have just men-

tioned to you, and called for greater enforcement of marketing regulations, as well as additional trials.

By their very nature, the observations I made in 1999 and the more sophisticated analyses by Dr. Nissen are only useful to generate questions, not to provide answers. And the most important question is today, what should patients and doctors do with regard to Avandia. I think the data are sufficient that there is a reason for concern. But I think if a patient is very well controlled on Avandia with good cholesterol control, good blood pressure control, good diabetes control, that with the available data, there might be greater risk to switching than to staying. Unfortunately, most patients with diabetes are not well controlled across the board.

To be fair, there is no currently available drug for diabetes that is known to reduce cardiovascular risks. That said, there is certainly no diabetes drug that is marketed where we are aware of a signal to increase cardiovascular events, except for possibly Avandia. 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 make adequately powered, independently executed studies that examine 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.

Thank you.

[The prepared statement of Dr. Buse follows:]

Committee on Oversight and Government Reform
U.S. House of Representatives
John Buse, MD, PhD
June 6, 2007

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.

Chairman WAXMAN. Thank you very much, Dr. Buse.

Dr. Psaty.

STATEMENT OF BRUCE M. PSATY

Dr. PSATY. Mr. Chairman and members of the committee, my name is Bruce Psaty. I am a professor of medicine and epidemiology at the University of Washington. I wrote the New England Journal editorials that accompanied Dr. Nissen's meta-analysis and the GSK RECORD study. I also served on the IOM drug safety committee. This testimony reflects my professional views as a public health scientist.

The crisis in confidence about the safety of medicines in America, which started with the withdrawal of rofecoxib in September 2004, sadly still awaits resolution. The loss of confidence has created an explosive atmosphere around drug safety issues. The problems raised by Avandia, the subject of the hearing today, point to the importance of several recommendations made by the IOM committee. The FDA needs leadership and authority to require sponsors to conduct high quality post-market trials in a timely fashion. Public posting of clinical trial data was crucial to the identification of heart attack risk associated with Avandia. Direct to consumer advertising increases demand for drugs, some of which, like Avandia, may have been incompletely evaluated.

The FDA needs additional resources, preferably from general revenues rather than PDUFA funds. Joint authority for regulatory actions in the post-market setting is also essential for the Office of Surveillance and Epidemiology. Decisions about safety matters need to be turned over in part or in whole to a new group with a more robust public health focus.

Dr. Nissen conducted a meta-analysis, which is a method of summarizing previously conducted trials. In that analysis, Avandia was associated with a significant increase in the risk of heart attacks. In other words, Avandia increases the risk by about as much as the statin-lipid lowering drugs reduce the risk of heart attacks.

The main limitations of Dr. Nissen's meta-analysis were the quantity and quality of the available data. The responsibility for the limited availability of high quality data resides with GSK, which did not conduct studies to definitively address heart attack risk in a timely fashion. The regulatory history of Avandia includes several key missed opportunities. It was approved on the basis of the ability to lower blood glucose, because high levels of blood glucose increase the risks of vascular disease, a glucose-lowering drug is presumed to reduce the risk of a heart attack. Paradoxically, Avandia appears to increase rather than decrease this risk.

GSK did not make a serious effort to verify the presumed health benefits of Avandia in a timely fashion. The ADOPT and the DREAM trials focused largely on marketing questions and failed to address directly questions of heart attack risk or benefit.

For drugs that will be used by millions of people for many years, it is essential to document the benefits of therapies approved on the basis of surrogate endpoints. If sponsors do not voluntarily initiate large, long-term trials of public health importance, then the FDA needs the authority to insist that they do so in a timely fashion.

In August 2006, GSK provided the FDA and the European Medicines Agency, the European equivalent of the FDA, with the results of several studies, including a meta-analysis similar to Dr. Nissen's. By October 2006, the product labels in Europe were revised to include this information. There was no uproar in Europe at this time when the labels were revised. The product label in the United States still does not identify heart attack risk as a potential adverse event in the general population of diabetics.

It is not clear why the FDA failed to make this information public before Dr. Nissen's meta-analysis was published. The primary measure of regulatory success is the timeliness of information, warnings or withdrawals. With Avandia, FDA failed to warn or inform in a timely fashion.

GSK's RECORD study has several major limitations in design and conduct, and even if it continues to its planned conclusion, information about heart attack risk is likely to be incomplete. Last weekend, after incorporating the interim results of the RECORD trial into the meta-analysis, Avandia is still associated with a 33 percent increased risk of heart attack. The possibility of heart attack benefit seems remote, and there is statistically significant evidence of harm.

Late and incomplete evaluation of the health risks and benefits of drugs such as Avandia create concern, confusion and uncertainty among patients, physicians and policymakers. The House of Representatives, which is about to take up drug safety legislation, has a unique opportunity to prevent future drug safety problems and to reinvigorate an essential regulatory agency that has many outstanding scientists.

Thank you.

[The prepared statement of Dr. Psaty follows:]

Testimony of Bruce M. Psaty, M.D., Ph.D.
Before the House Committee on Oversight and Government Reform
June 6, 2007

Mr Chairman and members of the Committee,

My name is Bruce Psaty. I am a professor of medicine and epidemiology at the University of Washington. I wrote the NEJM editorials that accompanied Dr Nissen's meta-analysis and GlaxoSmithKline's RECORD trial (1-4). I also served on the IOM drug safety committee (5,6). This testimony reflects my professional views as a public-health scientist.

The crisis in confidence about the safety of medicines in America, which started with the withdrawal of rofecoxib in September 2004, sadly still awaits resolution. The problems raised by Avandia, the subject of the hearing today, point to the importance of several recommendations made by the IOM drug safety committee (5,6). The FDA needs the leadership and authority to require sponsors to conduct high-quality postmarket trials in a timely fashion. Public posting of clinical trial data was crucial to the identification of the heart-attack risk associated with Avandia. Direct-to-consumer advertising increases demand for drugs, some of which, like Avandia, may have been incompletely evaluated. The FDA needs additional resources, preferably from general revenues rather than PUDFA funds. Joint authority for regulatory actions in the postmarket setting is also essential for the Office of Surveillance and Epidemiology. Decisions about safety matters need to be turned over in part or in whole to new group with a more robust public health focus.

Dr Nissen conducted a meta-analysis, which is a method of summarizing the findings of previously conducted trials. In Dr Nissen's meta-analysis, Avandia was associated with a significant 43% increase in the risk of heart attacks. In other words, Avandia increases heart attack risk by about as much as the statin lipid-lowering drugs reduce heart attack risk.

The main limitations of Dr Nissen's meta-analysis were the quantity and quality of the available data. The responsibility for the limited availability of high-quality data resides with GlaxoSmithKline, which did not conduct studies to definitively address heart attack risk in a timely fashion. The regulatory history of Avandia includes several key missed opportunities.

Avandia was approved on the basis of its ability to lower blood glucose. Because high levels of glucose increase the risks of vascular disease, a glucose-lowering drug is presumed to reduce the risk of a heart attack. Paradoxically, Avandia appears to increase rather than decrease heart-attack risk.

GSK did not make a serious effort to verify the presumed health benefits of Avandia in a timely fashion. The ADOPT (7) and DREAM trials (8) focused largely on marketing questions and failed to address directly questions of heart-attack risk or

benefit.

For drugs that will be used by millions of people for many years, it is essential to document the health risks and benefits of new therapies approved on the basis of surrogate endpoints (9). Laboratory measures such as blood glucose must be converted into clinically meaningful outcomes (10). If sponsors do not voluntarily initiate large long-term trials of public health importance, then the FDA needs the authority to insist that they do so in a timely fashion.

In August 2006, GSK provided the FDA and the European Medicines Agency, the European equivalent of the FDA, with the results of several studies, including a meta-analysis (11) similar to Dr Nissen's. By October 2006, the product labels in Europe were revised to include this information (12). The US product label still does not identify heart attack as a potential adverse reaction in the general population of diabetics.

It is not clear why FDA failed to make this information public before Dr Nissen's meta-analysis was published. The primary measure of regulatory success is the timeliness of information, warnings, or withdrawals. With Avandia, FDA failed to warn or inform in a timely fashion.

GSK's RECORD study has several major limitations in design and conduct (4), and even if it continues to its planned conclusion, information about heart attack risk from the RECORD trial is likely to be incomplete. After incorporating the interim results of the RECORD trial into the meta-analysis, Avandia is still associated with a significant 33% increase in the heart-attack risk (4). The possibility of heart-attack benefit remains remote, and there is still statistically significant evidence of harm.

Late and incomplete evaluations of the health risks and benefits of drugs such as Avandia create confusion and uncertainty among patients, physicians, and policy makers. The House of Representatives, which is about to take up drug-safety legislation, has a unique opportunity to prevent future drug-safety problems and reinvigorate an essential regulatory agency that has many outstanding scientists.

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June 4, 2007

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Chairman WAXMAN. Thank you very much, Dr. Psaty.

I will start the questioning of the three of you. I appreciate your being here.

Dr. Buse, I would like to start with you, because as far as I can determine you were the first outside person, outside of FDA, to suggest that there be a post-marketing trial to determine the risk of heart attacks and stroke in patients that were taking Avandia. Specifically, you recommended that the FDA should "encourage cardiovascular in high-risk populations, particularly with Avandia, where I believe there is ample cause for concern."

You sent that letter to FDA. What response did you get from the FDA?

Dr. BUSE. I actually don't remember getting any specific response. I may have gotten a letter saying thank you for the letter. But I don't remember, I certainly don't believe, our specific discussion in this regard. I do run into people from the FDA from time to time, and have had numerous conversations with them over the years. But nothing that specifically responded to my letter.

Chairman WAXMAN. Well, unfortunately, the FDA did not require Avandia's manufacturer to conduct the type of post-marketing trial you recommended. And here we are 8 years later, without that trial having been done, so that we know exactly what kind of risks people are taking.

Why are we in this situation? Do you have any idea of what went on in FDA? Dr. von Eschenbach said that they asked for a study that would have included that. And that was the ADOPT and the DREAM studies. Did those studies give us the answers we needed for this issue?

Dr. BUSE. No. As Dr. Nissen indicated, if anything, they suggested a trend toward risk of cardiovascular disease. In fact, the ADOPT study I don't think adjudicated or very carefully looked at heart attacks. I think it was more carefully looked at in DREAM. But both of those studies were fairly low-risk people, not the high-risk cardiovascular patients where my concerns were greatest. And even the RECORD study that Dr. Psaty mentioned is a fairly low-risk, though higher risk than DREAM and ADOPT.

Chairman WAXMAN. I believe that part of the problem is that the FDA can't insist that a study be conducted. It can only request it. They can negotiate before the drug is approved that a study be done. But then if the company doesn't do the study, and in fact most of them don't do the studies they commit to, then the only recourse the FDA has as an option is to take the drug off the market, which seems to me is sometimes called a nuclear option, because it deprives people of medicines that they are using and they are relying on.

Dr. Nissen, you did this meta-analysis. You or your people informed us that you were doing such an analysis, but we didn't tell you to do it, and we didn't tell the New England Journal of Medicine to publish it, did we?

Dr. NISSEN. No, and you didn't get to see the manuscript until everybody else got to see it, when it was published.

Chairman WAXMAN. Do you agree with Dr. Buse that it is going to be years before we get the result of an appropriately powered cardiovascular outcomes study with Avandia that is likely to pro-

vide an answer to the questions raised in your study, the questions that he has raised?

Dr. NISSEN. I did get a look at the RECORD interim results that were published yesterday by the New England Journal of Medicine. I agree with Dr. Buse that as currently designed, the RECORD study is unlikely to give an answer even when it is completed in 2009. And since it is the major ongoing cardiovascular outcome study, I think the answer is that we will be unlikely to have a definitive answer, even when it is completed in 2009.

Chairman WAXMAN. Dr. Psaty, how can we avoid this kind of problem in the future with drugs? It is going to take so long before a specific study can be actually done and give us the information we need.

Dr. PSATY. I think they can be started earlier and designed well. It is not clear to me whether the FDA didn't ask for the right study or whether the company didn't want to do it. So I don't know what happened in those sorts of negotiations. But clearly there were concerns about cardiovascular events. Then they do a trial where they don't adjudicate cardiovascular events. And if you want to not find an answer, that is a way to do it.

So we need the FDA, the FDA needs the authority to be able to determine the appropriate design and to insist that the company's conduct these studies in a timely fashion.

Chairman WAXMAN. I went through a number of timeframes when the FDA had the signal that they ought to be looking at this issue, starting with their own reviewer who approved the drug, Dr. Buse's letter, others who were raising concerns. It doesn't appear to me that until Dr. Nissen's mega-study was published in the New England Journal of Medicine have we seen real action by the FDA on this matter. I hope we can avoid this kind of problem in the future.

Dr. PSATY. Part of the problem is that the way things are set up now is we have, the FDA does a terrific job evaluating drugs in the pre-approval setting. And then they are approved and then it is marketing. And it is partly the responsibility of Congress, who set up PDUFA and prevented FDA from using any of these funds for drug safety for the first 10 years. We need additional attention to drug safety. It needs additional funding. And there needs to be a lot of work that takes place after the approval process.

Chairman WAXMAN. Thank you very much.

Mr. McHenry.

Mr. MCHENRY. Thank you, Mr. Chairman.

Dr. Nissen, you outline in your testimony a timeline of when you found, when you started going through the whole process. At what point did you begin your conversations with Chairman Waxman and his staff?

Dr. NISSEN. In February, I had looked at the DREAM and the ADOPT study. But I didn't have enough information to actually answer the question scientifically.

I wasn't aware that there was a Web site in the United Kingdom where GSK had disclosed the results of all their trials. So I really had an incomplete set of data. At the time, I was discussing with various members in various congressional committees the pending legislation around the similar version of the Kennedy-Enzi bill on

the House side. So I mentioned to them that I had concerns about the cardiovascular safety of Avandia and actually requested their assistance.

Mr. MCHENRY. So February?

Dr. NISSEN. In February. Requested their assistance in getting access to the data. I had essentially a scientific mystery. I didn't have the means to answer the question in a robust, scientific way, and I really was looking for help to be able to do that. I was looking to see whether they could use their influence and authority——

Mr. MCHENRY. Did you provide your interim results to them?

Dr. NISSEN. Well, to get access to any source of information. I was really inquiring, was there anything that the Congress could do——

Mr. MCHENRY. I am going to another question. Did you provide your interim analysis results to any member of the Hill or staff?

Dr. NISSEN. No. There were no interim results. Basically what we had done is, we had a very preliminary analysis, nothing formal.

Mr. MCHENRY. Did you provide your preliminary analysis to people on the Hill?

Dr. NISSEN. I did show them a preliminary analysis, yes. That's correct. Yes.

Mr. MCHENRY. At what point did you have that and did you share it with Mr. Waxman's staff?

Dr. NISSEN. Some time in February.

Mr. MCHENRY. February.

Dr. NISSEN. Yes.

Mr. MCHENRY. So they were aware of what you were going through the process of?

Dr. NISSEN. They were aware of what I was working on, yes.

Mr. MCHENRY. Why didn't you discuss your preliminary analysis with the Food and Drug Administration?

Dr. NISSEN. Well, the Food and Drug Administration had all of these studies already. Remember that when you do a study, you submit a study report to the FDA.

Mr. MCHENRY. But you were actually submitting to a medical journal a new study with meta-analysis, which is aggregating what was already public. So you proffer your work as original, do you not?

Dr. NISSEN. It is original.

Mr. MCHENRY. OK, then, why didn't you share that study with the Food and Drug Administration? After all, as Members of Congress, we have a regulatory structure that we put in place for drug safety. Why didn't you go to the FDA with that analysis?

Dr. NISSEN. This is not how it is done. We have to peer review——

Mr. MCHENRY. So going to Capitol Hill for a political purpose to get publicity here in a hearing is actually the way it is done? That's really medical research——

Dr. NISSEN. With all due respect, sir, this is about patients. It is not about politics.

Mr. MCHENRY. If it is about patients, why would you not go to the regulator who has the authority and oversight for drug safety?

Dr. NISSEN. Please let me finish. This is about patients, not politics. I had an incomplete result. I was looking for assistance to complete the study. When it was completed, I did what any scientist would do. I sent that for peer review and for publication. Why? Because it is my scientific, it is my ethical and it is my moral obligation to put such information into the public domain, so that other physicians, other scientists providers, and patients can consider our findings when making choices about drugs.

Mr. MCHENRY. Thank you, Dr. Nissen.

My additional question would be, what peers do you have on the Oversight and Government Reform staff for the Democrat staff? Because you shared your findings with them. Is that what you consider peer review? Is that what you consider putting patients above politics?

Dr. NISSEN. I did not give a copy of my manuscript to this committee or anybody else until it was published.

Mr. MCHENRY. Did you provide your initial analysis——

Dr. NISSEN. I provided preliminary suggest—I looked at the two trial——

Mr. MCHENRY. Did you provide a draft of your——

Dr. NISSEN. You are interrupting me, sir. I really would love to be able to answer your questions.

I provided a preliminary analysis.

Mr. ISSA. I would ask unanimous consent for two additional minutes so that this can go on appropriately without——

Chairman WAXMAN. No, the gentleman has his time and he still has time left.

Mr. ISSA. Then your time is limited.

Mr. MCHENRY. Well, my time is limited. And did the editors at the New England Journal of Medicine know that you shared this analysis with members of the Hill before?

Dr. NISSEN. I don't know what they knew or they didn't know. I submitted the manuscript to them.

Mr. MCHENRY. So, OK, as a final moment here, because I know the chairman will rap me down here, it seems very peculiar to me that if you are considering the patients first that you would not go to the regulator who is overseeing drug safety, that you would go to Capitol Hill, which as we know is a political body, and we don't have the authority to take a drug off the market, the FDA does. So you can respond to that if you like, but my time is up and I yield back the balance of my time.

Dr. NISSEN. I would like to respond if I could. The regulatory agency had all of the data that I had and much, much more. So what I had was a much more limited look at the data than what the FDA already had. It would make no sense for me to take study level data and submit it to the FDA when they already had the patient level data. So I would not have given them anything they hadn't had for many, many months.

Chairman WAXMAN. The gentleman's time is expired. Mr. Yarmuth is now recognized. I would request that the gentleman yield to me for just 30 seconds to ask the following question. You came to a number of committees, Democratic and Republican members of those committees, is that true?

Dr. NISSEN. That is correct.

Chairman WAXMAN. And you asked for help to get data to complete your evaluation. Did you get any help from anybody on the Hill?

Dr. NISSEN. No.

Chairman WAXMAN. And wasn't that the reason you came to the committees of the Congress?

Dr. NISSEN. Absolutely.

Chairman WAXMAN. OK, thanks. The gentleman is recognized.

Mr. YARMUTH. Thank you, Mr. Chairman. I would like to address a question to Dr. Buse and I understand that you have a very significant family event tonight, a commencement, and you have to leave early. So I want to get this question in. I congratulate you on that.

In your written testimony, you state that as far back as 1999, you had concerns about Avandia based on your analysis of the initial approval studies and your knowledge that Avandia might increase levels of bad cholesterol. You explained that you had discussed your concerns at a professional meeting in 1999, and that after you did that, you came under a great deal of fire and pressure from the manufacturer at the time, SmithKline Beecham, which is now GlaxoSmithKline.

You said that company representatives complained to your department chair. Exactly what did they say to him?

Dr. BUSE. There was a high-ranking member of the company that had a longstanding professional relationship before he joined the company with my chairman. And I don't know the details of the conversation. But it was characterized to me as being disturbing, and the two phrases that I remember, or three phrases, one involved that number, $4 billion. The second was that I was characterized as a liar. And the third was that I was characterized as being for sale.

Mr. YARMUTH. Was this something that happened frequently in your capacity as a researcher?

Dr. BUSE. No. That was a fairly unique experience.

Mr. YARMUTH. Was the company in any position to exert any specific pressure on you or your chair or the University of North Carolina? Were they funding research through UNC?

Dr. BUSE. I don't know the answer to that question at all.

Mr. YARMUTH. Was there any evidence, you mentioned the $4 billion figure as to reduction of market capitalization, was there any basis for that statement? Had the stock actually taken a hit?

Dr. BUSE. I didn't bother to look.

Mr. YARMUTH. That would be a lot of money on a professor's salary, though, wouldn't it?

Dr. BUSE. It would take a while. [Laughter.]

Mr. YARMUTH. You also testified that following those conversations with your department chair that you signed a clarifying statement. Was that statement something that you wrote or did the company prepare that?

Dr. BUSE. The company prepared it.

Mr. YARMUTH. During this committee's preparation, we requested documents from GSK relating to their meetings and dealings with you. In response, they supplied a copy of a three and a half page fax you sent to a Dr. Yamada, the company's chairman

of pharmaceutical research and development at the time. Do you recall writing this letter?

Dr. BUSE. I recall agonizing about writing that letter.

Mr. YARMUTH. I would like to request unanimous consent that a copy of the letter be included in the record, Mr. Chairman.

Chairman WAXMAN. Without objection, that will be the order.

[The information referred to follows:]

Facsimile

From: John B. Buse, MD, PhD, CDE
UNC Diabetes Care Center
5316 Highgate Drive, Suite 221
Durham, NC 27713
Telephone (Katie): 9
Fax:
Pager 8
E-mail:

To: Tadataka Yamada, MD
SmithKline Beecham
Chairman, Research and Development, Pharmaceuticals

Page 1 of 5

Dear Dr. Yamada:

I wanted to set the record straight regarding all the phone calls and questions I have received regarding one minute of a 25 minute presentation at a CME symposium sponsored by Lilly at which I was asked to present a talk on new therapies in diabetes by Dr. Alain Baron on behalf of Indiana University Office of CME. In case you have not heard, I have signed a statement "To whom it may concern" clarifying my presentation and sent it to James Huang out of respect to your company's "equity interest". In light of the nature of your communication with my chairman, I hope that you will do me the courtesy of reading this letter in its entirety at some point. I know you are busy and thus an "executive summary" is provided in the next to the last paragraph.

First, I want you to know that I went to extraordinary ends to try to understand the class of drugs and the available data prior to my presentation. I reviewed every paper published (and available in our library) on the thiazolidinedione class in humans (and many of the animal studies). I reviewed all the data slides presented at the FDA in the March and April meetings on the class of drugs. I reviewed the abstracts on the human trials at the ADA meeting and the Endocrine Society in detail. I spoke with the principals (investigators and marketing directors) at SB, Takeda and Parke-Davis. (Lilly was out of the loop in this process entirely as they do not primarily hold the pioglitazone data set.) In fact I discussed with James Huang and Elizabeth Rappaport of SB (as well as local and regional SB representatives) my impressions and concerns in the context of upcoming presentations at the Endocrine Society and ADA meetings by phone two weeks before the presentation in question and in person a week later in two separate meetings in San Diego to make sure that I understood the issues. I showed the slides that I had prepared to multiple colleagues and modified them several times over a period of about a week based on their suggestions. The slides that the SB sales representatives who attended this symposium apparently found offensive were made by me at my own expense without any assistance. I did substitute some professionally made data slides provided by Takeda for the ones that I had made on PowerPoint the night before the presentation based purely on aesthetics and not on content. I spent at least 40 hours (nights and weekends) preparing for this one lecture at the ADA meeting. In preparing a talk to be presented at a national meeting of my peers I agonize over how I

can tell them something that they cannot easily find out by reading an abstract or listening to someone else's presentation. People want to hear me (or any other "opinion leader") because of the information digested and assimilated not because I am capable of regurgitating it with excellence. I may over compensate as I do not think that I am a particularly good public speaker. I took the task of making that presentation and the other six presentations (sponsored by the Endocrine Society, Lilly insulin people, Hoechst Marion Roussel all under CME guidelines) that I was asked to make at the ADA and the Endocrine Society very seriously and received good reviews I believe becuase I do try to think ahead of the curve.

Now, I may have not explained the issues at that presentation as well as I could have if I had more time, but that may not be the good news. I would like you to know exactly what my concerns are regarding rosiglitazone as a clinical scientist and my approach as a clinician. On the basis of the increase in LDL concentration seen in the clinical trial program (whether the number we accept as the truth is the 18.6% at 4 mg bid in the package insert or the "average of 12%" now being discussed) one would expect an increase in cardiovascular events. If there had been a decrease in triglycerides or convincing evidence that it is was associated with an increase in particle size or no change in particle number, as is the case with fibrates (and arguably the other thiazolidinediones) it would have been an open question (as raised by many when troglitazone was launched). Based on this reasoning, I believe as a clinical scientist that the null hypothesis should be that rosiglitazone has the potential to increase cardiovascular events. Based on studies with statins and plasmapheresis, changes in LDL concentration can be associated with substantial changes in vascular reactivity and endothelial function over a time course of days to weeks. The increase in cardiovascular deaths and ischemic heart events are the relevant endpoints to be examined in the clinical trial program if one were to look for those kinds of changes in endothelial function. The event rate among all comparators is arguably the most relevant comparison group available from the data presented at the FDA hearing. (The event rate in the period of active comparison in both groups [4-6 months] would have been even better.) I know and fully agree that the effects seen are not even close to statistically significant (as I stated) and not different from effects seen with other anti-diabetic drugs (as I also stated). It may have been imprudent of me to say that they were increased 50% (which they are) instead of presenting the actual numbers and letting people do the math in their head, but I was trying to fit two hours worth of data into twenty minutes. That was a snap decision that I made realizing that I was going over the allotted 25 minutes and I regret that decision as it probably only saved me thirty seconds then and cost me ten hours since. I personally have told my patients in whom I have prescribed rosiglitazone that we will need to treat their LDL to a target of <100 mg/dl and TG < 150 mg/dl (as we recommend and usually do for all patients) and that if they do not have at least a 0.5% reduction of hemoglobin A1c at 4 mg bid, that I would recommend stopping the drug. I strongly believe that the rosiglitazone data set supports this kind of clinical decision making. I believe that caution is required until additional data are available.

Finally, before suggesting what I hope will be the nature of SB and my relationship in the future, I would like to convince you that you will never meet a person who is more open minded and less prone to being "bought" by anyone than I. I have devoted my career to not only increasing my personal understanding of the therapy of diabetes through both research and clinical practice. I am the son of two diabetologists. My father was the first endocrinologist in the state of South Carolina and widely regarded as a consummate academic physician and teacher. My mother has had the same R01 grant for over 40 years and is rumored to have the longest running grant at NIDDK. I have very large shoes to fill and work very hard to fill them. I spend a great deal of time trying to increase public awareness and provider competence in diabetes giving approximately 100 oral presentations a

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year. Approximately 60% of those are provided with minimal honoraria (<$100) including many in which I do not even receiving reimbursement for my personal expenses despite substantial personal sacrifice. I do get paid an honorarium of between $500 and $2000 for the other 40 or so talks I give a year. The majority of these presentations are sponsored by CME providers. Some are sponsored directly by the pharmaceutical industry. To my knowledge, I have spoken for every company that markets drugs for diabetes in the U.S. except SB. In fact, I have been offered many times to speak for SB but have only accepted one offer (as I am trying to get my partner who will be the first author on the Jack Gerich rosiglitazone clamp studies to get out on the road more and as she has much greater experience than I do with the drug as a result of her study in Rochester). In fact, in my career I have probably received less personally or for the UNC Diabetes Center from Lilly or Takeda than any other company in the United States. To this date, I am sure that I have received more support from SB than Takeda and Lilly combined. I have been to as many or more consultant meetings for SmithKline than for Lilly or Takeda. I was not upset when my chairman called me into his office to tell me that some in your company perceive me as being "for sale" as he knows me well enough to doubt it. I will take tremendous offense to hear about it from others who know me less well as it is obviously not supported by any reasonable understanding of the facts and arguably libelous.

I assume that you can tell that I am angry. It is not because of what has been said or the implied threats of lawsuits that I have heard from my chairman and James Huang, but because of the amount of time I have spent trying to understand the issues, giving people every opportunity to explain to me why my perceptions are illogical, and then having to spend more hours trying to deal with the consequences of my understanding of the issues. The thing that really ticks me off is that I went through this when troglitazone was launched. I publicly stated on many occasions that I thought it was incredible that there was no LFT monitoring requirement from the FDA, that the drug was associated with weight gain and that it was only going to be modestly effective as monotherapy based on a similar detailed analysis of all available data (and I had more access for troglitazone as I had conducted about 5 trials and written or reviewed two or three papers for them). The same dance that we are now engaged in occurred with Parke-Davis in 1997. It took about a year for the marketing people to get over it and to realize that I was right. Now I am their best friend and I have not changed my belief that they have a lovely drug, warts and all, that can be used safely and effectively with certain stipulations.

I hope a similar process will play out with SB with regards to rosiglitazone. I have offered to everyone that I have spoken to that I am happy to help me (and in that process hopefully SB and others) understand what is going on with regards to the vascular system in the setting of rosiglitazone therapy. There is a bunch of data out there that suggests that there are major differences in the genes activated between the drugs in this class. My strongest of all opinions is that head to head studies need to be done and that they will be done. I am afraid that if SB does not set the agenda in this regard, others will and it will further develop the case that this potential Achilles' heel is in fact a real vulnerability of the drug. There are hints which can be read between the lines of presentations that I have heard at SB consultants' meetings which should raise questions and suggest studies if one were inclined to believe the null hypothesis I propose a few paragraphs above is relevant. I am happy and anxious to continue giving SB and your marketing partner BMS my five cents worth regarding these issues for free. I want a safe thiazolidinedione more than anyone does. To establish rosiglitazone's safety will require studies designed to test the hypothesis and not innuendo and marketing "spin" on data. I am also very afraid that if another drug in this class turns out to have a major issue which was in hindsight preventable, the call of people like Michael Stern to hold diabetes/obesity drugs to the

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standard of statistically significant outcomes studies with hard endpoints may seem more reasonable to the detriment of us all and our clients/patients.

Executive Summary: I work very hard and am both serious and creative. I may disagree with SB's interpretation of data. I am not for sale. I am anxious to help in any way that I can to establish rosiglitazone as a safe and effective antidiabetic agent with certain stipulations. I cannot change my opinions in the absence of new data or understanding, in large part because I am not for sale. I look forward to working with SB in the future, but will understand and not take offence if I do not. Please call off the dogs. I cannot remain civilized much longer under this kind of heat. Fortunately, I will be out of the country for three weeks on vacation starting on Friday.

I apologize for my lack of brevity in written communication (Fred Sparling has noted that frequently) and thank you for giving me the chance to respond to your company's concerns. Feel free to share this with anyone that you like.

Sincerely,

John B. Buse, MD, PhD, CDE
Associate Professor of Medicine
Director, Diabetes Care Center

Cc: Fred Sparling, Chairman of Medicine, UNC
James Huang, Product Director, SB

Enc: "To whom it may concern" letter

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Mr. YARMUTH. I would also like to read an excerpt from the letter. It says, "I may disagree with SB's, that is SmithKline Beecham's, interpretation of the data. I am not for sale. I am anxious to help in any way that I can to establish Avandia as a safe and effective anti-diabetic agent with certain stipulations. I cannot change my opinions in the absence of new data or understanding, in large part because I am not for sale. I look forward to working with SB in the future, but will understand and not take offense if I do not. Please call off the dogs. I cannot remain civilized much longer under this kind of heat."

Dr. Buse, I regret that you were the subject of this type of intimidation. I certainly hope it has not recurred since you sent that letter. It goes without saying that this type of conduct is completely unacceptable. We can't have a post-market regulatory environment in which manufacturers attempt to intimidate science. So I thank you for your testimony.

Dr. BUSE. If I could just add to that. I do think that most of the really ugly bits of that interaction were out of frustration, anger of a limited number of individuals who felt that they were trying to be forthright in presenting the data with regard to their drug. I have not had issues since then.

Mr. YARMUTH. That is comforting. I yield back.

Chairman WAXMAN. Mr. Cannon.

Mr. CANNON. I apologize, we have a markup on energy, in the Committee on Natural Resources. So I have been back and forth, and I apologize for not being here more. I note that you lose your entire status if you leave the dais for a few minutes here.

Thanks for coming. I think you were here earlier when I was questioning Dr. von Eschenbach. My concern in this process is sensationalization. I think, Dr. Nissen, we probably agree that the FDA can do things differently and better. But in this process, it has become, I think, well, at least sensational.

Do you buy stocks yourself, Dr. Nissen?

Dr. NISSEN. I do not.

Mr. CANNON. Do you have friends that do?

Dr. NISSEN. I am sure I do, but I don't know what they own.

Mr. CANNON. And of course, that is not what we care about really. Are you familiar with what has happened to various drug stocks when they have been politicized over, say, the last 8 or 10 years?

Dr. NISSEN. I really don't follow the stock market.

Mr. CANNON. When the Clintons took over the Presidency, and Mrs. Clinton did her exercise in oversight of the health care system, she announced at one point that the drug companies were the villains and that the administration was going to go after them. Do you have any idea what happened to the stock price of those companies?

Dr. NISSEN. I don't.

Mr. CANNON. Oh, you have to.

Dr. NISSEN. Pardon?

Mr. CANNON. You have to have an idea. It didn't go up, of course.

Dr. NISSEN. Well, again, I don't know. I am not an expert on stock prices.

Mr. CANNON. Stock prices fell by about half in that period of time. Then about 2 weeks later she came out and announced that

the drug companies weren't really the problem and stock prices went up, back to their normal state. A huge, multi-billion dollar transition in a market we try to keep stable and we try to have it work for other reasons.

Have you taken a look at or considered what has happened to GlaxoSmithKline's stock?

Dr. NISSEN. I have seen news articles to the extent that the stock prices dropped.

Mr. CANNON. Do you know how much?

Dr. NISSEN. I don't have specific figures.

Mr. CANNON. It dropped about 20 percent. About that, in that range, over one study that is at least, I don't think either of you would say that the study is definitive. There are certainly a whole bunch of questions that the study raises. Do you have a concern about the kind of sensationalism that results in a 20 percent stock movement?

Dr. NISSEN. As a physician-scientist, and first of all, I respect your perspective, Mr. Cannon, but as a physician-scientist, I have to ask different sets of questions. I did have concerns about publishing the study and I did have concerns about how it would be interpreted. So I have three questions I have to ask before publishing a study: is it scientifically sound, did I use the right methods, did I consider alternatives and did I do a good job.

Mr. CANNON. And everybody agrees that you are very good at that, by the way.

Dr. NISSEN. Thank you. But we can make mistakes. So——

Mr. CANNON. Sure, so that is why we have a peer-review process.

Dr. NISSEN. That is exactly right.

Mr. CANNON. Oh, I didn't think about that, let's go back. But in your case, this case, it was probably not a mistake. You had studies that GlaxoSmithKline had already done.

Dr. NISSEN. Yes.

Mr. CANNON. Their data was available online, it was not anything that was being hidden, by any means. So it was a study of various studies and a lot of assumptions were made in the process, and we came up with a signal.

Dr. NISSEN. That is right. So the first question is scientific, and the second question is, is it ethical and moral, is it appropriate. And I knew that when we published this that it would in fact, there would be concerns on the part of patients, that people would be potentially frightened. As a consequence I tried to be as measured as I could in how I wrote the manuscript. I really would encourage everybody to read what I said.

Mr. CANNON. I understand that, and apparently I have missed some of the discussion here. But there is some question about whether or not you came to the committee, majority staff, and talked to them about this issue.

Dr. NISSEN. What I told them earlier is that I did not share the manuscript. I did tell them I was working on it, I told them I had concerns. But ultimately, what I wanted to have happen was, we had to make a scientific judgment. We came to the judgment. I had to make an ethical and a moral judgment.

Let me tell you what the alternative was. And it was an alternative I considered. The alternative would be not to publish, to

come to the conclusions and say, gee, this is so explosive that I just won't put it out there. And I did plenty of soul-searching. And I realized that I had absolute, absolute ethical and moral obligation to——

Mr. CANNON. My time is almost gone. Can I just ask this, didn't the FDA have that obligation as an institution, and wouldn't it have been as well to have gone to them and talked to them about the issue?

Dr. NISSEN. Well, the FDA, Mr. Cannon, I think has that responsibility, and I recognize that. The FDA, however, had the same data that I had.

Mr. CANNON. Right.

Dr. NISSEN. They actually had more data than I had. As I was explaining a little bit earlier, they had all the patient-level data. They had enough data to do a much more powerful analysis than I did. The question obviously on the table here is, where were they at in the process. Were they——

Mr. CANNON. I think the question on the table here is, why do we have this sensationalist hearing when everybody agrees that the data is indeterminate and you have a really important drug and in the middle of all that, you are whacking on a business that is doing its job to create a better world for people who are sick?

Dr. NISSEN. There is a reason, sir. The reason is that I wanted my colleagues who practice medicine and I wanted patients who take these drugs to be aware of our analysis. I thought that it was my obligation to inform them that there was a potential risk. I could not allow patients with diabetes——

Mr. CANNON. Mr. Chairman, I see my time has expired. If I can just make a comment.

Chairman WAXMAN. The gentleman's time has expired. And we haven't really allowed other Members to extend their time.

Mr. CANNON. I wouldn't dream of doing that. I yield back, Mr. Chairman.

Chairman WAXMAN. Thank you, Mr. Cannon.

Mr. Cummings.

Mr. CUMMINGS. Thank you, Mr. Chairman.

I have a lot of questioning, but I have to say that after being here for 11 years, I hate it when witnesses are attacked, it bothers me. Particularly when they are trying to do the best they can, in the words of Thurgood Marshall, with what they have. I believe that you all are honorable men, simply trying to be the best that you can be. So I am going to ask one or two questions to clear this up. And I hate that we have to make, that these accusations are made that people are putting politics over the health of the American people. That bothers me.

So let me ask it this way. Dr. Buse and Dr. Psaty, you have heard this line of questioning, you heard what Dr. Nissen has said. Do you all have any issue with the professionalism that he has, the way he has gone about doing what he has done to get this information published? Dr. Buse first.

Dr. BUSE. I have no issue with it at all. I think he did a nice job of organizing the data and setting out that it was imperfect but important for people to be aware of.

Mr. CUMMINGS. Dr. Psaty.

Dr. PSATY. I agree. I think he did a terrific job in a difficult situation. There were opportunities to prevent this. GSK could have published their meta-analysis. The FDA has had this information for months. It was released in Europe in October. I don't know why it takes so long for the FDA to release information. Detailed analysis is important, but at some point, it looks like a lack of transparency and a lack of communication. It would have been perfectly reasonable in August to say, we have two studies from GSK, they suggest this risk, it is not clear, they contradict each other. It is important for people to know this information.

What Steve is dealing with is a safety issue. And it is prudent to warn patients about risks. We have to first do no harm.

Mr. CUMMINGS. The reason why I did that is because, you guys have to go home. You have to go back to where you came from. And I don't want, on national television for folks to believe that somebody is doing something that is improper if they are not doing it.

Let me ask you this. Let me say this. In my district, in Baltimore, we have a high, high degree of diabetes and heart disease. I represent Johns Hopkins. But today, I guarantee you, people will die, today, from diabetes. And now I have learned something interesting, that they will die from diabetes, but probably the heart disease will kill them.

So today, would you recommend, Dr. Nissen, based upon what you see right now, would you, if your physicians came to you and said, should we be prescribing this drug, what would you say? Just what would you say? If they say, look, Doc, we just saw you on C–SPAN and we are kind of concerned about this.

Dr. NISSEN. I deliberately did not answer that question, in the manuscript or subsequently. Let me tell you why. With science, you have to allow individual physicians to make their own minds up about how to interpret the data. My job was to get the data into the public domain in the best journal possible, carefully reviewed and thoughtfully articulated. What I have said is, individual physicians should look at the results, discuss it with their patients and make their own minds up about what the right thing to do is. We knew that it wasn't the definitive end, we knew there were more questions to be asked. Rather than come to conclusions, we said, here it is, you decide.

Mr. CUMMINGS. What kinds of tests would you recommend that give us, would bring you to a conclusion where you would say, yes or no?

Dr. NISSEN. What would need to be done is an adequately sized, long-term trial, probably in fairly high-risk patients, comparing Avandia to other therapies. That would, now, unfortunately, because such a trial doesn't exist, it would not be completed for probably about another 7 years. So it is a long, long way off. The problem is, as Dr. Psaty said, the time to have launched such a study would have been 1999 or 2000.

So we are in a very tough quandary here, in that we don't have the data to definitively answer the question. We just have the meta-analysis, which is all we are ever going to have, because it looks like RECORD isn't going to give the answer, either.

Chairman WAXMAN. Thank you. Thank you, Mr. Cummings.

Mr. Issa.

Mr. ISSA. Thank you, Mr. Chairman.

Dr. Nissen, I guess I am going to keep following up a little bit. One thing that was said in the previous panel, and it is unfortunate that the FDA you think so little of that you go to Congress before you go to the scientists and the doctors who we entrust to make these decisions, said, and they weren't willing to commit to the statistical likelihood, but you are somebody who reads some statistical likelihood. You are responsible for this compilation of meta-data.

Why did you choose to ignore or to leave out meta-data in which nobody died, in which nobody had a heart attack? And before you answer why you chose to leave it out, by definition, if you had put it in, wouldn't it have lowered the conclusions that you reached? Please, Dr. Nissen.

Dr. NISSEN. You can't calculate, in a meta-analysis, you can't use trials in which there are no events. It simply can't be done statistically. Let me explain why. I know you want a short answer, but——

Mr. ISSA. Well, no, unfortunately I insist on a short answer, so I will rephrase it to help make that happen. If you put zeroes in, statistically, yes, you would get a lower number. So now, the fact that you can't put it in, anyone with common sense says, well, these studies where nobody got sick were not something, nobody had heart attacks, those were studies in which the public and the doctors that you say you are providing this information to, even though you are providing, I mean, you might as well just have everyone do studies and every doctor evaluate it if we are not going to use the FDA.

But in this case, you left that information out of what the doctors got to know, didn't you?

Dr. NISSEN. That information cannot be used to calculate——

Mr. ISSA. No, no, my question was rephrased to make it a yes or no. You left that information out so the doctors did not have the knowledge that hundreds or thousands, whatever number of people were in all those studies, did not have heart attacks. You left that out, didn't you?

Dr. NISSEN. That information is publicly available on the FDA Web site.

Mr. ISSA. No, no. Of your, of your report, they are relying on your report as part of the balancing act, you left it out, didn't you?

Dr. NISSEN. Mr. Issa, you can't calculate an effect size when there are no events.

Mr. ISSA. OK, look, we already did this——

Dr. NISSEN. The manuscript was——

Mr. ISSA. No, no, sir, I have limited time. You are not willing to answer the simple question of did you leave it out, were the doctors aware of it. And to say that doctors can pore into research that you came to the majority staff and asked for help getting back in February as you planned to release this very, very earth-shattering effect, whether you intended it to be or not. And I suspect you intended it to be. You came to Congress, you planned with them to essentially bring this out. You asked for additional information and then you are going to come here, I am a little disappointed, and tell me that doctors can find it out themselves, it is public. I am

sorry, but leaving that out is the reason that you clearly should have gone to the FDA.

I am going to ask you a question related to that. Did you have discussion with the FDA back in January, February or March, when you were having discussions with the majority staff here?

Dr. NISSEN. No.

Mr. ISSA. OK. So you didn't go to the very body that we held here accountable, that we are holding oversight hearings on, and yet we are going to ask them why they didn't do their job, you didn't even give them the benefit of the doubt. Did anyone from the majority staff suggest that you at least bounce these off of the FDA?

Dr. NISSEN. That was never discussed.

Mr. ISSA. Did anyone here, as you were trying to get a political body to get you more information, did anyone suggest that you ask the FDA to assist you?

Dr. NISSEN. No.

Mr. ISSA. OK. So it very much looks like this was a political entity designed to make a big, public splash. It is clear from letters that I have here that in fact, before your study was published, we were asked to ask for a hearing. So in fact, didn't you reach a conclusion, back in February, that this was in your opinion a potentially dangerous drug, and decide that you wanted to shed light on it using this body in a public hearing in your article? Didn't you decide that all the way back at least in February?

Dr. NISSEN. I did not come to that conclusion until I finished the meta-analysis.

Mr. ISSA. OK, so what were you doing in February when you were saying you were concerned, and asking for this information from a political body rather than in fact from the fundamental group that we hold accountable at the end of the day?

Dr. NISSEN. I had incomplete information. I didn't have access to all 42 clinical trials. I knew that I needed it.

Mr. ISSA. And you hadn't asked the FDA for it.

Dr. NISSEN. The FDA is not allowed to give the data out.

Chairman WAXMAN. How about GSK? Did you ask them?

Dr. NISSEN. I did.

Chairman WAXMAN. Did they give you the information?

Dr. NISSEN. No. Well, we were unable to reach agreement on getting the information.

Mr. ISSA. When committee staff went with you, with the primary drug reviews were raised, did they suggest that they could in fact get that information and did you ask them to try to get it through other channels, and did you wait for that before publishing?

Dr. NISSEN. I am sorry, I didn't hear your question. I don't understand your question.

Mr. ISSA. When you met with committee staff, or I am sorry, when committee staff met with the FDA, reviewers were raising the same concern. You said the FDA included studies with their meta-data analysis that you did not. Can you understand why they included the studies and you didn't?

Dr. NISSEN. My understanding is, they have not in fact announced what studies they have included, so I have no way of knowing how they did their analysis. Remember, their analysis has

not been published or presented. So we have no way of comparing the two analyses.

Chairman WAXMAN. The gentleman's time has expired. Dr. Psaty and Dr. Buse have been raising their hands.

Mr. ISSA. Mr. Chairman, they can do what they want on somebody else's time. If you are going to interrupt me during my time to ask a question and then you are going to bring it to a close, please use somebody else's time to do this. I wish we had more time, because this very much does, Mr. Chairman, as I said in my opening remarks, this does look like in fact this was a political concoction to anecdotally go after a company rather than to do legitimate oversight on the FDA. I object to it.

Chairman WAXMAN. The gentleman is being demagogic. This is not anything that is political. Dr. Nissen's paper was peer-reviewed and published in a very respectable journal. It is that article that has raised a lot of concern. It is certainly appropriate for this committee to raise these issues and bring in the various parties to talk about the issue. You are the one who wants to politicize this issue.

Now, you asked a lot of questions and two of the witnesses wanted to respond to your questions. Do you object to having them respond?

Mr. ISSA. I asked and did not get answers from one individual who continually wanted to evade giving me the proper yes or no that I deserved when I rephrased the question.

Chairman WAXMAN. That is not my fault. You did what you could and he answered to the best of his ability.

Mr. ISSA. Mr. Chairman, in regular order, I would appreciate that we can have a second round and certainly those can be asked and answered on either one of our times. I would look forward to a second round if you think it is appropriate, Mr. Chairman.

Chairman WAXMAN. Do you object to these two gentlemen responding to your——

Mr. ISSA. Mr. Chairman, I would ask for regular order.

Chairman WAXMAN. Well, let's go on to, I think Mr. Shays' time. Maybe he wants to be recognized.

Mr. SHAYS. I would be happy to let Mr. Issa pursue his questions.

Chairman WAXMAN. OK, Mr. Issa——

Mr. SHAYS. Beforehand, I just want to, having come late to this, Dr. Nissen, and I will allow the two other gentlemen to respond to the questions that were asked, because I would like to know the answers.

What I am unclear about, in just one area, is did you come to this committee because you wanted this committee to use its resources to get data for you?

Dr. NISSEN. That is correct.

Mr. SHAYS. And did you feel that this committee had legislative ability to get this information that someone else didn't have the ability?

Dr. NISSEN. I didn't know what authority it had. But I had met the staff, because we had discussed some pending legislation. So I said, look, I have a concern here.

Mr. SHAYS. What pending legislation was that?

Dr. NISSEN. This is the Waxman-Markey bill that is being considered, that is the companion to Kennedy-Enzi.

Mr. SHAYS. See, my problem is that sometimes I feel Congress has been used to go after companies, and that the trial lawyers and everybody else uses the mechanism of Congress to then build a case and to be able to get information from the company that you wouldn't have a right to unless you mis-used Congress to do it. That is where I start to become very defensive about the process. I believe that once people come before a committee, my colleague on the other side of the aisle says he objects to how witnesses are treated. I think it is just as important, once you walk into this territory, you have to be willing to have the scrutiny and to be able to respond to questions. But I would like to the two other gentlemen to respond.

Chairman WAXMAN. Would the gentleman yield to me?

Mr. SHAYS. Yes, absolutely.

Chairman WAXMAN. I don't know if you were here at the time, but Dr. Nissen came to Senator Grassley's staff, our staff, Mr. Dingle's staff, others that I might not be aware of, asked for help getting data. And he did not get the help with getting the data. He asked the company to give him the data. He did not eventually get that information.

So that was the extent of our involvement.

Mr. SHAYS. All right, thank you.

Chairman WAXMAN. I don't know if there is anything improper about it.

Mr. SHAYS. I would like the two gentlemen to respond to that. And I would be happy to yield.

Dr. BUSE. Just very briefly in response to Congressman Issa's questions for Dr. Nissen, I have had the opportunity to speak with two statisticians in part of various duties I have regarding the analysis that Dr. Nissen did. By the technique, he had to leave out those studies and he disclosed in the paper that, I left out those studies because I have to to be able to do this meta-analysis. And GlaxoSmithKline and the FDA have done their own analysis, the best that they could do, and basically all the analyses come up with the same result.

So from my perspective, we don't have to have a big discussion about what kind of analysis was done and whether it was done properly. Everybody gets the same result.

Mr. SHAYS. Is your answer the same, sir?

Dr. PSATY. It is, but I think I can perhaps, I am a biostatistically inclined epidemiologist. If you think about it, if a study has no heart attacks, it can add no information to a meta-analysis about heart attacks. This is not an effort to create incidents routes. It is ratios, and they are not affected by leaving out trials that——

Mr. SHAYS. Well, to my non-scientific mind, if you do a study and there is not an outcome that is negative, it strikes me from a non-scientific mind that is certainly important data.

Dr. PSATY. The studies compare heart attack rates in one group to another. And if you have two groups and there are no heart attacks, you have no information about heart attack risk. This is a standard approach.

Mr. SHAYS. Other than they are not getting heart attacks. [Laughter.]

With all due respect, let me——

Dr. PSATY. But it is not an incidence rate that you are looking at.

Mr. SHAYS. I understand there is something I don't get because I am not a scientist. And I don't mean that in any way, you are just not going to be able to connect with me. Logically, if people don't have heart attacks, that is data.

Mr. ISSA. Earlier we heard that there was a study left out that had one heart attack, but they didn't die. So I guess if you don't die, you don't count, either.

Dr. PSATY. I think that was in the analysis of cardiovascular deaths.

Mr. ISSA. OK, well, the FDA in its review with our staff, when we were preparing for this, said that by leaving out that data, you did bias the risk assessment, that clearly if you take 1,000 people who all took the drug and you say 43 percent are more likely to have a heart attack, that 43 percent is a relative number and it can be expressed in a number of ways.

So having said that, my concern here today is not whether or not this drug is more dangerous, because I think the science is still to be worked out on that, and I look forward to it being done. My concern here today, and the chairman is calling it demagogy, but it is part of the minority's job, is to second guess what is being simply handed to us. And what is being handed to us is the various Democrat leadership, you prepared for paper in harmony with them. And Doctor, you obviously did not intend to get peer review quietly. You intended to get it loudly and you are getting it here today.

I yield back.

Chairman WAXMAN. You didn't get peer review, Dr. Nissen, from Members of Congress, did you?

Dr. NISSEN. No, they didn't see the manuscript.

Chairman WAXMAN. OK. Well, that completes the questioning from Members. I want to thank the three of you for your presentation here. I note, Dr. Buse, you were reluctant to participate in the hearing, so I especially appreciate your participation.

Ironically enough, if the FDA and the drug manufacturer, GlaxoSmithKline, had listened to you 7 years ago, we would have had a more definitive answer on the very important question that affects millions of Americans. We don't have the answer to it, although some Members of Congress have answers as to how the scientific evaluation ought to be done statistically. But most of us can't reach these conclusions. The conclusion I reach is that we have wasted a lot of time and as a result of the information, the meta-analysis, we have an ongoing question that people have to grapple with, which is unfortunately not resolved.

I thank you very much and appreciate your being here.

Our last witness is Dr. Moncef Slaoui. Dr. Slaoui is the chairman of research and development of GlaxoSmithKline. Dr. Slaoui has a Ph.D. in molecular biology and immunology in Belgium, completed post-doctoral studies at Harvard Medical School and Tufts University School of Medicine. In his current position at GlaxoSmithKline, he has served on the research and development executive team and

spearheaded recent changes to enhance drug discovery and accelerate product development.

Dr. Slaoui, we are pleased to welcome you to our hearing today. As you might have been aware from earlier witnesses, it is the practice of this committee to ask you to rise to take an oath, if you would.

[Witness sworn.]

Chairman WAXMAN. The record will indicate you answered affirmatively.

We are pleased to have you, and I want to recognize you for your oral presentation. Your full statement will be in the record in full. We would like to ask you, if you would, to limit your presentation to 5 minutes.

STATEMENT OF MONCEF M. SLAOUI, PH.D., CHAIRMAN, RESEARCH AND DEVELOPMENT, GLAXOSMITHKLINE

Mr. SLAOUI. Mr. Chairman and members of the committee, thank you for having me here today. My name is Moncef Slaoui, and I am the chairman of research and development at GlaxoSmithKline [GSK]. I am here to share with you GSK's extensive and ongoing efforts to research both the safety and the benefits of Avandia, the important medicine that helps patients fight the devastating effects of type 2 diabetes.

GSK has initiated the most comprehensive research program for any oral anti-diabetic medicines available today, with experience in over 52,000 patients studied in clinical trials. By doing so, GSK has already undertaken what Congress has suggested all pharmaceutical companies should do; that is, rigorous scientific studies of a medicine's safety and benefit after it is approved by the FDA.

The data we have collected from those studies not only confirm Avandia's efficacy in controlling blood glucose levels in diabetes patients, but those data also show that Avandia controls blood sugar for longer periods than other currently available oral anti-diabetes medicine. Avandia has shown 30 percent and 60 percent superior efficacy to Metformin and to sulfonyureas, the two most commonly used oral anti-diabetes medicines.

As concerns the very important point of safety, the comparable data that we have generated over the last 8 years establishes that when compared to other widely used oral anti-diabetes medicines, Avandia is not associated with an increased risk of death, including death from a cardiovascular event. The data also show that except for the well described increased risk for congestive heart failure associated with this class of medicines, the TZDs, not just with Avandia, Avandia has a comparable cardiovascular safety profile to that of the most widely used oral anti-diabetes medicine.

Let me take you through this. From day one, GSK and regulatory agencies believed it was important to develop the highest level of scientific evidence to assess the cardiovascular benefits to the risk profile of Avandia. Accordingly, in the year 2000 and again in the year 2001, we started two very large prospective long-term clinical trials, respectively the ADOPT and the RECORD studies. Both trials allowed us to compare over a period of 3 to 4 years the safety of Avandia to that of the two most widely used oral anti-diabetes medicine, each in more than 4,000 diabetes patients.

Specifically, the primary goal of the RECORD study was to compare the risk of cardiovascular deaths and cardiovascular hospitalization in these patients, including heart attack, stroke, congestive heart failure in patients using Avandia or patients using other medicines.

Importantly, given the length of these prospective clinical studies, we did not just sit there and rely on ADOPT and RECORD studies to come out. We proactively used other available scientific methodologies, albeit less robust than the prospective clinical trials, we just heard the discussions around that analysis, to assess Avandia's cardiovascular safety profile.

We ran our own meta-analysis in 2005 already and also in 2006, which we knew would be useful for generating hypotheses, yes, but not for providing definitive answers. We also ran a very large real world epidemiological study in over 33,000 diabetes patients. That study showed that there was no increased risk for Avandia.

While the meta-analysis conducted in 2005 and 2006 did suggest a potential increase in cardiovascular patients using Avandia, all other more robust scientific evidence that we have, and that is coming from four independent, high-level scientific experimentation, three large trials, the ADOPT trial, the DREAM trial, the RECORD trial and the large epidemiological study that I just spoke about, all those studies have shown that the hypothesis is not accurate that there is an increase of cardiovascular risk associated with the use of Avandia, when we compare it to the two most widely used oral anti-diabetes medicines.

Throughout this time, we also communicated diligently with the FDA the data that we received from the meta-analysis. We transparently published the DREAM study and the ADOPT study in reputable journals and we posted all our clinical trial results as well as our meta-analysis on GSK's clinical trial registry, actually in October 2006, well before the publication in the New England Journal of Medicine.

We also diligently communicated to physicians and patients Avandia's scientifically established safety risks. In summary, at every step, GSK examined the questions generated by our meta-analysis and by that of others. We determined that more robust scientific data consistently conflicted with the signals raised. The complete body of evidence available to date clearly supports our conviction that the cardiovascular safety of Avandia is comparable to that of the two most widely used oral anti-diabetes medicines.

As we all work together here today on these issues, I do ask that we all remember that we are working on behalf of diabetic patients who are at risk of many major complications. They were cited: kidney failure, limb amputation, nerve injury, blindness, cardiovascular events, deaths. Unfortunately, the worldwide epidemic of type 2 diabetes shows no signs of abating.

All medicines have risks. But the benefits of oral anti-diabetic medicines like Avandia help millions of patients control their diabetes and live healthier, more productive lives.

I will say that we found the RECORD data which we published yesterday in the New England Journal of Medicine very reassuring, recognizing that it is interim and therefore not fully conclusive. We are extremely disappointed by the editorials published yesterday in

the New England Journal of Medicines that cherry-picked data points when the data taken as a whole supports the safety profile of Avandia.

I thank you very much for your attention, and I would be happy to take your questions.

[The prepared statement of Mr. Slaoui follows:]

Statement of Moncef Slaoui, PhD, Chairman
Research & Development
GlaxoSmithKline

Testimony before the House Committee on Oversight and Government Reform
June 6, 2007

Mr. Chairman, Ranking Member and Members of the Committee: Good morning, my name is Dr. Moncef Slaoui, and I am the Chairman of Research & Development for GlaxoSmithKline, or GSK. GSK is one of the world's leading research-based pharmaceutical and healthcare companies. I'm here to share with you GSK's extensive and ongoing efforts to research both the safety and the benefits of Avandia®, an important medicine that has been proven to help patients fight the devastating effects of type 2 diabetes.

My colleagues and I at GSK strongly believe that the overall safety of Avandia® is comparable to other available oral anti-diabetes medicines, and that Avandia® provides substantial benefit for diabetic patients. Our commitment to Avandia® patients is demonstrated by our extensive and continuous study of this medicine before and after its approval by regulatory agencies worldwide.

An objective look at GSK's extensive commitment to patients will demonstrate:

- GSK has initiated the most comprehensive and rigorous program of scientific analysis for any oral anti-diabetes medicine available to patients today, with experience in over 52,000 patients. By engaging in this extensive scientific research program over many years, GSK has already undertaken what Congress has suggested all pharmaceutical companies should do; namely, rigorous scientific analysis of a medicine's safety and benefit after it is approved for wider use in patients.
- The data collected from this wide variety of studies – including real-life experience and long-term clinical trials designed to meet the highest standards of sound science – demonstrate that Avandia® has a comparable cardiovascular profile to the two most commonly prescribed oral anti-diabetes medicines, recognizing the risk of congestive heart failure acknowledged for all medicines in the TZD (thiazolidinedione) class.
- Over time, GSK has faithfully and in a timely way reported its findings to regulatory agencies including the Food and Drug Administration (FDA). GSK also made data available to scientists in the public domain in a variety of ways, including postings on the company's Clinical Trial Register.
- Questions about Avandia®'s safety profile are best answered by prospective clinical trials such as ADOPT, DREAM and the RECORD cardiovascular outcomes trial, a large long-term clinical trial in people with diabetes which is specifically designed to look at cardiovascular outcomes.

Our view is that decisions on the safety of medicines should be made on the basis of science and an objective examination of all the data available. The sum of the science, including two recently completed long term prospective clinical trials ADOPT and DREAM as well as the new interim data available from the RECORD trial, establishes that Avandia®, when compared to other widely used anti-diabetes medicines, is not associated with an increased risk of death, including death from a cardiovascular event.

The most important message today for the Committee and the public is this: The cardiovascular profile of Avandia® is comparable to that of the two other oral anti-diabetes medicines that are most widely used in the United States today.

On May 21st, *The New England Journal of Medicine* published an article ("NEJM article") raising concern about the safety of Avandia®, which has generated controversy among scientists and anxiety among diabetes patients. The article contained the results of a meta-analysis, a type of statistical analysis that is useful for generating hypotheses but which has significant limitations and lacks the rigor required to reach definitive conclusions about adverse events. This is especially so when the analysis deals with an issue that has a very low event rate. Acknowledging these limitations, the editorial accompanying the study stated: "*A few events either way might have changed the findings for myocardial infarction or for death from cardiovascular causes. In this setting, the possibility that the findings might be due to chance cannot be excluded.*"

On May 23rd, *The Lancet*, an independent medical journal, responded to this controversy with an editorial statement. Here is what *The Lancet* said:

> *Until the results of RECORD are in, it would be premature to overinterpret a meta-analysis that the authors and NEJM editorialists all acknowledge contains important weaknesses. To avoid unnecessary panic among patients, a calmer and more considered approach to the safety of Avandia is needed. Alarmist headlines and confident declarations help nobody.*

A similar position has also been taken in a joint statement by the American College of Cardiology, the American Heart Association, and the American Diabetes Association.[1] GSK strongly agrees with these statements and stands firmly behind the safety of Avandia® when used appropriately.

We face a world-wide epidemic of type 2 diabetes. Diabetic patients are at risk for many major complications such as kidney failure, limb amputation, nerve injury, and blindness. Importantly, diabetics are at very high risk for cardiovascular disease, and in fact, it is the main cause of death in these patients. Diabetes gets progressively worse over time, with

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[1] Statement from the American College of Cardiology, the American Heart Association, and the American Diabetes Association related to NEJM article, "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes"
http://www.acc.org/media/releases/highlights/2007/may07/rosiglitazone.htm

complications developing over many years. We know from outcome clinical studies that effective treatment of diabetes requires intensive, long term, day-to-day control of blood sugar levels to save lives and significantly reduce the risks of cardiovascular and other complications.

Given the seriousness of diabetes, it is critical to understand how any treatment affects cardiovascular disease in these patients. Since the development and launch of Avandia®, GSK has diligently followed a thorough, long-term program of scientific study, aimed at continuously assessing cardiovascular events in treated patients.

Two specific and different cardiovascular events in diabetic patients will be discussed today: congestive heart failure and ischemic cardiovascular disease.

First, let's discuss congestive heart failure.

Avandia®, and other medicines in its class, increase the risk of the serious problem of congestive heart failure. Diabetics are known to be at risk of developing congestive heart failure, a weakening of the heart's normal pumping power. In this setting, the increased retention of fluid can lead to edema and symptoms of congestive heart failure. Drugs in the same class as Avandia®, including Actos®, can lead to retention of fluid, promotion of edema and hence development of congestive heart failure. Prior to marketing Avandia®, GSK and the FDA recognized the potential for edema and the serious side effect of congestive heart failure. For this reason, the original Avandia® product information label from May 25, 1999, specifically reported that edema had been seen in some patients and that Avandia® was not indicated in patients with moderate or severe symptoms of heart failure.

Since then the label has undergone six changes and warnings as new information has become available from clinical studies regarding congestive heart failure. We are in discussions with the FDA to further enhance the prominence of such heart failure warnings on Avandia®'s label and that of other medicines from the same class.

Now I would like to turn to the question that is our major focus today: Does Avandia® increase the risk of ischemic cardiovascular events, heart attacks and cardiovascular related death in diabetic patients? We believe the data show it does not.

At the time Avandia® was approved, GSK and regulatory agencies believed it was important to develop the highest level of scientific evidence to assess its cardiovascular benefit-to-risk profile. Accordingly, in 2000 and 2001, we started two large, prospective, long-term clinical trials, respectively, the ADOPT and the RECORD studies. Both trials allow us to compare over a period of 3 to 4 years the safety of Avandia® to that of the two most widely used oral anti-diabetes medicines in more than 4000 patients each. Specifically, the primary goal of RECORD is to compare the risk of cardiovascular death and cardiovascular hospitalization, including heart attack, stroke, and congestive heart

failure in patients using Avandia® to the two other most commonly prescribed oral anti-diabetes medicines.

While awaiting the ultimate scientific evidence from the prospective clinical trials including RECORD, and in order to further study Avandia®'s cardiovascular benefit-to-risk profile, GSK has diligently and proactively used other available methods which can provide useful but less definitive information. I will now take you through a chronological description of the key studies and analyses conducted by GSK in this regard.

Let's begin with the meta-analyses that GSK itself has conducted, posted publicly, and communicated to the FDA. GSK performed patient-level meta-analyses of safety data from multiple clinical trials primarily designed to assess end points other than Avandia®'s cardiovascular safety profile. Because of their different focus and the small size of the individual studies, we knew that this approach could NOT yield conclusive information, but rather, could generate hypotheses to be tested using more scientifically robust strategies.

In September, 2005, results from the first meta-analysis became available. This meta-analysis, which pooled data from 37 clinical trials completed prior to September, 2004, compared 6976 patients on Avandia® and 4610 patients on other treatment regimens including no treatment, metformin, sulfonylureas, and insulin. This analysis showed an overall incidence of ischemic cardiovascular events of 2.24% in Avandia® patients versus 1.71% in the pooled comparison group. This equates to a non-statistically significant estimate of excess risk of ischemic cardiovascular events of 29% associated with the use of Avandia®. The data from this first meta-analysis were officially communicated to the FDA in October, 2005, as well as to the independent Data Safety Monitoring Boards of the various ongoing clinical trials with Avandia®. This potential excess cardiovascular risk prompted GSK to perform a second meta-analysis as well as a separate epidemiologic study, called the Balanced Cohort Study, and both studies were initiated in January, 2006.

The second meta-analysis, that was initiated in January, 2006, was conducted in order to include 5 studies that had finished between September, 2004, and August, 2005. This second analysis included a total of 42 separate randomized clinical trials that compared 8,604 patients on Avandia® and 5,633 patients on other treatment programs. The results were reviewed in March, 2006. The overall incidence of cardiovascular events was 1.99% in Avandia® patients versus 1.51% in the pooled comparison group, with a hazard ratio of 1.31. This equates to a statistically significant excess risk of ischemic events of 31% associated with the use of Avandia®. This hazard ratio is in the same direction as the NEJM article's meta-analysis.

Like meta-analyses, balanced cohort studies do not provide the same high level of scientific evidence that is provided by a large randomized clinical trial. However, they complement the findings of clinical trials because they represent what happens in the

"real world setting." Using an independent managed care database, the Balanced Cohort Study was a real world observational study that compared diabetic patients who began treatment with Avandia®, with metformin, a sulfonylurea, or combinations between 2000 – 2004. The analysis examined the specific ischemic endpoint of heart attack and coronary revascularization events (such as coronary bypass surgery or angioplasty). This analysis in 33,363 patients showed that the incidence of ischemic cardiovascular events was 1.75 events per 100 patient years for use of Avandia® vs. 1.76 for other treatments. Thus, this study of over 30,000 patients did not confirm that the meta-analyses' signal of a possible increase in ischemic cardiovascular risk was accurate.

These data were communicated to the FDA in early May, 2006, as well as to other regulatory agencies world-wide, and the results of both this meta-analysis and the Balanced Cohort Study were reviewed with the FDA in a formal submission in early August, 2006. In addition, these data were again communicated with the Data Safety Monitoring Boards of the various ongoing trials using Avandia®, including RECORD. It is important to note that the Data Safety Monitoring Boards are entitled and expected to regularly run an unblinded analysis of the safety of patients enrolled in a clinical trial and decide to either pursue or stop the trial depending on what safety data they saw from the analysis. The decisions of the independent Data Safety Monitoring Boards' panels to continue the trials conduct unchanged clearly signaled to us that no significant cardiovascular risk was identified in these ongoing large cardiovascular outcome trials.

GSK has and will continue to perform meta-analyses of its databases as further clinical trial data become available because they are helpful in generating hypotheses which can then be further assessed using more accurate scientific strategies. However, GSK also concurs with the NEJM article's own assessment of the serious limitation of a meta-analysis: *"a meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest."*

Three such large, long term, prospective clinical trials allow scientifically robust conclusions about the safety of Avandia®. Two of these trials were completed in the later part of 2006 shortly after our second meta-analysis, and the third one, the RECORD trial, is still ongoing.

The ADOPT trial, which GSK launched in 2000, studied 4,360 newly diagnosed diabetic patients over a follow-up period of four to six years. The primary purpose of this randomized controlled trial was to compare the effectiveness of Avandia® versus metformin and glyburide on improvement and maintenance of blood sugar control in 4,360 newly diagnosed diabetics. Avandia® was shown to be significantly superior in maintaining control of blood sugar levels compared to the broadly used oral diabetes medicines metformin and glyburide. This superiority of long-term blood glucose control compared to other classes of diabetic agents has <u>not</u> been tested with the use of Actos®, the other drug in the same class as Avandia®. This study, and many others, has clearly established the benefits of Avandia® in treating diabetes patients. Data from the ADOPT trial were published in the *New England Journal of Medicine* in 2006.

In addition to efficacy, ADOPT also allowed us to compare the cardiovascular benefit-to-risk profile of these widely used oral anti-diabetic medicines. An analysis of cardiovascular deaths, myocardial infarctions, and a composite end point of cardiovascular death, heart attack, and stroke showed that the three medicines are comparable. The ADOPT clinical trial data were submitted to the FDA in February 2007, and recently published in a letter to *The Lancet*.

In September, 2006, the DREAM trial was published in *The Lancet* and the results became available to GSK. This large randomized prospective clinical trial, launched in 2001 by independent investigators, studied nearly 5,300 pre-diabetic patients with 3 year follow-up. It was designed to determine if either ramipril, a drug with well-established benefits on cardiovascular events, or Avandia® delayed the onset of diabetes in comparison with placebo. The trial also collected cardiovascular safety information. The independent investigators reported that the rates of cardiovascular death, heart attack, and stroke were similar in the Avandia® groups versus the placebo groups, whereas congestive heart failure was, as expected, more common.

In February, 2007, once the DREAM database became available to GSK scientists, a further ad hoc refined analysis was performed by GSK and provided to the FDA in May, 2007. These data, which were published in the May 30th letter to The Lancet, clearly show that Avandia® has no increased risk of heart attack, stroke, or cardiovascular death as compared to placebo treatment in pre-diabetic patients.

Finally, in May, 2007, GSK decided, in concert with the RECORD study DSMB and Steering Committee and with the knowledge of the EMEA and the FDA, to conduct an unblinded safety interim analysis of the cardiovascular outcome RECORD trial. This interim safety analysis provides the highest quality scientific evidence on the cardiovascular safety of Avandia®. The RECORD trial is a large prospective randomized clinical trial in over 4,400 diabetes patients currently followed up for an average of 4 years. It is designed to specifically examine the risk of adding on Avandia® to either metformin or a sulfonylurea versus combination metformin and sulfonylurea therapy regarding the primary endpoint of cardiovascular death and cardiovascular hospitalization, including heart attack, stroke, and congestive heart failure. The RECORD trial is also specifically designed to examine the risk of death from any cause.

In the RECORD trial, all reported cardiovascular events are independently evaluated and adjudicated by an independent committee that is blinded to which drugs the individual is taking in the study, making these data substantially more accurate than the spontaneously reported – but not adjudicated - serious adverse events reports that make up the events considered in the meta-analyses that I discussed earlier with you. The data from the interim analysis have been submitted as a publication to the *New England Journal of Medicine*.

These interim data show that Avandia®, metformin, and sulfonylurea have a comparable cardiovascular safety profile and are consistent with the results observed in the two other large prospective clinical trials, ADOPT and DREAM. Taken together, data from these three independent prospective clinical trials fail to support the hypothesis generated by any of the meta-analyses.

The totality of the science I have shared with you today establishes that Avandia®, when compared to other widely used anti-diabetes medicines, is not associated with an increased risk of death, including death from a cardiovascular event. Furthermore, all data presented today also show that Avandia®'s overall cardiovascular safety profile is comparable to that of the two most widely used oral anti-diabetes medicines: metformin and the sulfonylureas. We have consistently shared our data with regulators and others to help better inform physicians about the safety of Avandia®, so they can make the right treatment choices for their patients.

In addition to our confidence in the overall safety profile of Avandia®, my colleagues and I believe Avandia® provides substantial benefit for diabetic patients over the long-term in controlling blood sugar. For these patients, having multiple treatment options to manage a progressively debilitating disease like diabetes is critical. Two and three medicines are often needed to help these patients control their blood sugar. If left uncontrolled – as is the case for two-thirds of diabetic patients – the health costs can be catastrophic in terms of heart disease, blindness, amputations, kidney disease and other complications.

Thank you. I look forward to answering any questions you may have.

Chairman WAXMAN. Thank you very much, Dr. Slaoui. I want to recognize Mr. Issa for questions.

Mr. ISSA. Thank you, Mr. Chairman.

I want to note that I appreciate your being here today. The first panel was mutually agreed to as being the Commissioner, that is common for administration officials. Unfortunately, we hoped to have you on the second panel, so that we could have the kind of interface that I am afraid we are being denied right now. But I will work with what we have.

Dr. Nissen has been quoted as saying that Avandia as a drug has no established health benefits. Would you like to comment on that?

Mr. SLAOUI. Well, I completely disagree with that. I think that the scientific field has established in the 1990's very clearly that if you decrease the blood sugar levels over a period of time, you significantly decrease the risk to diabetes patients for what is called microvascular disease, which is blindness, amputation, renal failure, as well as cardiovascular disease. Every single oral anti-diabetes medicine that is today approved in the United States by the FDA, including two medicines approved last year, have been approved on those grounds.

Mr. ISSA. So essentially by definition, for the FDA to approve, your efficacy has already been established and that is a really unfortunate statement, since it flies in the face of the approval process, isn't that true?

Mr. SLAOUI. That is absolutely true. I would like to add, Congressman, that not only is Avandia effective, it is actually superior to the most widely used medicines. It as, as I said, 30 percent and 60 percent superior.

Mr. ISSA. I have been commenting on this being a political process. And I am not going to back away from that, because I think unfortunately we are playing science here when in fact we shouldn't be.

Let me just ask you one question. How do you believe doctors and statisticians should handle meta-analysis results prior to receiving data from large clinical trials? We don't want to alarm the public unnecessarily or needlessly. But we also don't want to sit and let patients not have facts as soon as we have them. So how should this have, not only how should we do it in general, but how should this have been presented, if you don't believe it was presented appropriately by meeting with the majority folks behind closed doors and then in fact publishing without dealing with your company or with the FDA?

Mr. SLAOUI. Congressman, I would like not to comment on exactly what Dr. Nissen has done. I will tell you what I would have done, what actually GSK has done. In 2004, we knew that it was important for us to continuously look at the cardiovascular safety of Avandia. Actually as of 1999, we had a very stringent pharmacovigilance system that looks at cases of cardiovascular deaths or cardiovascular heart attacks, etc., to assess whether there is an imbalance. We have not seen such an imbalance.

Yet there was some report in some patient population, in combination with the incident that was cited earlier, that attracted our attention to myocardial infarcts. We immediately ran a meta-analysis ourselves. However, we knew exactly what we were dealing

with. These are hypothesis generating technologies, methodologies. These are not fact-establishing methodologies.

So we did that analysis and we immediately came with another scientific strategy, which was a real life epidemiological study on 33,000 patients that has shown absolutely no increased risk. We communicated both information to the agency and I think we did the right thing.

Mr. ISSA. Now, GlaxoSmithKline, I don't want to get into the secret work you are doing, but I am assuming with TZD having, we believe, a side effect, in other words, that it can have secondary effects as a class, not your drug but all the drugs, wouldn't it be reasonable, and say yes if you can, that you are working on the next generation that is going to reduce that either by changing the basic class of drug or by reducing the tendency of TZDs to have those potential side effect, isn't that true?

Mr. SLAOUI. Congressman, ourselves as well as many other companies have and continue to work on second generations of medicines.

Mr. ISSA. OK, now, there has been a lot of talk about statistics. But if in fact this study was normalized for the fact that TZDs all have a certain higher risk, at least anecdotally, it is believed that they tend to, that you get a good and maybe a little bad, if it had been reduced for that, wouldn't in fact the study have had different outputs? And I am only asking for one reason. Isn't it true you could have sliced these statistics several different ways to get much less alarming and yet equally accurate statistics?

Mr. SLAOUI. Congressman, meta-analyses are as good as the studies you put into them. The studies that we, the FDA and Dr. Nissen have put into the meta-analyses, the raw materials, if you wish, on which the technology acts, were not designed to look for cardiovascular events. You have heard experts here talking about adjudication of cases. The cases were not adjudicated.

So the starting material, the raw material, is not designed for the question that is being asked. The right way to ask the question, Congressman, are prospective controlled large studies. We have three of them. The three studies do not show a significant increase in cardiovascular events. We think that is very clear evidence and we seriously look forward to the discussion of the FDA advisory committee on the 30th to have an in-depth scientific debate around this.

Mr. ISSA. I thank you for that conclusive answer.

Chairman WAXMAN. The gentleman's time has expired.

Mr. McHenry, I will recognize you now for 5 minutes.

Mr. MCHENRY. I appreciate the chairman recognizing me.

I have actually one question to begin with. I know GSK was one of the first pharmaceutical companies, I believe the first pharmaceutical company to put the company's clinical, to actually publicly distribute the clinical trial register, is that correct?

Mr. SLAOUI. That is correct, yes.

Mr. MCHENRY. And there are some other companies that are now following suit. But can you describe what this means for patient safety and what this really means for public access?

Mr. SLAOUI. Congressman, it is actually very easy to access our clinical trial register. You just need to remember the name of the

company, GSK, and you put dot com next to it. I am disappointed that some may have taken a long time to reach that information.

When you get onto our clinical trial register, you can click on the name of a medicine and that takes you to every single clinical trial that has been completed, whether it was a positive outcome or a negative outcome. The trial is summarized there and you can have all the information. I think what this means is full transparency. We do not withhold any information on a completed study.

Mr. MCHENRY. I also know that we have disclaimers on all, there are disclaimers available for all prescription medicine. And it describes specifically what the manufacturer has found in the clinical trials and the research. And Avandia, beginning 1999, Avandia's label stated it was not indicated for patients with moderate or severe symptoms of heart failure.

Now, that was out of what was derived through your clinical trials, is that not correct?

Mr. SLAOUI. That is correct, sir.

Mr. MCHENRY. And that was available to the FDA before they allowed GSK to take it to the market, is that correct?

Mr. SLAOUI. Absolutely. And discussed very clearly and it was a known effect of the whole class of medicines called TZDs.

Mr. MCHENRY. I think a larger question here today is beyond that. There are short-term studies and long-term studies. GSK is very involved through third party sources, I believe, being a North Carolina company, I try to pay attention to what Glaxo has been doing. But the long-term study about the effectiveness and what medicines can do to reduce diabetes. Can you talk about some of the data and the difference between a long-term study and a short-term study?

Mr. SLAOUI. Yes. Short-term studies, usually lasting about 6 months observation period, usually allow you to have a very thorough and clear assessment of what has been called the surrogate marker here for the control of the level of blood glucose. Long-term studies allow you to look at somewhat more of the clinical events.

Diabetes is a very long-term chronic disease. It takes 10 years, 15 years, 20 years, as the expert had said earlier, for all the clinical outcomes to unfold. Running a study for 20 years is simply impractical, and those can be large population studies, not clinical trials.

So we elected to run trials over a period of 3 or 4 years that, for instance, one trial was, when you take a diabetes medicine, in fact you are condemned to fail on your medicine, because your diabetes evolves and all of a sudden your medicine doesn't work any more. So you run a trial, we ask, does Avandia allow diabetes patients to succeed controlling their glucose levels for a longer period of time than all other medicines. That is where Avandia was shown to be 30 percent or 60 percent better than the other medicine. There is another study where people that are going to develop diabetes can be identified, and within a year or two you will become a diabetic. When tested in this setting, Avandia was shown to prevent 60 percent the development of diabetes in such-called pre-diabetes patient.

So Avandia has significant public health impact and clinical advantages, above and beyond the advantages of the other available oral anti-diabetes medicines.

Mr. MCHENRY. Additionally, talk about clinical trials. Because that is something that GSK, you outsource to a third party for verification of your research, do you not?

Mr. SLAOUI. Yes. Actually, when we run the large clinical study, we have what we call a steering committee of investigators, who are totally independent from GSK, could be Dr. Nissen or Dr. Buse, who control the clinical study, control the communication around the clinical trial. We also have what we call an independent drug safety monitoring board. This is a group of experts, again, physician scientists, who look at the safety of the patients in the clinical study. And if they see an imbalance in any event, they actually have the authority to stop the study.

Every one of our studies has a BSNB. None of the BSNBs who have all been informed of all the data we are discussing have decided or elected to stop or in any way, shape or form impact the course of the studies.

Mr. MCHENRY. Thank you for your testimony.

Chairman WAXMAN. The gentleman's time is expired.

I want to ask you a few questions, if I might. Dr. Slaoui, we are not here to make the scientific determination of whether Avandia makes patients healthier or whether it harms them. That is the job of the FDA. Hopefully the new data that you have generated will go to the FDA's advisory committee that is going to be convened to address this issue and help them.

But what I am interested in is why it took 8 years after Avandia was approved for market that doctors and their patients still don't have a clear answer. Now, a major reason we don't have the data has been that there is no large, adequately designed post-marketing study of whether Avandia increases or reduces the risk of heart attack in patients with diabetes. ADOPT, the study ADOPT was a post-marketing study that your company conducted. And it was not designed to answer these questions.

Can you help us understand why, despite the recommendations of the FDA's medical reviewer, ADOPT was not designed to address the reviewer's concerns about deleterious long-term effects on the heart?

Mr. SLAOUI. Certainly, Congressman. I think as the experts from the FDA have clearly explained to this committee, and I will clarify it further, a clinical trial, in the design, addresses more than one question. The questions that the ADOPT study addressed were several, of which four very specifically were safety questions. At the time Avandia was approved, hepatic failure was a very important concern.

Chairman WAXMAN. So it wasn't a study just on heart disease, it involved other issues? That is what Dr. von Eschenbach told us. Do you agree with that?

Mr. SLAOUI. Yes.

Chairman WAXMAN. And as a result of that study, did you have enough information to tell you specifically on the heart attack question that there was no additional risk?

Mr. SLAOUI. I will share with you the data, Congressman, because everybody needs to hear it. This study had 4,400 and some patients included into it. There were 24 cases of heart attacks in the Avandia group and 20 cases in the Metformin group, the control medication. These are 4 out of 4,400 patients treated with—this a 4 individual difference. The reason we conclude that this is not a demonstration, it is a statistical methodology, is because the number of events is so small that we cannot conclude.

Chairman WAXMAN. Right.

Mr. SLAOUI. Let me share with you other information, if I may. You know and you are aware we ran a second study, the RECORD study, where the primary input for cardiovascular——

Chairman WAXMAN. That wasn't requested by FDA. That was requested by the Europeans, isn't that accurate?

Mr. SLAOUI. Yes, England.

Chairman WAXMAN. And that hasn't been completed.

Mr. SLAOUI. Yes. But I have great news for diabetes patients.

Chairman WAXMAN. I know you have some preliminary information. But let me ask you, because I only have limited time and we also have votes on the Floor, you might have heard the bells, in 2005 and then later in 2006, you did a meta-study. And of course, your meta-study could be more complete than Dr. Nissen's, because you have information that he didn't have.

As I understand it, as a result of your 2006 meta-study, you reported to the FDA, not you personally, but the company, that there was a 31 percent increased risk of heart attack and that was statistically significant. Is that an accurate statement?

Mr. SLAOUI. That is accurate. And as you have heard from every expert, including Dr. Nissen, meta-analyses generate hypotheses. They do not provide answers. We immediately acted on that information. We took it extremely seriously. We ran an epidemiological study on 33,000 patients. We analyzed the ADOPT and the DREAM studies. These are higher quality standards, scientific experimentation. When you can take a plane to Europe, you don't take a bus or a boat. Meta-analysis is a boat.

Chairman WAXMAN. Dr. Nissen's study was peer-reviewed. You didn't have to have yours peer-reviewed. Would you be willing to make available to our committee the data and the information on the meta-studies that you did in 2006 and 2005?

Mr. SLAOUI. Congressman, I would be of course very happy. Actually, for your information, this data has been available in full as of October 2006 on our Web site. And Dr. Nissen knows it.

Chairman WAXMAN. OK, that is very good. He had asked you for some information that would have made his analysis more complete. Did you ever give him that information?

Mr. SLAOUI. No, sir, but I believe that this committee has a full report on our communication with Dr. Nissen.

Chairman WAXMAN. The information on your Web site is not patient-level data. Will you make that available to us?

Mr. SLAOUI. We will provide that to this committee.

Chairman WAXMAN. We appreciate it.

I thank you very much for being here. I think your presentation was important for us to hear. We didn't have anybody request you to be on the second panel as opposed to the third panel. My staff

asked you or your representatives if you minded being on the third panel or if you wanted to be on the second panel. So I would just point that out, because it is hard to keep up with these grievances that suddenly come up. I find hard to believe there is a partisan oversight investigation.

But we are trying to get the truth, as all Members want us to get. My time is up and I am going to have to leave. But I do want to point out that I think it was pretty shocking the way Dr. Buse was treated when he came in with his complaints. Did you, did GSK ever apologize to Dr. Buse?

Mr. SLAOUI. Dr. Buse, as he stated, made actually a mistake in a very balanced and good presentation that he made in 1999. GSK, I think appropriately, requested that the mistake be corrected. There was a lot of passion, as Dr. Buse expressed at the time, on his side and on the side of the scientists which were involved——

Chairman WAXMAN. He has described intimidations. He was going to have to personally pay the $4 billion in drop in stock prices, that his university was going to be complained, the department was going to get complaints from the company. It sounded like real intimidation. You heard what he had to say, didn't you?

Mr. SLAOUI. I know the person that Dr. Buse was referring to. That person was my boss for the last 4 years, I succeeded him in this role.

Chairman WAXMAN. Who was?

Mr. SLAOUI. Dr. Yamada, who is a world-renowned scientist and currently dedicating his life to the Bill and Melinda Gates Foundation to help children and patients in the developing world. He is passionate about his work. He dedicated his life to developing drugs. And as scientists, they had quite a hefty debate and I probably would not have done it the same way. We regret that Dr. Buse felt pressured, absolutely.

Chairman WAXMAN. Thank you.

Well, I appreciate your being here. Your testimony concludes our hearing, so we stand adjourned.

[Whereupon, at 2:10 p.m., the committee was adjourned.]

[The prepared statement of Hon. Peter Welch follows:]

Statement of Rep. Peter Welch

Thank you, Mr. Chairman. And thank you for calling this important hearing.

Prescription drugs save lives. And the pharmaceutical companies are to thank for that. They are not to thank, however, for the skyrocketing costs forced upon patients and their families. This must change.

At issue today is whether pharmaceutical companies should be allowed to continue their monopoly on certain life-saving medications? The answer is clear. The answer is no.

For far too long, these companies have enjoyed staggering profits at the expense of the consumer. As we all know well, generic drugs--- drugs that the FDA approves because they are safe, pure and potent--- save patients money.

Since the passage of the Hatch-Waxman Act in 1984, we've seen just how safe and cost-effective generic drugs can be. American consumers have saved billions of dollars on prescription drugs due to generic competition---in fact, the CBO estimates that generics save consumers between $8 and $10 billion a year at retail pharmacies. In 2004, the average price of a brand name drug was $95.54, but the generic equivalent was only $28.71.

Generic equivalents work and they save patients and the public money.

Biotech, or specialty drugs, are special and unique. They are produced from living cell cultures and that is what makes them particularly effective for the treatment of anemia and cancer. And they are expensive. Many of these drugs cost patients tens of thousands of dollars each year---and some over $100,000.

No one wants to penalize or not reward the pharmaceutical industry for their innovation or their research and development. No one wants to change the patent process or interfere with current patents. But by 2010, more than $10 billion dollars worth of biotech drugs will come off patent. At that time, competition --- the backbone of the American marketplace --- should be introduced.

The FDA should have the discretion to approve safe, pure and potent copies of brand name drugs and this monopoly must end.

I look forward to hearing from the witnesses.

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