DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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STATEMENT OF

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FOOD AND DRUG ADMINISTRATION

BEFORE THE

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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.