DATE: September 2, 2010

TO: Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

FROM: John K. Jenkins, M.D.
Director
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SUBJECT: Recommendations for regulatory actions – rosiglitazone

This memorandum serves to document my evaluation of the available data and recommendations for regulatory actions for all rosiglitazone containing drug products. Please also refer to the separate memoranda from Drs. Parks and Rosebraugh dated August 19 and 23, 2010, respectively, in which they outline their conclusions and recommendations.

**Background**

The question of whether rosiglitazone increases the risk of ischemic cardiovascular events in patients with Type 2 diabetes mellitus has been the subject of intense review and analysis within and outside FDA since GlaxoSmithKline (GSK), the manufacturer of rosiglitazone, submitted the results of a meta-analysis of controlled clinical trials to the FDA in August 2006. In July 2007 the FDA presented the available data[1] to a joint public meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees.

After hearing multiple presentations from GSK, FDA staff, and the public and considering the available data, the committee members voted 20 "yes" and 3 "no" in response to the question "do the available data *suggest* a conclusion that Avandia increases cardiac ischemic risk in Type 2 diabetes mellitus?"[2] In response to the question "does the overall risk-benefit profile of Avandia support its continued marketing in the United States?" the committee members voted 22 "yes" and 1 "no".

It is important in evaluating these votes, which some inside and outside FDA have suggested are internally inconsistent and illogical, to understand that while nearly all committee members thought the available data raised a concern about an increased risk of

[1] The data presented included the GSK meta-analysis of 42 controlled clinical trials, an FDA meta-analysis of the same 42 controlled clinical trials, a meta-analysis of 42 controlled clinical trials (not the identical trials in the GSK and FDA meta-analysis) conducted by Nissen and Wolski published in the NEJM, the results of several long-term controlled clinical trials of rosiglitazone (DREAM, ADOPT, interim results of RECORD), the results of a long-term controlled clinical trial of pioglitazone (PROactive), and a meta-analysis of 19 controlled clinical trials conducted by Takeda, the manufacturer of pioglitazone.

[2] The question as originally worded by FDA asked the committee to opine on whether "the available data *support* a conclusion that Avandia increases cardiac ischemic risk", however, committee members asked that the wording of the question be changed to substitute "suggest" for "support."

cardiac ischemic events in patients treated with rosiglitazone they did not find the results persuasive enough to offset the demonstrated benefits of rosiglitazone as a treatment for Type 2 diabetes or to recommend that it not be marketed as a prescription drug. The issue of the persuasiveness of the available data suggesting an increased risk of cardiac ischemic events and how those data should influence FDA's regulatory decisions and actions for rosiglitazone remain at the core of our decisions today.

Following the advisory committee meeting there were further discussions within CDER regarding the appropriate interpretation of the data and regulatory actions, the issue was presented for review at a meeting of the CDER Drug Safety Board, staff in OND and OSE reached differing conclusions on the recommended regulatory actions, and, after considering the available data and various staff recommendations, a decision was made by Dr. Woodcock, the Acting Center Director, in October 2007. Dr. Woodcock concluded that:

- rosiglitazone containing products should not be withdrawn from the U.S. market,
- the package insert should be revised to include a boxed warning regarding the cardiac ischemic risk,
- a Medication Guide should be developed to inform patients of the risk, and
- GSK should be required to initiate a controlled clinical trial to compare rosiglitazone to pioglitazone.

CDER implemented these decisions as follows:

- the package insert was updated in November 2007 to include a boxed warning that included the findings from the meta-analysis regarding an increased risk of myocardial ischemic events such as angina and myocardial infarction as well as a statement that three long-term controlled clinical trials (DREAM, ADOPT, and interim results of RECORD) "have not confirmed or excluded this risk." The boxed warning statement concludes that "In their entirety, the available data on the risk of myocardial ischemia are inconclusive."
- the Warnings and Precautions section of the package insert was updated to recommend against co-administration of rosiglitazone with insulin or nitrates based on the subgroup analyses with the highest risk from the FDA meta-analysis.
- in May 2008 GSK was required under FDA's new authorities provided by FDAAA to conduct a long-term controlled clinical trial to assess cardiovascular outcomes of patients treated with rosiglitazone, pioglitazone, and placebo (in addition to other anti-diabetic background treatment). The protocol for this trial (i.e., the TIDE trial) was submitted to FDA in July 2008 and enrollment of patients began in February 2009.

In October 2008 Drs. Graham and Gelperin of OSE completed a review of the available data, including newly published observational trials, and concluded that rosiglitazone should be withdrawn from the market. While awaiting a determination from Dr. Dal Pan, the Director of OSE, on whether this new review included new data or arguments that should lead to a reconsideration of the Dr. Woodcock's October 2007 decision on

rosiglitazone, staff in OND continued to work with the sponsor to ensure timely initiation of the TIDE trial and submission of the final results of the RECORD trial.

In August 2009 GSK submitted the final results of the RECORD trial for FDA review. GSK also submitted an updated meta-analysis that included 10 additional controlled clinical trials that were not included in the original 2006 GSK or 2007 FDA meta-analysis. Based on these new data, GSK requested that the boxed warning for cardiac ischemic risk be removed from the package insert. OND immediately convened a review team to review these new data and initiated plans to convene a public advisory committee to revisit the cardiovascular safety of rosiglitazone in the spring of 2010.

In October 2009 Dr. Dal Pan completed a memorandum in which he concluded, as he did in 2007, that rosiglitazone should be withdrawn from the market. Following internal discussions between Drs. Dal Pan and Woodcock and myself regarding the path forward, in December 2009 Dr. Woodcock determined that OND and OSE should work together with other appropriate offices in CDER (e.g., the Office of Biostatistics) to rapidly evaluate the new data on the cardiovascular safety of rosiglitazone and present this for discussion at another public advisory committee meeting in the spring of 2010. Due to the amount of data that needed to be reviewed and the logistics involved in convening the second advisory committee meeting, the original goal of spring 2010 could not be achieved and a second joint meeting of the EMDAC and DSARM committees was held on July 13 and 14, 2010.

**The July 2010 Advisory Committee**

The background materials, agenda, questions, and transcripts of the July 2010 AC meeting are available on the FDA website.[3]

The detailed voting results from the second AC meeting are included in Dr. Parks' August 19, 2010, memorandum. The committee's discussion and voting on the proposed FDA questions was notable in that the committee members once again were uncomfortable with the wording of FDA's questions regarding the cardiovascular risk of rosiglitazone. In drafting the questions we intentionally chose to ask the questions about risk in definitive terms; i.e., "do you *find* that rosiglitazone increases the risk….." This was an effort on our part to avoid the ambiguity that arose after the first AC meeting when the committee members changed the wording of the question on risk from *"support"* to *"suggest,"* which has been widely and persistently misstated in the media and scientific journals as a more definitive determination of an increased risk.[4] Despite our encouragement that the committee vote on the questions as originally written, the committee changed the wording to "…these data are *sufficient to raise significant safety concerns* for ischemic CV events…." I interpret this change in wording to once again

[3]http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm

[4] For example, in the slides presented by Dr. Nissen at the July 2010 AC meeting the July 2007 committee's vote on the risk question was misstated as: "Advisory Committee voted 20-3 that rosiglitazone 'increases the risk of myocardial ischemia,' but 22-1 that benefits exceed risks."

reflect the committee members' discomfort with being able to reach definitive conclusions regarding the CV risk of rosiglitazone based on the available data.

In the actual voting, a majority of committee members found that the data were *sufficient* to raise significant safety concerns for ischemic CV events for rosiglitazone relative to non-TZD anti-diabetic agents and to pioglitazone, the other currently marketed thiazolidinedione. The vote was slightly stronger in favor of a *suggestion* of an adverse finding in comparison to pioglitazone than in comparison to non-TZD anti-diabetic agents. It is should be noted that 45% (for the non-TZD anti-diabetic comparison) and 36% (for the pioglitazone comparison) of committee members voted that the data either were not *sufficient* to support an increased CV ischemic risk or they were unable to make a finding based on the available data.

With regard to the question on whether the data were *sufficient* to raise significant safety concerns for mortality, a large majority of the committee voted no with regard to both comparisons. In fact, 97% (for the non-TZD comparison) and 79% (for the pioglitazone comparison) of the committee members voted that the data either were not *sufficient* to support an increased risk of mortality or they were unable to make a finding based on the available data.

When asked to vote on one of five possible regulatory actions they recommended the FDA pursue regarding rosiglitazone, there was no clear majority opinion. No members voted to allow continued marketing and removal of the boxed warning (as had been proposed by GSK in their August 2009 supplemental applications). Essentially equal numbers of committee members voted in favor of options that would allow continued marketing with no changes to the current labeling or changes that might contraindicate use in certain patients or make rosiglitazone "second line", allow continued marketing with additional label warnings and restrictions on use (e.g., restriction to prescribing to certain physicians under a REMS), or market withdrawal. Depending on one's perspective on this issue, the vote could be interpreted as a majority recommending continued marketing (20/33, 61%) or that the single option that received the most votes was market withdrawal (12/33, 36%).

Despite an impassioned presentation by Dr. Graham from OSE regarding his personal view that the TIDE trial was unethical, exploitative of study subjects, and should be stopped, the majority of the committee recommended that the TIDE trial be continued (19 yes, 11 no, 1 abstention, 1 member absent) if rosiglitazone remains on the U.S. market.[5] This suggests that the majority of committee members felt the available data are inconclusive, additional data are needed to evaluate the cardiovascular risk of rosiglitazone as compared to non-TZD anti-diabetic agents and pioglitazone, and that the TIDE trial is ethical.

**Data Sources**

[5] Note that a majority of committee members voted for a regulatory option that included continued marketing of rosiglitazone.

Data to evaluate the cardiovascular risk of rosiglitazone come from four main sources;

- meta-analyses of rosiglitazone controlled clinical trials,
- large, long-term rosiglitazone controlled clinical trials,
- observational studies of rosiglitazone compared to non-TZD anti-diabetic agents, and
- comparisons between rosiglitazone and pioglitazone from cross-study comparisons of separate meta-analyses, cross-study comparisons of large, long-term controlled trials, and observational studies that have compared the two drugs.

Detailed reviews of each of these data sources have been completed by FDA staff and were part of the background materials made available to the public as part of the recent AC meeting. I will briefly summarize here an overview of these data and their findings.

Meta-analyses of rosiglitazone controlled clinical trials

There have been numerous meta-analyses of rosiglitazone controlled clinical trials; however, I will focus on the updated meta-analysis that was completed by staff in the FDA Office of Biostatics for the 2010 AC meeting. The OB meta-analysis was based on patient level data, used rigorous statistical methodology, and importantly, was conducted by "neutral" parties in this debate, a fact that is not true of some of the other meta-analyses that have been conducted by GSK or vocal public advocates for the withdrawal of rosiglitazone (e.g., Nissen).

As has been true since the initial meta-analysis submitted by GSK to FDA in 2006, the 2010 OB meta-analysis found elevated odds ratios for important cardiovascular endpoints such as MACE, CV death, and MI in addition to the well recognized TZD class adverse effect of worsening CHF. While no statistical corrections were done for multiple comparisons, some of the endpoints achieved nominal statistical significance, and the point estimate for the odds ratio was consistently above 1.0 with the exception of stroke.[6] The OB reviewers also conducted a sensitivity analysis comparing the 2007 42-trial OB meta-analysis to their 2010 52-trial results.[7] The results of the two analyses were generally similar, although for some of the endpoints (e.g., mortality) the findings were less adverse for rosiglitazone in the 2010 analysis. The rosiglitazone meta-analysis findings remain worrisome from a safety perspective if in fact they represent the true risk of rosiglitazone in patients with Type 2 diabetes mellitus.

It is interesting that the results suggesting an increased risk for rosiglitazone were mainly driven by comparisons of rosiglitazone to placebo and were strongest in relatively short-term trials (e.g., $\leq$ 6 months). When analyzed based on trials in which rosiglitazone was compared to active comparators such as metformin or sulfonylurea, the adverse

[6] Refer to slide 26 of Dr. Callaghan's presentation to the July 2010 AC meeting.
[7] Refer to Table 1 in Dr. Rosebraugh's August 23, 2010, memorandum, which shows a comparison of the 2007 42-trial meta-analysis (updated to use the same methods used in 2010) and the 2010 52-trial meta-analysis.

cardiovascular finding was less marked overall, and actually favorable in comparison to metformin.[8] The adverse findings in short-term, placebo-controlled trials remain unexplained. Some have pointed to the fact that rosiglitazone causes an adverse shift in serum lipids (e.g., increases in LDL) to account for this finding. This explanation is not completely satisfactory for two reasons. First, in general, a beneficial effect of treatment with lipid-lowering drugs is not seen in controlled trials as early as the adverse findings seen in the short-term trials in the rosiglitazone meta-analysis.[9] Second, in long-term trials of rosiglitazone significant increases in CV risk have not been seen despite the persistence of an adverse lipid profile in those treated with rosiglitazone.

It is possible that there is some short-term adverse CV effect of rosiglitazone that is no longer active after longer-term use, but a mechanism for such a short-term effect has not been identified to date and it remains unclear why such an effect would not also be observed in comparison to other anti-diabetic agents.[10]

While the meta-analysis findings are worrisome, there are important limitations to the findings that raise doubt about how conclusive they can be considered for regulatory action, particularly a withdrawal recommendation. Some of these limitations have been outlined by other reviewers, including by the OB staff in their review and July 2010 AC presentations. Probably the most concerning in my mind is the relatively small magnitude of the increased risk (e.g., the point estimate for MACE is 1.44), the lack of statistical significance or borderline significance for the various endpoints (with no correction for multiple comparisons), the inconsistent direction of findings for MI and stroke, and the fact that the historical view of meta-analyses has been similar to that for observational studies, i.e., the observed hazard should be large and the p value very small in order to support conclusions, as opposed to hypotheses for further study.

I am not aware of any case in which results of a meta-analysis with results of the magnitude seen for the rosiglitazone controlled clinical trials have supported withdrawal of a drug. The only example I can identify where a meta-analysis of controlled clinical trials provided the data to support marketing withdrawal was Zelnorm (tegaserod). Zelnorm was indicated for the treatment of constipation-predominate irritable bowel

[8] Refer to slide 28 in Dr. Callaghan's July 2010 AC presentation. Note that these subgroup analyses must be considered with caution, for example, the metformin comparison is based on only 613 patients out of the overall meta-analysis population of 16,995 subjects and the 95% CI are very wide.

[9] Note that most trials in the rosiglitazone meta-analysis were primarily designed as efficacy trials, which generally do not emphasize to the same extent treatment of co-morbid CV risk factors, such as increased lipids and hypertension, as occurs in planned CV outcome trials.

[10] Note that no currently approved drug for the treatment of diabetes has been demonstrated to reduce the risk of cardiovascular disease. In fact, the sulfonylurea class of drugs has long carried a bolded warning regarding a 2.5 fold increased risk of cardiovascular mortality that was seen in patients treated with tolbutamide versus diet alone in the UGDP trial. It is somewhat ironic that despite this finding sulfonylureas (generally newer agents for which we do not have long-term CV outcomes data) continue to be widely used today for the treatment of Type 2 diabetes mellitus and that some individuals who have called for the withdrawal of rosiglitazone have pointed to sulfonylureas as an available alternative. In the OB 2010 meta-analysis the point estimate for the comparison of rosiglitazone to sulfonylurea for MACE was 1.17, however the 95% confidence intervals were very wide and the number of patients in this subset analysis was less than 20% of the total included in the overall meta-analysis.

syndrome and was voluntarily withdrawn by the sponsor (at FDA's request) in 2007. The FDA request for market withdrawal was based on a meta-analysis of controlled clinical trials that showed an increased risk of heart attacks, strokes, and heart-related chest pain.[11] While the numbers of patients who suffered these adverse CV events on Zelnorm was small (0.01%), the rate of events seen in patients on placebo was many fold less (0.001%), depending on the analysis performed. While not directly comparable to the rosiglitazone case in several ways (e.g., indication, seriousness of the disease) this case, and other recent cases of small adverse findings in meta-analyses, point to a general FDA philosophy that views the results of meta-analyses with great caution. FDA often communicates results of meta-analyses to the public in Drug Safety Communications or requires their addition to a package insert to ensure informed decision-making by prescribers and patients, but only in the most extreme cases have meta-analyses supported withdrawal of a drug from the U.S. market.[12]

Large, long-term rosiglitazone controlled clinical trials

Around the same time that GSK submitted their rosiglitazone meta-analysis to FDA in 2006 the results of two large, long-term controlled clinical trials comparing rosiglitazone to placebo in pre-diabetics (DREAM) or to sulfonylurea or metformin (ADOPT) in patients with diabetes became available. Dr. Parks summarized the results of these trials in her AC presentation at the July 2010 meeting and they were discussed in greater detail at the 2007 AC meeting.[13] In short, neither of these studies supported a finding of a significant adverse effect of rosiglitazone on MACE, MI, or mortality.[14] These findings are somewhat reassuring despite the fact that the trials have weaknesses for estimating risk. Specifically, neither trial was designed as a CV outcomes trial and the background risk of CV events for patients enrolled in both trials was low, decreasing the power of the trials to detect differences if they were present.

Shortly before the 2007 AC meeting, an interim analysis of the RECORD trial was published. These data were discussed in detail at the 2007 AC meeting and probably served to reassure some members to the AC regarding the CV safety profile of

[11] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051284.htm

[12] Note that despite the multiple fold increase in risk seen for Zelnorm in the meta-analysis, some have questioned FDA's reliance on such small numbers of events to withdraw the only approved treatment for constipation-predominate irritable bowel syndrome. They note that while this disease is not generally life-threatening, it is very disabling to many patients and that other available (off-label) treatment options do not work for these patients. This highlights the fact that even large potential increases in risk of serious events may be tolerated by physicians and patients depending on their individual risk tolerance, the baseline risk of the patient involved, the absolute magnitude of the risk, the effect of the drug in individual patients, and the benefits and risks of available alternatives.

[13] Refer to slides 8-11 of Dr. Parks' July 2010 AC presentation.

[14] Note that I am focusing on the comparison of rosiglitazone to placebo in DREAM, which is most relevant to the signal seen in the meta-analysis, and not the comparison of rosiglitazone plus ramipril versus placebo plus ramipril where a non-significant increased risk of MACE and MI, but not mortality, was seen. To my knowledge this finding has not been explained and was not confirmed by sub-group analyses of ADOPT and the interim results of RECORD. The data from this comparison are included in the rosiglitazone package insert.

rosiglitazone since RECORD is the only long-term controlled clinical trial that was prospectively designed to assess CV outcomes of rosiglitazone.

RECORD was undertaken by GSK as a postmarketing commitment to the EMEA and FDA was not involved in its design or conduct.[15] The final results of RECORD were submitted to FDA by GSK in August 2009 and have been subjected to extensive review and audit by FDA staff.[16]

Interpretation of the RECORD trial has proven to be quite controversial, both within and outside FDA. The main area of contention relates to the fact that RECORD was an open-label trial and the protocol left considerable discretion to the study investigators in determining which adverse events to refer for adjudication by the blinded central adjudication committee. It should be noted that many CV outcomes trials have by necessity been open-label, so that design feature is not in-and-of itself a fatal flaw. In order to provide reliable results, an open-label trial requires a protocol that is very carefully designed to minimize the potential for bias (intentional and unintentional) and the protocol procedures must be rigorously adhered to by all participants. The concerns related to an open-label trial design are further heightened in the case of a non-inferiority trial, such as RECORD, since "sloppiness" in trial conduct tends to bias toward the null and a finding of non-inferiority. The hypothetical concerns about the reliability of the RECORD results were increased by the findings of Dr. Marciniak from DCRP, who in the course of his audit of the trial found cases that raised legitimate concerns about whether there was a bias favoring rosiglitazone in referral by investigators of adverse events to the adjudication committee.[17]

These legitimate concerns about the RECORD trial make it impossible for FDA to use the results as reported by GSK and the study investigators (and Dr. Marciniak) as a basis for a regulatory decision, with the possible exception of the findings on overall mortality. While I understand Dr. Marciniak's concerns about possible bias and under ascertainment of mortality, I agree with Dr. Unger that the RECORD mortality findings are probably

[15] There have been many criticisms of the design and conduct of the RECORD trial and suggestion that the design does not meet FDA's current standards. Such statements are factually accurate, but do not outweigh the need to review RECORD carefully to learn what we can from this large trial.

[16] Refer to reviews and slides from the 2010 AC meeting from OND (DCRP, DMEP, ODE I), OB, and DSI staff.

[17] Dr. Marciniak conducted a limited audit of case report forms from the trial and noted 8 patients he considered should have been referred for adjudication, but were not. All 8 were on rosiglitazone. DSI evaluated these 8 cases as part of their audits of the RECORD trial and found that 7 of the 8 were handled according to the study protocol and there was no evidence of investigator misconduct. The DSI findings, do not, however, mean that referral bias was not operational in RECORD or that these cases would not have been referred for adjudication in a well designed trial. Subsequent to the July 2010 AC meeting, Dr. Unger reviewed a limited subset of CRFs from the RECORD trial and noted 3 patients he felt should have been referred for adjudication, but were not. All 3 were on placebo. Note that Dr. Marciniak also conducted a re-adjudication of the RECORD trial results and presented these new analyses in his review and AC presentation. This re-adjudication did not follow well recognized scientific principles for such efforts, and as such, the resulting analyses cannot be viewed as fairly representing the true outcomes of the RECORD trial. FDA would not accept such analyses from a sponsor if conducted in this manner and cannot base our regulatory decisions on Dr. Marciniak's results.

reliable based on the fact that vital status was reported known for approximately 97% of the trial participants and mortality is much less subject to investigator bias than other endpoints, such as MI or stroke. There was no evidence of an adverse effect of rosiglitazone on mortality, in fact, the Kaplan-Meir analysis reported by GSK favored rosiglitazone with a HR of 0.79 (95% CI 0.62 – 1.02).[18]

In my view, the data from RECORD as currently reported by GSK and the study investigators is of limited value in addressing the MI or MACE findings from the meta-analysis, but it provides reasonably strong evidence to address the non-significant, but worrisome, finding on overall mortality seen in the 2010 OB meta-analysis. The lack of an effect on overall mortality in RECORD is an important finding.

I agree with Drs. Parks and Rosebraugh that RECORD should be re-adjudicated in a proper and step-wise fashion to provide reliable data. The re-adjudication should first address overall mortality and if the re-adjudicated results are similar to those reported by GSK and the study investigators, should move to consider other events (e.g., hospitalizations, MACE), which will be more labor intensive and time consuming.

I do not agree with some in CDER who have suggested that a proper re-adjudication of RECORD would not be of value in helping to further address the outstanding questions regarding the safety of rosiglitazone. While the protocol allowed for the introduction of bias in referral of adverse events for adjudication, the underlying records of the study participants can still provide useful information. In addition to confirming (or not) the GSK-reported mortality findings, a properly conducted re-adjudication could require that ALL hospitalizations be referred to a blinded committee, independent of GSK, for adjudication. While a decision to hospitalize a patient is a subjective decision, it is less likely that investigators would have been biased in making a decision on hospitalization, which is a routine part of medical care, as compared to a decision on whether to report the event for adjudication. A re-adjudication of hospitalizations would provide new data on the components of the MACE endpoint, which are the key adverse events in question. It would be a disservice to the subjects who enrolled in the RECORD trial to allow legitimate concerns about investigator bias in adverse event referral to deter us from learning all that is possible from the trial data.

Observational studies of rosiglitazone compared to non-TZD anti-diabetic agents

This section will be limited to observational studies versus non-TZD comparators. Dr. Gelperin from OSE presented a systematic review of published epidemiology studies of cardiovascular risk in patients treated with rosiglitazone at the July 2010 AC meeting. She identified 7 observational studies (4 case control studies and 3 cohort studies) that compared rosiglitazone to other non-TZD anti-diabetic agents. Taken as a whole, these studies failed to demonstrate a signal of concern for acute myocardial infarction and all-cause mortality in rosiglitazone treated patients, while the studies did detect the well recognized increased risk of CHF in rosiglitazone-treated patients.[19] These findings are

[18] Refer to slide 30 from Dr. Unger's 2010 AC presentation.
[19] Refer to slides 8-10 from Dr. Gelperin's July 2010 AC presentation.

consistent with the OB 2010 meta-analysis, which did not identify a signal of concern for the subset of trials where rosiglitazone was compared to an active control, and also consistent with the findings from the large, long-term trials (ADOPT and RECORD) in which rosiglitazone was compared to metformin or sulfonylureas.[20]

Comparisons of rosiglitazone to pioglitazone

A natural question in making regulatory decisions regarding a serious safety concern is how the drug in question compares to the other members of the same class.[21] Unfortunately, as is often the case, there is no adequate head-to-head comparison of rosiglitazone to pioglitazone in a controlled clinical trial. This has led to many cross-study comparisons and observational studies to try to compare the safety risks and benefits of these two drugs. Cross-study comparisons are fraught with hazards and conclusions on their basis should be considered with great caution. In this case, such comparisons do shed light on how the data available for safety of rosiglitazone compares to that available for pioglitazone from the various sources.

*Large, long-term controlled clinical trials of pioglitazone*
PROactive was a large, long-term cardiovascular outcomes trial that compared pioglitazone to placebo when added to background anti-diabetic therapy. The primary endpoint was a composite of a variety of cardiovascular outcomes that included outcomes not typically included in a CV outcomes trial (e.g., major leg amputations). The primary analysis failed to demonstrate a statistically significant benefit of pioglitazone (HR 0.90, 95% CI 0.80 – 1.02, p=0.0954), but a secondary analysis of the composite of all-cause mortality, MI, and stoke was nominally statistically significant (HR 0.84, 95% CI 0.72 – 0.98, p=0.0277).[22] FDA did not consider this study adequate to support labeling for CV risk reduction with pioglitazone as the sponsor requested, but the results were not suggestive of CV harm in patients treated with pioglitazone.

*Meta-analysis of pioglitazone controlled-clinical trials*
The FDA Office of Biostatistics conducted a meta-analysis of 29 pioglitazone controlled clinical trials and presented these results at the July 2010 AC meeting. The pioglitazone meta-analysis was conducted using selection criteria and statistical procedures that were the same as those used for the 2010 OB meta-analysis of rosiglitazone controlled clinical trials. This was done to ensure that the meta-analyses were as comparable as possible, however, there were many differences in the types of trials and the patient populations enrolled as outlined by the OB reviewers. The OB reviewers included strong warnings in

[20] For RECORD I'm mainly referring to the mortality findings, which I believe are interpretable. For the other endpoints, such as MACE, the GSK and investigator reported findings cannot support a regulatory action pending confirmation by the suggested re-adjudication.
[21] Comparative assessments of drugs are generally limited to two situations in our regulatory decision-making. First, if one drug in a class appears to cause a serious adverse effect that does not occur, or occurs at a lower frequency or severity, for the other drugs in the class we consider whether the drug in question offers unique benefits to offset the unique risks. Second, if a drug appears to be less effective for an important endpoint such as mortality or irreversible morbidity, we consider whether the drug has other attributes, such as a better safety profile, that might offset the efficacy differences.
[22] Refer to slides 12-13 from Dr. Parks' July 2010 AC presentation.

their review and AC presentations about the appropriateness of cross-study comparisons of the rosiglitazone and pioglitazone meta-analyses, but I believe it is useful to compare the findings in a qualitative manner.

For the primary analysis, the pioglitazone group tended to have odds ratios that were close to or below 1.0 for endpoints such as MACE, CV death, MI, and stoke, and none were nominally statistically significant. There was a statistically significant increase in CHF in the pioglitazone group, a well recognized adverse event associated with TZDs. A sensitivity analysis that included the results of two large, long-term pioglitazone controlled trials (including PROactive) demonstrated very similar point estimates for the OR for all endpoints, tighter 95% CI, and for some endpoints the results were nominally statistically significant.[23] The results for MACE were analyzed by subgroups based on the type of comparator therapy and showed a point estimate for placebo-controlled trials that favored pioglitazone, unlike the finding of increased risk that was seen for the placebo-controlled trial subgroup in the rosiglitazone meta-analysis. For the active controlled trials, the findings for MACE for pioglitazone were essentially neutral and very similar to what was seen in the rosiglitazone meta-analysis.[24] Thus, the main driver of differences between the overall pioglitazone and rosiglitazone meta-analyses was from placebo-controlled trials. As noted in the OB presentations at the July 2010 AC meeting, 81% of the subjects in the rosiglitazone meta-analysis were from placebo-controlled trials, while 39% of the subjects in the pioglitazone meta-analysis were from placebo-controlled trials.

While, in general, the results of the meta-analysis for pioglitazone tended to show neutral or favorable results; the pattern was not true for all endpoints. This contrasts with the general pattern that was seen for rosiglitazone, where most results were neutral to adverse, with a few findings beneficial to rosiglitazone. Again, these general observations must be taken with great caution in making scientific and regulatory inferences since there were significant differences in the sources of data underlying the two meta-analyses with regard to comparators, trial duration, types of patients enrolled, etc.

*Observational studies comparing rosiglitazone and pioglitazone*
Since the 2007 AC meeting a number of observational studies have been published that have attempted to compare the CV risks of rosiglitazone and pioglitazone. Dr. Gelperin presented a systematic review of these published studies at the July 2010 AC meeting. She identified 4 case-control and 5 cohort studies that provided comparative data.[25] Dr. Gelperin concluded that "overall, comparisons of rosiglitazone and pioglitazone for outcomes including myocardial infarction, congestive heart failure and all cause mortality favor pioglitazone." She further noted that "no studies were identified in this review with results suggesting a protective cardiovascular effect of rosiglitazone compared to pioglitazone."

[23] Refer to slide 13 from Dr. McEvoy's July 2010 AC presentation.
[24] Refer to slide 45 from Dr. McEvoy's July 2010 AC presentation.
[25] Not all studies provided data on all endpoints or comparisons.

The forest plots that Dr. Gelperin showed in her advisory committee presentation would seem to support these conclusions, however, it is important to note that the odds ratios and hazard ratios from these studies were almost all under 2.0, and in the vast majority of the cases were less than 1.5. Due to the fact that observational studies are not prospective randomized comparisons, one must always be cautious in interpreting results with small effect sizes since they could be false positives due to unidentified confounding factors. That is not to dismiss the findings from the observational studies, but rather an attempt to keep them in perspective as they are considered to support scientific and regulatory inferences, particularly inferences that might lead to an action as significant as market withdrawal of a drug. It is also important to keep in mind the possibility of publication bias when considering published observational studies.

More recently, Dr. Graham from OSE and colleagues from CMS reported the results of a very large cohort study that was conducted using data from Medicare claims. The study involved more than 220,000 patients over 65 years of age who were initiated on either rosiglitazone or pioglitazone. This study has much strength, including the fact that even though the groups were not randomized to therapy, their baseline characteristics were very similar. The study found statistically significant increases in adjusted hazard ratios for stroke, heart failure, death, and composites of these three endpoints for patients treated with rosiglitazone, however, there was no significant difference for acute myocardial infarction. This latter finding is of interest since that was one of the "hypotheses" that came from the original rosiglitazone controlled trial meta-analyses.

Dr. Graham and his co-authors postulated that their failure to demonstrate an adverse finding for MI might be due to a higher percentage of acute MIs in older patients resulting in out-of-hospital death, which would not be captured in the medical claims data that were used for this study. They, in effect, concluded that there was in fact a greater risk of MI in the study population, even though such an effect was not actually observed. While an interesting hypothesis, such an explanation is highly speculative and has been met with great skepticism by experts in OND with experience in evaluating CV outcome trials and some experts on the AC.

It is noteworthy that the two other published observational studies included in Dr. Gelperin's review that were conducted in elderly patients also showed a finding of no increased risk of acute MI and significant increases in other CV endpoints. In all three studies the magnitude of increased risk observed was small. In the CMS study the magnitude of the effects seen were generally in the range of HR of 1.15 – 1.25. These are very small effects and their interpretation is the subject of much debate since they are derived from observational studies where patients were not randomized to treatment. For observational studies, hazard ratios under 2.0, even if nominally statistically significant, are generally viewed with great skepticism and caution in making scientific and regulatory inferences both inside and outside FDA. Of course, these effect sizes of increased risk <u>if real</u> would be of significant concern.

During the open public hearing at the July 2010 AC meeting, representatives from Healthcore presented the results of an observational study comparing CV effects of

rosiglitazone and pioglitazone that was conducted using the Wellpoint insurance claims database. A preliminary version of this study was presented at the July 2007 AC meeting and the final report was recently published.[26] The study was a cohort design and used propensity score matching to control for potential confounders. The data were collected prior to the May 2007 publication of the Nissen meta-analysis. The study included over 36,000 total patients, and matched over 29,000 patients for baseline variables. The mean duration of follow up was approximately 19 months and the mean duration of treatment was approximately 14 months for both drugs.

The primary endpoint in the Healthcore study was a composite of acute MI, acute heart failure, or death. There was no significant difference for the primary endpoint between rosiglitazone and pioglitazone-treated patients for either the matched patients (HR 1.03; 95% CI 0.91 – 1.15, p=0.666) or for all patients (HR 1.00; 95% CI 0.90 – 1.11, p=0.981). There was also no significant difference for any of the individual components (AMI, AHD, or death) of the composite endpoint in the matched patients. A subset analysis was conducted in over 5300 patients over 65 years of age and no significant difference was seen for the primary endpoint (HR 0.97, 95% CI 0.83 – 1.12) or any of its individual components. The estimated event rate per 1000 person-years for AMI was 6.18 for rosiglitazone and 6.74 for pioglitazone in the matched patients and 16.45 for rosiglitazone and 15.22 for pioglitazone in the patients over 65 years of age. The estimated event rate per 1000 patient-years for death was 11.44 for rosiglitazone and 11.22 for pioglitazone in the matched patients and 42.9 for rosiglitazone and 44.75 for pioglitazone in patients over 65 years of age.

The results of the Healthcore study are of great interest since the study was conducted by a "neutral" party in the rosiglitazone debate and appears to have well designed and conducted. While the study is much smaller than the CMS study, the authors used propensity score matching of baseline variables to control for confounding and the duration of average study drug treatment was much longer than that reported in the CMS study. The results of this study do not support the findings seen in the CMS study and raise doubts regarding the true comparative CV safety of rosiglitazone and pioglitazone. In order to explore these data further, we have requested that Healthcore submit the underlying study data for further review by FDA. That request is pending.

**Discussion**

Despite the vast amount of data that have been accumulated and analyzed to address the question of cardiovascular safety of rosiglitazone, the interpretation of these data remains highly controversial among experts both inside and outside FDA. While many have concluded that the available data demonstrate that rosiglitazone definitively increases the risk of ischemic CV events in patients with Type 2 diabetes and have loudly called for market withdrawal, others consider the data inconclusive and believe additional controlled clinical trials are need to more definitively answer the question. Recently, an

[26] Wertz DA, Chang CL, Sarawate CA, Willey VJ, Cziraky MJ, Bohn RL. Risk of cardiovascular events and all-cause mortality in patients treated with thiazolidinediones in a managed care population. Circ Cardiovasc Qual Outcomes. 2010;3:538-545.

expert panel from the American Heart Association and the American College of Cardiology Foundation concluded that the available data were inconclusive and "insufficient…to support the choice of pioglitazone over rosiglitazone."[27] The panel further stated that "More data are urgently needed to clarify the effects of all existing and future glucose-lowering agents, including the thiazolidinediones, on IHD (ischemic heart disease) events," and that "thiazolidinediones should not be used with an expectation of benefit with respect to IHD events."

The rosiglitazone case is an example of the reality that the science (specifically the data) rarely is so definitive that it points to an obvious and widely agreed upon regulatory decision. In the absence of definitive data FDA must still make sound decisions. These are necessarily based on the available data and our understanding of its strengths and weaknesses, but must also consider the law, regulations, precedents for similar cases, the disease treated by the drug, alternative treatment options, patient and physician preferences, "population" benefit-to-risk considerations and even the role of the practice of medicine versus government decision-making and the importance of autonomy of physicians and patients to make decisions about medicines. In the end, all the decisions we make at FDA become a judgment of whether the benefits of the drug outweigh the risks when used as labeled, and these judgments are very much influenced by how one considers all the complex factors that must be considered and weighed.

Unfortunately, in the passion of debate on such critical public health issues some parties lose focus on this reality and begin to demonize those who interpret the data differently and do not agree with their conclusions. Such movement away from healthy debate to name calling and accusations of malfeasance do not serve the public health and can jeopardize the integrity of the FDA decision-making process. As noted by Dr. Rosebraugh in his August 23, 2010, memorandum, the public scrutiny of FDA and its decisions regarding rosiglitazone safety has been unprecedented in its scope and intensity. In making our decisions in such an environment, which is becoming more and more common in today's rapid access to information and increased avenues for voicing one's opinion, we must listen carefully to these voices to understand their underlying assumptions and positions, but also take care to not allow the loudness or intensity of the stated positions to unduly influence our decision making. Our job as regulators and servants of the public health is to reach the best possible decision, not simply one that responds to the loudest voice. It is important to recall that in science, often the loudest voices and conventional wisdom are later proven to be wrong

As I consider the available data, I agree with the majority of the advisory committee members that there continue to be signals of concern regarding the possibility that rosiglitazone is associated with an increased risk of serious ischemic CV adverse events in patients with Type 2 diabetes mellitus. What is less clear is whether the newly

[27] Kaul, S., Bolger, A., Herrington, D., Guigliano, R., Eckel, R. Thiazolidinedione Drugs and Cardiovascular Risks – A Science Advisory From the American Heart Association and the American College of Cardiology Foundation. Journal of the American College of Cardiology 2010;55(17)1885-94. Note that this was published before the July 2010 AC meeting and therefore did not include FDA's review of the RECORD trial or the CMS observational study.

available data that inform this issue are sufficient in their magnitude and consistency to warrant a change from the regulatory action that was taken by CDER in 2007; i.e., including warnings in the package insert and Medication Guide so that physicians and patients can make informed decisions about whether to use rosiglitazone as part of a treatment regimen.

The CDER decision in 2007 to allow continued marketing also included a clear goal to obtain more data to definitively answer the important outstanding questions. That prompted FDA to require GSK to conduct the TIDE trial, which is designed to directly compare rosiglitazone, pioglitazone, and placebo (added to standard of care) in a prospective, randomized trial designed to assess cardiovascular outcomes. Such a trial remains the best option to generate the scientific data needed to more definitively answer the question, but some have raised questions about the ethics of the TIDE trial and have called for it to be halted. In reality, the ethical debate about the TIDE trial comes down to the question of how persuasive one considers the available data regarding ischemic CV risk of rosiglitazone. If one has concluded that the signals of increased risk represent the real effects of the drug and are of a magnitude that warrants withdrawal of the drug or imposition of severe restrictions on its use, then the TIDE trial as currently designed would be unethical. On the other hand, if one considers the available data to be inconclusive, equipoise would still exist and the TIDE trial would be ethical.

In my view the available data for ischemic CV risk of rosiglitazone, while concerning, do not rise to the level that would support a regulatory conclusion that the benefits of the drug as a treatment for Type 2 diabetes no longer outweigh its risks, which is the statutory finding FDA must reach to withdraw approval of a drug. Such decisions as this require a careful balance between placing the threshold for action too high or too low. If the threshold for action is placed too high there is greater protection against actions based on false positive results, but there is also a greater risk that patients will be subjected to undue harm by continued availability of a harmful drug. On the other hand, if the threshold for action is placed too low there is a greater chance of actions based on false positive results with the unintended consequence that physicians and patients do not have access to a safe and effective drug.

In weighing the available data for rosiglitazone the primary signals of concern arise from meta-analyses of controlled clinical trials that were not designed to rigorously collect CV outcome data and observational studies. Data from these sources provided risk estimates of a magnitude that fall well short of what has traditionally been considered a level that would support scientific and regulatory inferences, even in the face of nominal statistical significance. Further, there is considerable inconsistency in the findings across the various sources of data, which calls into question the reliability and robustness of the signals. For example, in the meta-analysis the results for stroke are favorable for rosiglitazone, but in the CMS study they are adverse. Similarly, the signal of increased risk of MI from the meta-analysis, the original signal of concern, was not seen in the CMS study or in some other published observational studies, including the recently published Healthcore study. Also, the adverse findings on mortality suggested by the meta-analyses and seen in the CMS study were not seen in the Healthcore study or in the

long-term controlled trials (i.e., DREAM, ADOPT, and RECORD).[28] While I do not believe the available data are adequate to support a decision to withdraw approval or severely restrict use of rosiglitazone, I do think it is important to ensure that prescribers and patients are aware of the concerns regarding increased risk, and that such information can and should be taken into account in making treatment decisions for individual patients.

Based on my conclusion that the available data are inconclusive in showing an increased risk of ischemic CV risks in patients treated with rosiglitazone, I believe that the TIDE trial is ethical and its conduct remains critical to providing the answers needed to allow the FDA to make an informed regulatory decision regarding the risks and benefits of the TZD class of drugs. I believe that under these assumptions the criteria outlined in the IOM expert committee report letter are met and the trial should continue once the informed consent documents and investigator's brochure are updated to appropriately reflect the currently available data and FDA's decision on the safety of rosiglitazone (i.e., the partial clinical hold imposed on the trial by FDA after the July 2010 AC meeting should be lifted). Just as individual prescribers and patients can consider the available data and make informed individual treatment decisions, I have confidence that local IRBs and ethics committees, investigators, and potential trial subjects can make informed decisions about whether to participate in the trial. Despite the conclusions of others to the contrary, I believe, and the votes and discussion from the July 2010 AC meeting support, that equipoise exists regarding the comparative risks and benefits of rosiglitazone, pioglitazone, and placebo, when added to background standard of care for treatment of Type 2 diabetes mellitus. I believe that a conclusion that pioglitazone is safer than rosiglitazone for CV endpoints remains uncertain and such a critical question warrants a well designed head-to-head comparative trial.

As noted by Dr. Rosebraugh in his August 23, 2010, memorandum, many of the same issues regarding comparative risk/benefit and ethics for rosiglitazone are extant in the ongoing PRECISION trial comparing the CV effects of celecoxib, ibuprofen, and naproxen. Just as that trial is viewed as vital to support valid scientific and regulatory inferences about the NSAID/COX2 class of drugs, where serious concerns have been raised by other controlled trials and observational studies about differential risk/benefit properties of the members of the class, the TIDE trial is vital to address the risk/benefit profile of the TZD class of drugs. The PRECISION trial is just one example of important large, post-marketing safety trials that could be placed in jeopardy if FDA sets the bar too low on the question of when a concern about differential safety between drugs in a class leads to a conclusion that it is unethical to conduct a more definitive trial. That would have a very damaging long-term impact on the ability to actually collect information to

[28] The FDA/CMS partnership provides an exciting new source of data on drug utilization and outcomes in the U.S. elderly population covered by Medicare. I believe it is important for FDA to do further work to explore the sensitivity and specificity of this new tool. Given the large size of the database, we need to better understand how to interpret small, but statistically significant, findings like those seen for the rosiglitazone versus pioglitazone comparison. This could be done by running analyses of variables that are not linked to the outcome of interest to see how often a finding might be reported simply by chance. It is my understanding that OSE staff are working on such analyses. I suggest that these be conducted by experts independent of the recent rosiglitazone study to avoid any perception of intellectual bias.

confirm or refute safety concerns and to provide the evidence needed to support appropriate use of drugs. I believe that trial subjects can be appropriately informed of the potential risks and that their safety can be ensured by employing an independent expert Data Monitoring Committee to oversee the trial in real-time with clear stopping rules should a signal of harm emerge.

I recognize that others may come to different conclusions regarding the appropriate path forward and regulatory actions for rosiglitazone. If the FDA decides to allow continued marketing of rosiglitazone and continuation of the TIDE trial as I recommend, it is safe to assume that the critics of the drug will remain vocal in their opposition and the attendant public attention may jeopardize the ability to complete the trial in a timely manner. A similar situation arose several years ago related to Crestor and the JUPITER trial. Once FDA carefully reviewed and rejected the claims made in a Citizens Petition of increased risk of serious adverse effects, the trial was completed and provided important new information regarding the benefits (an effect on survival in a lower risk population) and risks (the concerns raised in by the Petitioner were not observed) of Crestor. It is my hope that a clear FDA statement that the available data are inconclusive and that the TIDE trial should continue will allow for rapid completion of trial enrollment and timely completion of the trial. Under FDAAA we have clear authority and enforcement tools to ensure that GSK devotes the necessary resources to complete the trial in a timely manner.

There was discussion at the July 2010 AC meeting about whether rosiglitazone should be made "second line" in its labeling as a way to mitigate the concerns about increased CV risk. No clear consensus developed on what was meant by "second line," although some advocated for labeling that would state that rosiglitazone should be reserved for patients who are judged to need a TZD and who have failed to adequately respond to, or cannot tolerate, pioglitazone. As noted above, the data to support such a labeling path are inconclusive and I do not support such language. I agree with Dr. Parks that the labeling for all TZD's should be changed to indicate that they are not for initial use in patients who have failed a trial of diet and exercise and now require pharmacologic intervention to treat their diabetes. This is warranted given the well recognized class effects of TZDs on fluid retention and exacerbation of CHF. I also agree with Dr. Parks that the labeling for rosiglitazone should be amended to state that a signal of increased CV risk has not been seen with pioglitazone, and while this does not clearly support preferential use of pioglitazone in all patients, it should be considered by the prescriber and patient in making decisions about which TZD to initiate and be considered in making decisions about whether to continue a patient on rosiglitazone.

Finally, there was discussion at the July 2010 AC meeting about the possibility of a REMS with restricted distribution if rosiglitazone remains on the market. I do not support imposition a REMS with restricted distribution. First, I believe that the available data to support the concern regarding differential risk of rosiglitazone to non-TZD anti-diabetic agents and pioglitazone remains inconclusive, and thus a REMS is not warranted. Second, the data presented at the AC show that few new patients are initiating use of rosiglitazone since the 2007 publicity about the potential ischemic CV risk and the labeling changes that followed the July 2007 AC meeting. It appears that most of the

patients who are currently taking the drug have been on it for some time, and given the widespread media coverage, it is unlikely that they and their physician have not considered the issues in dispute in making their decision to continue use of the drug. In other words, if the goal of the REMS would be to restrict use, that has already occurred and the usage pattern would likely be maintained if the package insert for rosiglitazone were changed as described above. Third, I do not believe this case meets the criteria we have applied in imposing a restrictive REMS on the healthcare system. We have generally limited the use of restrictive REMS to cases where the drug with a unique safety concern is felt to offer a unique benefit to patients. I agree with others that there are no data to support a conclusion that rosiglitazone is more effective in treating Type 2 diabetes than pioglitazone; however, in making our decisions on benefit and risk of drugs one of the important factors we consider is the availability of a choice of therapies for prescribers and patients. Given that I find the available data on a differential risk between the two TZDs to be inconclusive, I believe that it is important to retain both drugs as choices in patients who are felt to need a TZD to manage their diabetes. I believe that prescribers and patients can make, and have been making, informed decisions in the absence of a restrictive REMS and recommend the labeling changes outlined above instead of a burdensome new REMS.

**Recommendations**

In summary, I recommend that:

- rosiglitazone continue to be marketed as a prescription drug,
- the package insert and Medication Guide be updated as described above to reflect the newly available information so that physicians and patients can continue to make informed decisions regarding its use,
- the sponsor be required to re-adjudicate the RECORD results,
- the partial clinical hold on the TIDE trial should be lifted once the informed consent and investigator's brochure are updated to reflect the new data and the FDA's decision on the marketing status,
- the sponsor be required to commit the necessary resources to ensure that the TIDE trial is fully enrolled and completed in a timely manner, and
- a truly independent DSB be charged with closely monitoring the TIDE trial so that the trial can be stopped at the earliest sign of a clear adverse safety signal.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-21071 | SUPPL-35 | SB PHARMCO PUERTO RICO INC | AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T |

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/s/

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JOHN K JENKINS
09/02/2010
Recommendations for regulatory actions regarding safety issues.