DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-002

DIVISION DIRECTOR'S MEMO

DATE: August 19, 2010

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TO: Curtis J. Rosebraugh, M.D., M.P.H.
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SUBJECT: Recommendations on marketing status of Avandia® (rosiglitazone maleate) and the required post-marketing trial, Thiazolidinedione Intervention and Vitamin D Evaluation (TIDE) following the July 13 and 14, 2010 public advisory committee meeting

I. INTRODUCTION

On July 13 and 14, 2010, the Food and Drug Administration's Center for Drug Evaluation and Research (CDER) held a second advisory committee meeting involving members of the Endocrine and Metabolic Drugs Advisory Committee (EMDAC), the Drug Safety and Risk Management (DSARM) Committee, and invited experts in biostatistics, epidemiology, endocrinology, and ethics to discuss cardiovascular safety concerns involving Avandia®, hereafter referred to as rosiglitazone. This memo serves as the final recommendations from the Division of Metabolism and Endocrinology Products (DMEP) regarding the marketing status of rosiglitazone and the status of the required postmarketing trial, Thiazolidinedione Intervention and Vitamin D Evaluation, hereafter referred to as the TIDE trial.

On the second day of the meeting, panel members were asked six voting questions. These questions were preceded by requests for discussion. Prior to the formal discussion session, a majority of the panel members voted to revise four of the six voting questions (Questions 2, 3, 5, and 6 were revised). I have summarized below all voting questions posed to the panel members, including the revisions made, and the final votes. The results of the votes and the explanations for each member's vote, along with the discussions from the meeting, were considered in the Division's decision. Please see the transcripts from the two-day advisory committee meeting for a detailed account of all presentations, discussions, and recommendations available at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm191113.htm

VOTING QUESTIONS (ORIGINAL AND REVISE) AND FINAL VOTING RESULTS

2. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
B. Does not increase the risk of ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
C. I am not able to make a finding A or B.

REVISED QUESTION #2
Considering the available data, do you find that, for rosiglitazone (choose 1):

A. These data are sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
B. These data are not sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents.
C. I am not able to make a finding A or B.

VOTING RESULTS:
A. 18
B. 6
C. 9

3. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
B. Does not increase the risk of ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

REVISED QUESTION #3
Considering the available data, do you find that, for rosiglitazone (choose 1)

A. These data are sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
B. These data are not sufficient to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

VOTING RESULTS:
A. 21
B. 3
C. 9

5. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
B. Does not increase the risk of mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
C. I am not able to make a finding A or B

REVISED QUESTION #5
Considering the available data, do you find that, for rosiglitazone:

A. These data are sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
B. These data are not sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to non-TZD anti-diabetic agents
C. I am not able to make a finding A or B

VOTING RESULTS:
A. 1
B. 20
C. 12

6. (ORIGINALLY WORDED) Considering the available data, do you find that rosiglitazone (choose 1):

A. Increases the risk of mortality in patients with Type 2 diabetes relative to pioglitazone
B. Does not increase the risk for mortality in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

REVISED QUESTION #6
Considering the available data, do you find that, for rosiglitazone (choose 1):

A. These data are sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to pioglitazone
B. These data are not sufficient to raise significant safety concerns for mortality in patients with Type 2 diabetes relative to pioglitazone
C. I am not able to make a finding A or B

VOTING RESULTS:
A. 7
B. 12
C. 14

8. Based on the available data, which of the following regulatory actions do you recommend FDA pursue regarding rosiglitazone? Please select only one option or if you wish to abstain, do not vote. (These options are listed from most favorable to rosiglitazone to least favorable to rosiglitazone and do not reflect any prejudgment on the part of FDA.)

A. Allow continued marketing and revise the current label to remove the boxed warning and other warnings regarding an increased risk of ischemic CV events, or
B. Allow continued marketing and make no changes to the current label, or

C. Allow continued marketing and revise the current label to add additional warnings (e.g., contraindications for certain patient populations, recommendation for second-line use in patients intolerant of or uncontrolled on other anti-diabetic agents); or
D. Allow continued marketing, revise the current label to add additional warnings, and add additional restrictions on use (such as restricting prescribing to certain physicians or requiring special physician and patient education)
E. Withdrawal from the U.S. market

VOTING RESULTS:

A. 0
B. 3
C. 7
D. 10
E. 12
Abstain: 1

9. If rosiglitazone remains on the U.S. market, do you recommend that the TIDE trial be continued in order to provide further data on the comparative CV safety of rosiglitazone, pioglitazone, and standard-of-care management of type 2 diabetes (placebo add-on)?

Vote Yes/No/Abstain

VOTING RESULTS:

YES: 19
NO: 11
ABSTAIN: 2
NON-VOTING: 1 (member departed before meeting adjourned)

In reviewing the data presented and the advisory panel recommendations I have concluded the following:

1. Rosiglitazone should not be withdrawn from the market
2. The labeling for rosiglitazone and all rosiglitazone-containing products must be revised to reflect current information on cardiac ischemic risks
3. A postmarketing trial, such as TIDE, should be conducted to obtain interpretable data on the CV safety of rosiglitazone to inform FDA on an appropriate regulatory action.

In the remainder of this memo I will outline the reasons for my recommendations and action items for each of these recommendations.

II. RECOMMENDATION #1: Rosiglitazone should not be withdrawn from the market

I am making this recommendation because I do not believe there is sufficient evidence from available data to conclude that rosiglitazone is associated with significant cardiovascular risks to outweigh its benefits as an effective glucose-lowering agent. We also do not have adequate and well-controlled data comparing rosiglitazone to pioglitazone to conclude that pioglitazone is a safer alternative and should be the only marketed thiazolidinedione available to patients.

The clinical evidence put forward to conclude rosiglitazone has cardiovascular risks has come from:

A. Meta-analyses of controlled clinical trials of rosiglitazone
B. RECORD trial
C. Indirect comparisons of rosiglitazone to pioglitazone from observational studies of health claims database
    1) Published observational studies
    2) Retrospective cohort study of Medicare claims
D. Separate meta-analyses of controlled clinical trials of rosiglitazone and pioglitazone

As there are well over 1000 pages recently prepared by the FDA on these four sources of clinical data, I will only highlight the key findings from and the characteristics of these data which have swayed me in the direction of recommending the continued availability of rosiglitazone in the U.S. In this memo, I will only discuss the new information presented by FDA at the July 13 and 14, 2010 advisory committee meeting.

A. Meta-analyses (MA) of Randomized Controlled Clinical Trials of Rosiglitazone

There were multiple meta-analyses performed of randomized controlled clinical trials of rosiglitazone, all suggesting a risk for cardiovascular harm associated with rosiglitazone use. Although the large sample size of these databases (data from 16,995 patients in FDA's 2010 MA and 35,531 patients in Nissen's 2010 MA) and the inclusion of only randomized, controlled trials are strengths of these databases, the limitations were numerous and outweighed these strengths. Unlike rare drug-related safety concerns such as Stevens-Johnsons syndrome, agranulocytosis, or rhabdomyolysis, which are more easily identified and attributed to drug exposure, CV events are common in the diabetes patient population and require more precision in their ascertainment and adjudication. Reliance on meta-analyses, particularly the ones considered for rosiglitazone, is problematic for the following reasons:

- The MAs were comprised of studies that were not prospectively designed to evaluate cardiovascular risk in patients with type 2 diabetes. These studies, like all other clinical trials for anti-diabetic therapies approved at that time, were designed to assess glycemic control effectiveness. As a result, CV events were not prospectively adjudicated in a blinded fashion but relied on investigator reporting of adverse events in the clinical trial which has the potential for biased ascertainment and misclassification contributing to an imprecision in assessing CV risk.
- The overall event rates were too low to allow a meaningful assessment on a common condition. In the FDA's 2010 MA, the overall incidence of MACE was 0.6%. In order to accurately determine whether a drug is associated with an excess CV risk, a sufficient number of events is needed to determine if different event rates between treatment groups reflect true risk differences and not chance finding.
- The majority of these trials were < 1 yr duration. In the FDA 2010 MA, 45/52 (86%) of the trials were < 1 yr duration. Trials of short duration may not be adequate to assess long-term CV risks and benefits. To highlight this point the following table shows the risk estimates in the FDA's 2010 MA broken down by duration of trials for MACE, CV death, MI, stroke, and all-cause death where a trend of decreasing risk is noted with longer duration of evaluation on all events except stroke.

Table 1. FDA's Meta-analysis of Rosiglitazone Trials Subgrouped by Trial Duration

Outcome	Trials < 6 mos (21 trials)			Trials ≥ 6 mos to < 1 yr (24 trials)			Trials ≥ 1 yr to ≤ 2yrs (7 trials)		
	RSG N=2942	Control N=2258	OR (95% CI)	RSG N=5729	Control N=3504	OR (95% CI)	RSG N=1368	Control N=1194	OR (95% CI)
MACE	12	2	4.5(0.97,4.2)	36	19	1.3(0.73,2.5)	22	18	1.19 (0.6,2.38)
CV death	2	0	Inf (0.09,inf)	12	3	2.8(0.73,15.6)	3	6	0.5(0.08,2.37)
MI	10	0	Inf (1.75,inf)	22	10	1.57(0.7,3.78)	13	10	1.21(0.49,3.13)
Stroke	2	2	0.6(0.04,9.04)	10	9	0.74(0.26,2.12)	6	5	1.23(0.3,5.1)
All-cause death	5	1	3.78(0.4,183.4)	15	5	2.02(0.68,7.22)	9	11	0.83(0.30,2.22)

Similarly, in the long-term CV outcomes trial with pioglitazone (PROactive), assessment of CV risk at 6 months in this 3-yr trial showed an unfavorable trend for this drug compared to placebo for nonfatal MI, stroke, acute coronary syndrome, major leg amputation, coronary intervention, and leg revascularization procedures (Table 2 below).

Table 2 Results for Predefined Secondary Endpoints for PROactive (Measured at 6 Months)

Endpoint	Pio N=2605 n (%)	Pbo N=2633 N (%)	HR[1]
Cardiovascular mortality	20 (0.8)	27 (1.0)	0.8
All-cause mortality	25 (1.0)	30 (1.1)	0.9
Nonfatal myocardial infarction	28 (1.1)	24 (0.9)	1.2
Stroke	20 (0.8)	17 (0.6)	1.3
Acute coronary syndrome	14 (0.5)	8 (0.3)	1.7
Major leg amputation	4 (0.2)	2 (0.1)	2.0
Coronary intervention (coronary artery bypass grafting or percutaneous coronary intervention)	33 (1.3)	32 (1.2)	1.1
Leg revascularization	18 (0.7)	9 (0.3)	2.3

Source: Tables 1-12, Table 2.1, Table 2.2, provided by Takeda by email 13 May 07
1 Pio rate/ pbo rate; confidence intervals for the 6-month hazard ratios not provided

If assessment for CV risk of pioglitazone was limited to just 6 mos or < 1 yr, a similar conclusion of CV harm might have been made for this drug.

- Choice of studies to include in a MA can have a marked effect on the risk estimate. This was noted in Nissen's 2010 MA when he presented data including and excluding the RECORD trial. The point estimate shifted by 10% and 37% for MI and CV death, respectively. In both analyses, exclusion of the long-term trial resulted in a higher risk estimate.
- There was no prospective analysis plan that would correct for multiple comparisons. Many CV events were analyzed in these MAs and no correction for multiplicity was applied. Disparate findings (e.g., increase risk of MI, decreased risk of stroke) may be weighted differently depending on what position one holds in this debate.

Overall, the meta-analyses of rosiglitazone trials suggest a signal of CV risk; however, the limitations of such a database in assessing this risk, the inconsistent findings between the MA and long-term controlled trials on stroke and mortality, and the non-robust increase with marginal statistical significance all require

the FDA to apply a more rigorous scientific standard beyond reliance on these MAs alone to withdraw rosiglitazone from the U.S. market.

B. Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) Trial

RECORD was an open-label trial comparing the addition of rosiglitazone to metformin when either one was added on to background sulfonylurea and the addition of rosiglitazone to sulfonylurea when either one was added on to background metformin. The primary objective was to show non-inferiority, defined as the demonstration that the upper bound of a two-sided 95% CI for the hazard ratio would be below 1.2, between rosiglitazone combined with either metformin or sulfonylurea to the combination of metformin and sulfonylurea on the primary composite endpoint of CV death and CV hospitalizations. The published results and data presented by GlaxoSmithKline (GSK) supported the company's conclusion that the primary objective was met and that rosiglitazone had no significant CV risk over two commonly prescribed anti-diabetic agents. In an efficacy supplement, GSK is proposing removal of language on increased risk of myocardial ischemia from the boxed warning and elsewhere in the product label based on the findings from RECORD.

Dr. Tom Marciniak from the FDA's Division of Cardiovascular and Renal Drug Products (DCRP) identified deficiencies in events reported to the adjudication committee and undertook a re-adjudication of a random sample of case report forms (CRFs) from the rosiglitazone and control groups. He identified 8 adverse events which should have been sent for adjudication by the investigator and all cases were in the rosiglitazone group. All 8 cases were reviewed by the Division of Scientific Investigations and an FDA medical officer from DCRP who participated in the inspection of several clinical sites. Only one of the 8 cases was identified as inappropriately dismissed by the investigator as a possible endpoint that should have been sent to the adjudication committee.

In his readjudication of events, Dr. Marciniak recalculated hazard ratios based on his assessment of which events should have been counted as MI, stroke, CV death, or MACE. His analyses yielded higher risk estimates for MI and MACE, not favoring rosiglitazone. Although his findings are concerning, I can not conclude that his numbers reflect the true event rates in this trial because an unblinded readjudication by one individual applying a more current definition for some of these events which occurred out to 10 years ago may also introduce its own bias. Furthermore, even though his re-analysis of CV death and all-cause death showed less of a risk reduction for rosiglitazone, the overall finding still favored rosiglitazone. I also agree with Dr. Ellis Unger, who wrote a secondary review accompanying Dr. Marciniak's review, that the mortality findings, which are less subject to biased adjudication and consistently show a lower risk for rosiglitazone in both the ITT and per-protocol analyses, provide me with reassurance that the RECORD trial may provide relevant long-term CV safety data for rosiglitazone since it has been argued that the majority of deaths in the diabetes population is CV-related.

Regardless of the differences in opinion, I agree with the important points made by both Drs. Marciniak and Unger, that the open-label design and the allowance for investigators to determine whether an event should be submitted for adjudication by the blinded endpoint committee diminishes the strength of this randomized, controlled trial. However, since RECORD remains the ONLY large, completed, prospectively-designed, controlled trial that might immediately address the concerns raised from the meta-analyses, I believe the FDA should require GSK to re-adjudicate events in this trial by an independent committee (no GSK representation) with clearly defined procedures for identifying events vetted by a team of cardiologists and neurologists. Because this will be a significant undertaking, I would propose a re-adjudication of mortality findings be performed initially. If significant problems are identified with completeness of vital status and causality of death, I would conclude that RECORD can not be relied upon and no further efforts should be placed into complete adjudication of this trial. If this initial re-adjudication yields similar findings to what the applicant reported in its efficacy supplement, a complete re-adjudication should then be undertaken for MI, stroke, and CV death, the components of

MACE, and the composite endpoint that is more widely accepted in intervention trials assessing CV risks and benefits.

I would note that Drs. Teerlink and Geller both recommended re-adjudication of RECORD in their responses to voting questions 2 and 3 and Dr. Flegal also raised concerns about Dr. Marciniak's "revisiting" events in RECORD without having his findings adjudicated.

C.1. Published Observational Studies

At the July 2010 advisory committee meeting, Dr. Kate Gelperin presented her review of published controlled epidemiologic studies of rosiglitazone and pioglitazone. The methodology for selecting published studies has been described in her review. She identified 21 studies: 7 nested case-control and 14 cohort, all retrospective in design. Events of interest included acute MI, stroke, mortality, coronary artery disease, heart failure, angina pectoris, transient ischemic attack, cerebrovascular accidents, coronary heart disease, coronary revascularization, unstable angina, cardiac death, and coronary artery procedures. Many of these outcomes were identified through ICD-9 or -10 codes but some studies relied on other identifiers unique to the healthcare database upon which the studies were based. Some of the studies identified the outcome of interest based on the primary reason for hospitalization. It should be noted that this endpoint was a component of the primary endpoint in RECORD and was criticized by Dr. Tom Marciniak as follows:*"CV hospitalization reasons are diverse and include ones that are unlikely to be affected by one drug."* And as noted by Dr. Gelperin, collection of only hospitalized events would miss events not requiring hospitalization. Consequently, complete ascertainment and appropriate adjudication of events are some of the limitations of this database.

Another concern about the observational studies is the contribution of publication bias to the availability of data. Since studies published after 2007 may be affected by the Nissen meta-analysis either as publication bias or biased reporting of events, it is important to note the year of publication for all 21 studies. Of the 21 studies, only two were published before 2007 (Karter and Rajagopalan) and both of these involved the comparison of pioglitazone to another anti-diabetic agent (SU or insulin). Therefore, we have no published observational studies evaluating rosiglitazone specifically prior to 2007. Of the remaining 19, 3 were published in 2007, 4 in 2008, 10 in 2009, and 2 in 2010.

The review was a qualitative evaluation of cardiovascular safety between rosiglitazone and other anti-diabetic agents, pioglitazone and other anti-diabetic agents, and rosiglitazone and pioglitazone. The FDA's Office of Biostatistics was consulted but as noted in their conclusions and recommendations, no quantitative analysis was performed due to dissimilarities across the 21 studies. They further noted that "interpretation of results from graphical displays (e.g., forest plots) that include different measures of effect (e.g., odds ratio vs. hazard ratio, adjusted vs crude) or different study designs (e.g., case-control vs cohort) should be done with caution."

One of the panel members, Dr. Sanjay Kaul, called attention to the reluctance of the biostatisticians to make inferences from these data and also questioned whether there was any pre-specified hypothesis in these studies that was justified by the findings (question not answered by FDA at meeting) and whether the analyses corrected for multiple comparisons. FDA statistician, Dr. LaRee Tracy responded that perhaps one or two adjudicated for multiplicity. In the FDA statistical review, Dr. John Yap stated under his Summary and Conclusions that "*many of the studies showed multiple comparisons for various anti-diabetic agents or assessed multiple outcomes. However, these studies did not provide any adjustment for multiplicity which could result in inflated type 1 errors.*"

Notwithstanding the limitations already outlined by FDA biostatisticians, I would again emphasize that these observational studies are retrospective analyses of non-randomized comparisons between drugs on unadjudicated outcome measures whose data are subject to biased reporting and decisions by medical journals to accept for publication. Differences in patient demographics, risk factors, concomitant medical

conditions and medications and other factors and their impact on the results, are largely unknown. At best, I view these data as hypothesis-generating and insufficient evidence to support regulatory action to withdraw rosiglitazone from the market.

C.2. Retrospective cohort study of Medicare claims

This study represented the most comprehensive effort of the agency to obtain comparative safety data between rosiglitazone and pioglitazone. It remains a retrospective and non-randomized comparison of the two drugs but its strengths, as listed below, should not be dismissed.

- Largest patient database comparing these two drugs
- Baseline characteristics and risk factors between the two drugs were comparable at T0 (time of initiation of each TZD)
- CV endpoints of acute MI, stroke, heart failure, and all-cause mortality were appropriate. Of note, the selection of only events coded by ICD-9 codes in only the 1st or 2nd position may reduce the potential for selecting non-specific events or remote events which might not be associated with drug use
- Patient population (≥ 65 years) is a relevant subset of patients with T2DM who are at greater CV risk than younger cohorts. Although clinical trials do not exclude patients ≥ 65 years of age, the percentage of such patients often make up a minority of those enrolled in prospective clinical trials.
- Information on concomitant anti-diabetes medication revealed that the majority of these patients received either pioglitazone or rosiglitazone as add-on therapy to metformin or sulfonylurea which may reflect the more appropriate use of the products
- The *post-hoc* analyses performed to assess the affect of the Nissen meta-analysis on different patients entering the study provided reassurance that the findings did not reflect differences in patients *enrolling* in the program

I believe this is a higher quality epidemiologic study with efforts to control many of the confounders often precluding definitive conclusions made from these types of data. However, I do not believe the results from this observational study support a regulatory decision for drug withdrawal for the following reasons:

- The signal of CV risk for rosiglitazone identified in the original and subsequent meta-analysis and observed in other databases has been increased myocardial infarction. The inability to demonstrate a significant difference in MI risk between rosiglitazone and pioglitazone in a database of this magnitude is perplexing. The explanation given by Dr. Graham that these older patients are manifesting their cardiavascular disease differently and are presenting with sudden cardiac death is speculative although means of obtaining cause of death in the 2562 fatalities should be explored.
- The mean and median durations of follow-up (162 and 105 days, respectively) represent a very short timeframe of assessment for the overall cohort. Similar to concerns raised about the short-duration of treatment exposure in the meta-analysis limiting ability to adequately evaluate CV risk for both these drugs apply in this study.
- After the Nissen MA in May 2007 there was a sharp decline in patient entry for the rosiglitazone cohort. Dr. Graham looked at the characteristics of patients in both treatment groups before and after May 2007 and did not identify any significant differences in the patients entering the two treatment groups before and after this time point. However, from Figure 8 in Dr. Graham's review, only 22.2% of this cohort were initiated on rosiglitazone for the remainder of the study whereas 63.5% of the pioglitazone were new initiators after this timepoint. So while there were no differences between the two cohort for new initiators (tended to be younger post May 2007), the rosiglitazone cohort after this time point had a higher percentage of patients who were not new initiators. As described by Dr. Mahoney in her presentation, the pioglitazone cohort after May 2007 was continually being refreshed with new initiators whereas the rosiglitazone cohort

after May 2007 had a greater percentage of patients who were initiated before this timepoint remaining in the trial. This imbalance in the two cohorts and what impact it had on the event rates for the remaining 25 months of the study is not known.

- The risk estimates are concerning but for an observational study, adjusted hazard ratios of 1.27 for stroke, 1.25 for heart failure, 1.14 for all-cause mortality, 1.11 for acute MI or death, 1.15 for acute MI, stroke, or death, and 1.18 for all four combined, are modest increases that we can not entirely dismiss the effect of unmeasured biases on these findings. This was also noted by voting DSARM member, Dr. Morrato, as she explained her votes on Questions 5 and 6. At a minimum, additional sensitivity analyses should be performed on this database to determine whether such modest findings are more likely due to the large sample size of the database.

In conclusion, I do not believe the Medicare study provides sufficient evidence for a regulatory decision on *both* the marketing status and labeling changes for rosiglitazone. As noted above, I believe there are strengths in this study and the FDA should carefully review it further as it was only recently completed.

There would also be value in querying the database for other differences between these two drugs. In particular, FDA should determine if there are differences between these two drugs for cancer risk. As pointed out in the FDA background package, pioglitazone and many other dual PPAR-alpha and -gamma agonists have nonclinical cancer findings. For pioglitazone, a finding of excess bladder tumors in male rats at clinically relevant exposures can not be dismissed given the imbalance in the rate of bladder cancer not favoring pioglitazone observed in two 3-year clinical trials. For the past three years, the primary focus has been on cardiovascular safety of rosiglitazone and whether it should remain on the market. Yet do we know enough about the safety of the remaining thiazolidinedione to confidently make it the sole TZD for patients? The uncertainty in risk of cancer with pioglitazone was raised in 2007 by one member (Dr. David Schade) and again in 2010 by two members (Dr. Weide and Dr. Henderson).

D. Separate meta-analyses of controlled clinical trials of rosiglitazone and pioglitazone

The last new piece of information presented at the July 13 and 14, 2010 advisory committee was the FDA's updated meta-analysis of rosiglitazone trials and its meta-analysis of pioglitazone trials. In 2007, FDA did not conduct a meta-analysis of pioglitazone trials, citing differences between the two clinical development programs and the lack of patient-level data for the pioglitazone trials that would not enable construction of a comparable set of databases for purposes of making definitive conclusions on CV safety between these two drugs. Despite these concerns, these comparisons were done both internal and external to FDA and have formed the basis for some to conclude that pioglitazone is a safer alternative to rosiglitazone to support withdrawal of this drug from the market.

To determine whether such comparisons or conclusions were scientifically justifiable, FDA biostatisticians performed a meta-analysis of trials of each of these two drugs. The rationale for study selection and methodology has been described in their reviews but to reiterate, the objectives of the meta-analyses were to assess the CV risks of each of these drugs individually, to assess the differences between the clinical trials available for the two drugs, and to the extent possible, to make qualitative comparisons between the safety profiles of the two drugs. The same endpoints and statistical analytical approaches were applied to both meta-analyses. Despite these efforts to achieve parity between these two databases, the two FDA biostatisticians, Drs. Callaghan and McEvoy, noted the obvious differences between the two development programs. And on multiple occasions, Drs. Callaghan and McEvoy, emphasized the limitations of comparing these meta-analyses to each other through the following points made in each of their presentations:

- most trials were not prospectively designed to evaluate cardiovascular endpoints
- results of trials were known before statistical analysis plan was developed
- statistical significance was not adjusted for multiple testing
- comparisons between the two meta-analyses are subject to the deficiencies of cross-trial comparisons

The overall findings for these meta-analyses were that pioglitazone tended to have less risk compared to controls whereas rosiglitazone tended to have higher risk compared to controls for the MACE endpoint (Figure 1). None of the findings reached statistical significance. For CHF, both drugs tended to have greater risk compared to controls (Figure 2).

Figure 1. Overall Results of Meta-analyses for Pioglitazone and Rosiglitazone on MACE Endpoints (Forest Plot created by Dr. Bradley McEvoy and presented at July 13 and 14, 2010 advisory committee meeting)

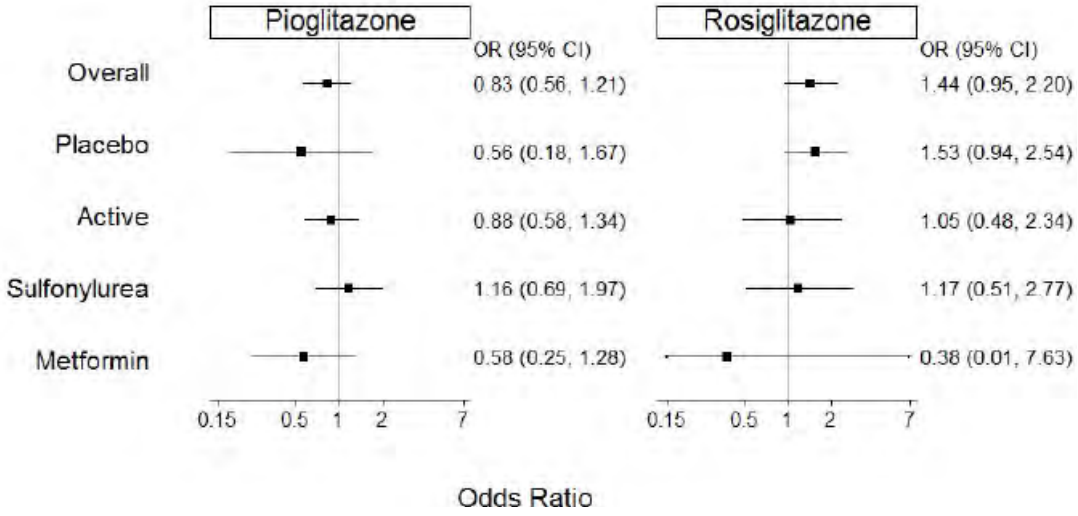
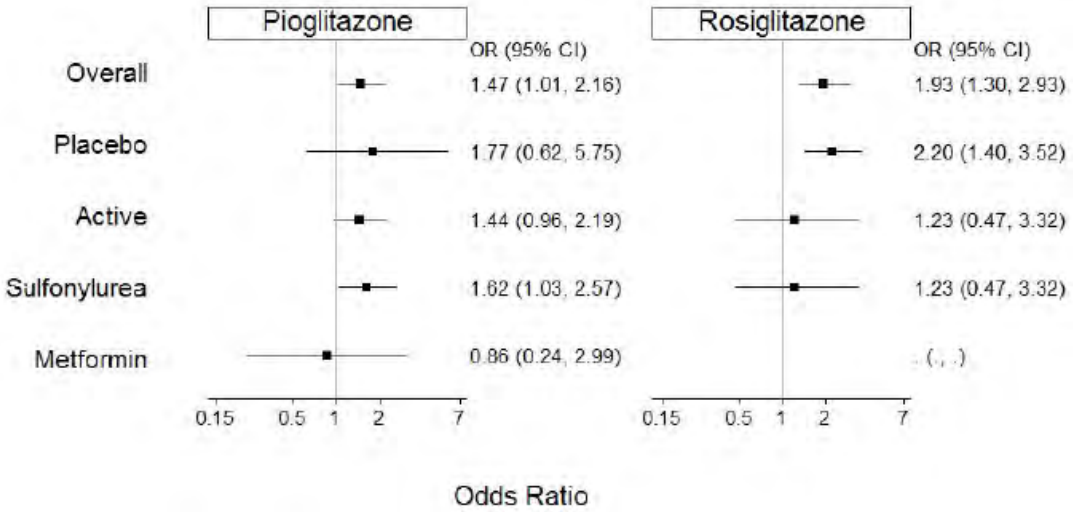


Figure 2. Overall Results of Meta-analyses for Pioglitazone and Rosiglitazone on CHF Endpoint (Forest Plot created by Dr. Bradley McEvoy and presented at July 13 and 14, 2010 advisory committee meeting)



In looking at these side-by-side forest plots, I would concur with many others that a concerning signal of increased risk for CV ischemic events defined as MACE (CV death, MI, and stroke) is present with rosiglitazone relative to comparators but not evident in the pioglitazone trials. For CHF, both drugs show

a greater risk than their comparators, which is consistent with the known class effect of these drugs. In both meta-analyses, comparators were primarily metformin and sulfonylureas. Except for one 24-week study to compare lipid effects of rosiglitazone and pioglitazone, none of the trials included in these meta-analyses compared rosiglitazone to pioglitazone. Hence, the FDA has no direct, randomized comparison of these two drugs in order to make accurate CV safety comparisons.

The limitations of these meta-analyses for evaluating CV risk of these drugs have already been outlined in earlier sections of this memo. Given these limitations and the magnitude of these risk estimates, I am concluding that neither of the meta-analyses represents adequate and well-controlled studies to support any definitive conclusion on the risks and benefits of pioglitazone or rosiglitazone individually. At best, these data should be viewed as signals requiring further investigation. By extension, if these meta-analyses are not sufficient for a definitive conclusion on risks and benefits of the individual drugs, it would be inappropriate to make comparative safety claims between the two products by taking each meta-analysis with its inherent limitations and compare it to the other because we lack a direct head-to-head study of the two drugs. Consequently, I have concluded that the individual meta-analyses provide insufficient evidence to recommend withdrawal of rosiglitazone by way of citing a safer alternative with pioglitazone.

III. RECOMMENDATION #2: The labeling for rosiglitazone and all rosiglitazone-containing products must be revised to reflect current information on cardiac ischemic risks

Although I have argued under Section II that each of the data sources does not provide sufficient evidence for me to conclude risks outweighing benefits for rosiglitazone to recommend its withdrawal, I believe the data sources meet the regulatory requirements to modify safety labeling for this drug. Sections of the package insert (or professional labeling) pertaining to safety that should be updated for rosiglitazone include its Contraindications, Warnings and Precautions, and Boxed Warning. Any changes to these sections of the package insert should then be reflected in the Medication Guide and other communication plans to the public.

In this section of my memo, I base much of my recommendations on the requirements for labeling cited under 21CFR201.57 and the Guidance for Industry titled, *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products*. The changes to the Contraindications and Warnings and Precautions sections of the rosiglitazone label should be reflected in its Boxed Warning.

Contraindications

In addition to the current contraindication for use in patients with NYHA Class III or IV heart failure, rosiglitazone should be contraindicated in:

- Patients currently receiving insulin

  The basis for this recommendation comes from the consistent observation of an increased OR of approximately 2.0 for CV ischemia in the MAs involving the insulin trials. There may be a reasonable explanation for this observation as all of these trials involved patients who were already receiving insulin and had a long duration of diabetes that would make them more sensitive to the fluid-retaining effects of rosiglitazone. Patients currently receiving insulin can achieve adequate glycemic control through appropriate dosing and titration of their insulin making the addition of rosiglitazone to insulin non-essential.

- Patients at high risk for a CV ischemic event as defined by recent acute coronary syndrome or who are symptomatic requiring use of anti-anginal therapies

  The basis for this recommendation comes from a concern that the fluid-retaining effects of rosiglitazone may be poorly tolerated in this vulnerable patient population limiting any benefit of glycemic control.

Warnings and Precautions

I believe the updated meta-analysis of rosiglitazone clinical trials performed by the FDA reflects continued concern about cardiovascular ischemic risk with this drug's use. Although the limitations of the meta-analysis preclude a definitive conclusion about this risk, the addition of 10 new studies has not weakened this signal but has rather shown a shift for myocardial infarction from slightly non-significant to slightly significant. Consequently, the labeling should be changed to discuss risk of myocardial infarction not myocardial ischemia, as observed in the updated meta-analysis. This recommendation will affect Section 5.2 of the currently approved label and the accompanying text in the boxed warning.

Twenty members of the advisory committee panel did not vote to remove rosiglitazone from the market. Three of these members did not recommend any changes to the current label while 17 voted for options which recommended revisions to the labeling, including 10 who voted for the addition of restrictions on use. However, in reading the explanations given by these 17 members, there was no clear universal recommendation on what to revise or add to the label. Recommendations broadly covered restricted use with a registry to no specific recommendation other than its availability would signify choices to prescribers. Several members made note that the market already shows preferential use of the alternative

drugs over rosiglitazone. In and among the pages of transcribed discussion was the suggestion that rosiglitazone be reserved for second-line use.

Second-line use was referred to in a variety of ways by panel members. Some suggested that rosiglitazone be second-line therapy only after pioglitazone while others suggested it be second-line after metformin. One member specifically suggested second line therapy for the class of TZDs. I highlight only a few direct quotes below to make these points.

- Dr. Hammerschmidt: "…I'm concerned that there might be a small group of people out there who don't do well on pioglitazone for whom this might be a good salvage drug."
- Dr. Kaul: "Make sure that this is available as a second line, not as a first line, especially if metformin cannot be used in the patients…."
- Dr. Vaida: "…I actually like the recommendation for second-line use. And I'd like to put the qualifier on second-line for thiazolidinediones so rather than just any agent."

My recommendation here is to label <u>against</u> use of rosiglitazone or any rosiglitazone-containing product (Avandamet or Avandaryl) as a first-line agent after the patient has failed to achieve adequate glycemic control on diet and exercise alone. I do not recommend that the label specifically advise physicians to select pioglitazone before rosiglitazone because the evidence upon which to base such a recommendation is not from adequate and well-controlled studies but from observational studies or comparisons of meta-analyses of two different clinical development programs. I am concerned about the precedent that would be set in which the quality of evidence from meta-analyses and observational data and there non-robust signal of excess risk will be relied upon to recommend use of one drug over another within and across a broad class of drugs. If the FDA makes such a labeling change with rosiglitazone, will it then entertain meta-analyses of other anti-diabetics, lipid-altering drugs, anti-hypertensives, or osteoporosis drugs and label a hierarchy for use which will circumscribe prescribing practices? How will FDA deal with a supplement containing a meta-analysis or observational study performed by a drug company to show that its drug has equal efficacy but a lower rate of a singled-out safety concern relative to its comparator supporting labeling changes for preferential use of its drug over the comparator?

Labeling against first-line use can be similar to what was done with the recent approval of the anti-diabetic agent, Victoza (liraglutide), in which the following statements were made under Indications and Usage, Limitations of Use:

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise (under Highlights section)
- Because of the uncertain relevance of the rodent thyroid C-cell tumor findings to humans, prescribe Victoza only to patients for whom the potential benefits are considered to outweigh the potential risk. Victoza is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise (under the Full Prescribing Information section of labeling).

In this setting, another drug is not identified as preferred over Victoza. Instead, prescribers are cautioned against using Victoza first.

For rosiglitazone, the Full Prescribing Information section might state the following:

Indications and Usage
Important Limitations of Use

- *A meta-analysis of 52 randomized controlled trials demonstrated an increased risk for major cardiovascular events (MACE) comprised of CV death, MI, and stroke associated with AVANDIA relative to comparators (metformin and sulfonylureas). Although the trials comprising the meta-analysis were not designed to investigate CV risk, there has not been sufficient evidence from large long-term trials to dismiss this finding of increase CV risk. Therefore, AVANDIA is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise or who are at increased risk for a heart attack such as those with prior heart disease or the elderly (see Warnings and Precautions).*

Although specific text for a revised label should involve others on the FDA review team, I would propose the following text for consideration under the Boxed Warning to replace the current language on CV ischemic risk. The class labeling for congestive heart failure will remain the same for both rosiglitazone and pioglitazone.

- *A meta-analysis of 52 randomized controlled trials demonstrated an increased risk for major cardiovascular events (MACE) comprised of CV death, MI, and stroke associated with AVANDIA relative to comparators (metformin and sulfonylureas). Although the trials comprising the meta-analysis were not designed to investigate CV risk, there has not been sufficient evidence from large long-term trials to dismiss this finding of increase CV risk (see Warnings and Precautions)*

- *No adequate and well-designed head-to-head studies have been conducted between rosiglitazone and another member of the thiazolidinedione class to assess CV risks. However, a similar finding of excess CV risk has not been identified with another drug in the TZD class. Consequently, this information should be considered in any clinical decision to initiate therapy with rosiglitazone, especially in patients with established heart disease or the elderly.*

- *Avandia is contraindicated in the following:*
  -Patients with NYHA Class III or IV heart failure
  -Patients currently receiving insulin
  -Patients with symptomatic heart disease (e.g., current use of nitrates) or with a recent acute coronary events (e.g., past 6 months)

I am proposing that a statement clearly describe the current situation in which there are no direct head-to-head comparisons between rosiglitazone and pioglitazone. I am also willing to describe the absence of an CV ischemic risk finding observed with pioglitazone so that a prescriber can be informed enough to decide what drug is appropriate for his/her patient.

IV. RECOMMENDATION #3: A POSTMARKETING TRIAL, SUCH AS TIDE, SHOULD BE CONDUCTED TO OBTAIN INTERPRETABLE DATA ON THE CV SAFETY OF ROSIGLITAZONE TO INFORM FDA ON AN APPROPRIATE REGULATORY ACTION

My recommendation to allow the continuation of TIDE stems from the arguments I have laid out under Sections II and III. Since I do not believe there is sufficient evidence to conclude that rosiglitazone has greater cardiovascular risk than other anti-diabetic agents and pioglitazone, I believe that each of the treatment arms proposed in TIDE is appropriate. Similarly, the two co-primary research questions in TIDE are appropriate as discussed below:

1. Does adding a TZD (either rosiglitazone or pioglitazone) reduce MI, stroke, or CV death vs placebo (N.B. this is standard diabetes care not NO treatment)?

This research question is not describing a non-inferiority trial design but a question of whether TZDs will result in CV benefit over current diabetes care. To date, this question has not been answered, including for pioglitazone in its PROactive trial. Safety concerns of weight gain, fluid retention, and heart failure associated with the TZDs are countered by beliefs that improved insulin sensitivity, durable glycemic control, and lower risk for hypoglycemia are characteristics of these drugs which will result in long-term benefits, including the prevention of diabetes. Absent data from adequate and well-designed trials, practice guidelines have not endorsed the use of these drugs as first-line therapy. TIDE would be able to test whether there is long-term clinical benefit of this class of drugs to better inform its use in the chronic management of Type 2 diabetes.

The fact that all FDA-approved labels for anti-diabetic agents carry the statement that "there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with *Drug X* or any other oral antidiabetic drug" is indicative that even this regulatory agency has not concluded CV benefit of one drug over another to oppose this research question from the TIDE trial.

2. Is rosiglitazone non-inferior to placebo with respect to the composite of MI, stroke, or CV death?

This is similar to what the FDA is requiring of all new anti-diabetic agents under its recent Guidance for Industry titled "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes"[1]. New anti-diabetic therapies need to show that they do not result in an unacceptable increase in CV risk by way of establishing non-inferiority to placebo add-on to standard-of-care diabetes therapies.

Both Drs. Graham and Gelperin from the FDA have been opposed to the conduct of TIDE. In Dr. Graham's presentation he stated in Slide 4 that the primary analysis will compare rosiglitazone vs non-TZD, not rosiglitazone vs pioglitazone, the more clinically relevant comparison. It should be noted that they have each already concluded that pioglitazone is a safer drug than rosiglitazone in their 2008 memo, so to modify the protocol to address this criticism would also contradict their position that such a comparison is unethical.

Nonetheless, the TIDE trial, as originally designed, included secondary analyses to determine if one TZD was superior to the other. Based on estimated event rates and proposed sample size, the trial had over 90% power to demonstrate a 25% relative risk reduction between these two drugs over a period of 5.5 years follow-up.

To help committee members determine whether it was ethical to conduct the TIDE trial, FDA invited Drs. Ruth Faden and Steven Goodman, co-chairs from the Institute of Medicine's Committee on Ethical and

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf

Scientific Issues in Studying the Safety of Approved Drugs to present on Day 2 of the meeting. Due to the timing of this advisory committee meeting, FDA requested a letter report of the committee to address the following question: "What are the ethical and informed consent issues that must be considered when designing randomized clinical trials to evaluate potential safety risks?" This letter report was also provided in the FDA background materials and provided a conceptual framework for which the advisory committee members (and FDA) can apply in its decision regarding the conduct of TIDE.

In this section of my memo I will present my arguments for why TIDE should be conducted using this conceptual framework as guiding principles.

The Public Health Context of Drug Safety

The FDA should determine that there is a substantial public health question about the nature or acceptability of the risks, or the risk-benefit profile, of a marketed drug-a question that requires a policy decision from FDA

The policy decision facing FDA is whether there is sufficient evidence regarding CV risk of rosiglitazone to warrant its removal from the U.S. markets. In the absence of sufficient evidence, the next policy decision facing FDA is whether a post-marketing trial should be required to gain important public health information.

I have already argued under previous sections of this memo that all available data *suggest* an increase in CV risk with rosiglitazone but that such data are fraught with limitations due to, but not limited to, their design, objectives, data collection, and duration, such that a reasonable conclusion can not be made that rosiglitazone causes myocardial infarction, strokes, or death at rates greater than other available anti-diabetic therapies.

Diabetes mellitus is a disease of chronic hyperglycemia that has well-known complications that one can not ignore poor glycemic control. Patients now have 11 different classes of anti-diabetic agents to choose from and given the chronic nature of type 2 diabetes, the majority of patients will require several drugs and many will eventually require insulin. All of these therapies have shown effectiveness at lowering blood glucose levels, an important clinical endpoint not a surrogate, as some have argued. But while we continue to develop and approve drugs based on their ability to treat hyperglycemia, we do not know whether they have an impact, negative or positive, on cardiovascular disease, a major long-term complication of diabetes. The TIDE trial, as currently designed is intended to provide us with knowledge on the long-term benefits and risks of rosiglitazone, pioglitazone, and other therapies currently approved for diabetes, a condition affecting over 20 million individuals in the United States. To that end, I believe TIDE will not only provide clarity on the debate about rosiglitazone but it will answer broader important public health questions.

Regulatory Science and Public Accountability

FDA should use regulatory-science principles and practices that include processes of public accountability and transparency to determine the need for a policy decision, the need for new knowledge to support a policy decision, and the policy decision based on the new knowledge.

On this issue, Dr. Faden remarked that the 2-day advisory committee represents the FDA's willingness to publicly disclose all available information and internal opinions voiced in this regulatory decision. In keeping with this principle, I would advocate that when the final decision is made for rosiglitazone and the TIDE trial, all FDA documents in this decision-making process be made available to the public.

Design Considerations

It is appropriate for FDA to require that a randomized controlled trial be conducted to provide additional evidence about an approved drug's efficacy and safety only when (i) uncertainty about the risk-benefit

balance is such that a responsible policy decision cannot be made based on the existing evidence or on evidence from new observational studies, and (ii) the trial is properly designed and implemented to reduce uncertainty about the risk-benefit balance sufficiently for a responsible policy decision to be made.

I have already presented my reasons for why current evidence, including observational studies, has not provided clarity on the CV risk of rosiglitazone relative to other anti-diabetic therapies, including pioglitazone. A majority of committee panel members (19/33) voted in favor of continuing the TIDE trial should rosiglitazone remain on the market. Eleven voted against its continuation, 2 abstained, and one member forfeited his vote as he left the meeting early. However, I find it intriguing that many members, even those who stated they were voting in a hypothetical sense because they had already voted for withdrawal of the drug, viewed such a trial as the only means of resolving a debate that has twice gone before an advisory committee. In my mind, such a view undermines the position that the trial is unethical. More importantly, I believe their votes and explanations are aligned with what Dr. Goodman said in the IOM presentation,

"……a precondition for the choice to require a randomized controlled trial by the FDA must be the determination that the current evidence base is insufficient, and that no other research or information-gathering effort, including new observational study, can reduce the uncertainty about the drug's risk-benefit profile sufficiently to support a responsible policy decision."

Additional Ethical Obligations to Trial Participants

FDA should ensure that the trial will answer the public health question with a design that minimizes the risks to trial participants and involves ongoing monitoring of risks. The risks should be judged to be acceptable by appropriate oversight bodies before and during the trial and by trial participants at enrollment and as appropriate during the trial. Specifically, FDA and appropriate oversight bodies should ensure that the trial includes a comprehensive and meaningful informed consent process that continues during the trial and that takes into account any substantial changes in clinical practice and professional standards and any new research findings relevant to a participant's willingness to accept the risks associated with the trial. The FDA and appropriate oversight bodies should ensure that those conducting the trial convey such changes to participants in a timely and understandable fashion.

I have already concluded that the TIDE trial objectives are appropriate and the research questions can be answered by its design. Unlike the criticism of RECORD, this is a double-blinded, placebo- and active-controlled trial with blinded adjudication by an independent endpoints committee. Its primary endpoint is also the more widely accepted composite of CV death, stroke and MI. However, from the discussions at this advisory committee I believe the protocol should be revisited to make certain inclusion and exclusion criteria reflect enrollment of patients for whom available data have not identified clear hazard from exposure to rosiglitazone. The protocol should also be reviewed with respect to duration and type of monitoring throughout the trial, stopping rules, and updates to the oversight bodies and participants. If necessary, participants might need to be consented annually to make certain they understand what the trial objectives are and the risk-benefits of all treatments studied. If rosiglitazone will remain on the market, its labeling will undoubtedly be modified. The informed consent will have to be updated to reflect accurately any new information. The informed consent should also be reviewed routinely by oversight bodies to provide updates on new knowledge about risks and benefits of any treatments in the trial.

V. CONCLUSIONS

In conclusion, I believe that there are clinical data suggestive of CV risks associated with rosiglitazone. However, the sources of data from which this signal arises have serious limitations upon which a regulatory decision for drug withdrawal should not be based. Despite this, the data suggesting increased CV risk can still be communicated to prescribers and patients to allow informed medical decisions and prescribing practices for rosiglitazone, including the decision to never use rosiglitazone or to select rosiglitazone only after failing other anti-diabetic therapies. Some might ask why I don't just recommend the drug's withdrawal given that the safety signal is sufficient enough to justify its relegation to second-line or even last-option therapy. After all, withdrawal would effectively eliminate any chances for the drug to continue to do harm. While I cannot dispute that fact, I believe withdrawal of rosiglitazone in the setting of scientific uncertainty is an inappropriate display of FDA's authority to make a decision for all healthcare providers because of concern that these trained professionals can not reasonably decide on or take responsibility for the use of this drug. I am also concerned that such an action would set an unsettling precedent for future regulatory decisions or may be referenced in legal challenges to the FDA to withdraw other drugs based on meta-analyses and observational studies of similar uncertainty for drug risk.

In making my 3 recommendations to CDER senior officials, I am heeding the advice of Commissioner Hamburg in her opening statement "to follow the science where it leads and the rest will fall into place". I have argued my position based on my interpretation of scientific evidence available which, in turn, has formed the basis for my recommended regulatory actions. In doing so, I am also cognizant that some of my labeling recommendations and the actions of others outside the agency may impact the ability of the company in conducting a required postmarketing trial to better inform us in our regulatory decision. If my three recommendations are adopted, FDA should monitor the progress of this postmarketing trial and the efforts of the company and investigators in conducting it in a timely fashion. If the impact from labeling changes or the negative publicity given to this matter from the media, members of Congress, or other individuals make this an unfeasible clinical trial, FDA should release GSK from this FDAAA-mandated required trial. If this should happen, I would support more restrictive use of rosiglitazone since the uncertainty of its CV safety will never been resolved without this required postmarketing trial.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21071	ORIG-1	SB PHARMCO PUERTO RICO INC	AVANDIA (ROSIGLITAZONE MALEATE)2/4/8MG T

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/s/

MARY H PARKS
08/19/2010