DEPARTMENT OF HEALTH & HUMAN SERVICES

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This memorandum will not be an exhaustive review but is a supplement of certain issues that should be considered in addition to Dr. Parks's review.

My assessment of the most recent rosiglitazone Advisory Committee (AC) meeting held on July 13 and 14, 2010, is that the members voting (exact questions and votes are in Dr. Parks's review) and discussion reflected that:

1. The majority of members felt that there were data to raise significant safety concerns for ischemic CV events in patients with Type 2 diabetes relative to non-TZD agents and relative to pioglitazone. However, the data were not sufficient to raise safety concerns for mortality (or they could not conclude the data were sufficient-a subtle difference) in patients taking rosiglitazone compared to non-TZD agents or to pioglitazone.

2. Panel members were fairly evenly divided between the following regulatory actions for rosiglitazone:

   a) Continued marketing, no change to labeling or changes that could range up to contraindications for certain patient populations, second-line use in patients intolerant of or uncontrolled on other anti-diabetic agents
   b) Continued marketing, revised labeling and restricted use to certain physicians or physician and patient education
   c) Market withdrawal

3. The majority of members felt that if rosiglitazone remained on the U.S. market that the TIDE trial should continue.

I agree with Dr. Parks conclusions which are:

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 Rosiglitazone should not be withdrawn from the market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 (continued) to obtain interpretable data on the CV safety of rosiglitazone to inform FDA on an appropriate regulatory action

Based on the distribution and 'spread' of votes above, while it appears that the panel members had concern regarding an ischemic cardiovascular signal with rosiglitazone use, they were not concerned that the signal led to a mortality disadvantage, there was not widespread agreement regarding the strength of

association from the body of evidence for the ischemia signal, and finally, there was not widespread agreement on what regulatory actions should be taken. One could make a compelling argument that this represents equipoise regarding whether there are cardiovascular risk differences between rosiglitazone and other anti-diabetic agents, including pioglitazone, and what regulatory action the agency should take.

There are four issues that I will specifically comment upon:

1. What new information do we have that is different from 2007 that would cause us to alter our thinking from that time and guide us further in determining future action regarding rosiglitazone?
2. What do we need to do, if anything, with the current evidence (i.e. RECORD, CMS) to increase or decrease our reliance on the results?
3. If further evaluation of existing data is warranted, what actions should be taken while it is being conducted?
4. What is the timeline for accomplishing these actions?

The comments that I make regarding rosiglitazone and the associated safety and regulatory issues should be viewed in the context of the extraordinary environment within which we have been conducting our review of these issues, including unprecedented attention and scrutiny specific to rosiglitazone by Congress, the lay press and the scientific community. My hope is that this environment will not have a detrimental influence on our ability to ensure sound, science-based decision making by the Agency. It is essential that we remain attentive to our regulatory framework, standards of evidence under that framework, the needs of patients and their healthcare providers and how these all merge to serve the public health. However, there should be a realistic appreciation of the potential for politics, public opinion, fatigue, and conflict avoidance to influence policy in this environment. We should be vigilant that this does not happen and that science drives the process.

1. What new information do we have that is different from 2007 that would cause us to alter our thinking from that time and guide us further in determining future action regarding rosiglitazone?

There are four major pieces of evidence that are new for 2010 compared to 2007. It should be recognized that these examined the cardiovascular safety of rosiglitazone in several ways, comparing it to agents in different classes (mainly sulfonylureas and metformin), and to the other agent (pioglitazone) within its class. The four sources evidence are:

1) An update of the FDA meta-analysis of rosiglitazone controlled clinical trials that now includes 10 additional trials,
2) A meta-analysis of pioglitazone controlled clinical trials
3) A retrospective cohort study of Medicare claims (CMS study) commissioned by the FDA
4) Review of the data for the final results of the RECORD trial

<u>Updated FDA rosiglitazone meta-analysis</u>
In order to best facilitate comparisons to the pioglitazone meta-analysis, the 2010 rosiglitazone meta-analysis (52 trials=42 original trials from 2007 meta-analysis + 10 new additional) was performed using different methodology than the 2007 meta-analysis (42 trials). However, the Office of Biostatistics (OBS) also performed an analysis of the original 42 trials from the 2007 meta-analysis using the same methodology as that used in the 2010 meta-analysis. The main results are given below.

Table 1: Rosiglitazone, primary and secondary endpoints 42 trials and 52 trials-primary analysis across all trials

Endpoint	Stratified OR (95% CI) 42 Trials	Stratified OR (95% CI) 52 Trials
MACE	1.4 (0.9,2.3)	1.4 (1.0,2.2)
CV Death	2.0 (0.7,6.3)	1.5 (0.6,3.8)
MIF	1.8 (1.0,3.6)	1.8 (1.0,3.3)
Stroke	0.6 (0.3,1.5)	0.9 (0.4,1.8)
All-cause Death	1.9 (0.83,4.7)	1.4 (0.7,2.7)
Serious Myocardial Ischemia	1.8 (1.2,2.7)	1.5 (1.1,2.0)
Total Myocardial Ischemia	1.6 (1.2,2.2)	1.3 (1.1,1.7)
CHF	2.0 (1.3,3.2)	1.9 (1.3,3.0)

From this data, we can see that for the most part, the precision around the point estimate has increased and that most of the point estimates have remained the same, or actually decreased. These new data would not seem to be an important determinant in changing our decisions from that made after the 2007 Advisory Committee meeting. It remains important we be cautious in placing confidence in, or draw final conclusions from, meta-analysis results with small differential estimates that are better used as hypothesis generators.

It should be noted that the above analysis is different from that recently published in the New England Journal of Medicine (NEJM) by one of the panel members, Cliff Rosen, MD.[1] In his perspective piece, Dr. Rosen appears to have used a slide from the FDA OBS presentation that contained the original 2007 analysis of 42 trials (different methodology) and also had the 2010 results of 52 trials. While the presenter explained the differences and that the two different analyses should not be directly compared, Dr. Rosen appears to have done this in his perspective piece. In order to directly compare what effect the addition of 10 trials would have to the original 42 trials, the same method of analysis should be used in both the pool of 42 trials and 52 trials as is presented above.

Pioglitazone meta-analysis

OBS also performed a meta-analysis on pioglitazone data. While they tried to have analyses comparable to that of rosiglitazone such that there could be a comparison of 'apples to apples' between the meta-analyses, they had limited success. The trials within each database were of different designs and patient populations resulting in systematic differences thereby limiting the ability to make direct cross meta-analysis comparisons. Of course, human nature being what it is, different people have done cross meta-analysis comparisons. Our OBS colleagues feel that if one were to do that, the most comparable groups would not be the overall comparison of all trials, but those in which both rosiglitazone and pioglitazone were compared to a common agent. The results from this comparison are below (from page 26 of statistical briefing material for 2010 AC Meeting).

Table 2. Odds ratio estimates for MACE across different trial groups by meta-analysis

		Stratified OR (95% CI)	
Comparator	Meta-analysis	MACE	CHF
Placebo	PIO	0.6 (0.2, 1.7)	1.8 (0.6, 5.8)
	ROSI	1.5 (0.9, 2.5)	2.2 (1,4, 3.5)*
Active	PIO	0.9 (0.6, 1.3)	1.4 (1.0, 2.2)

[1] Rosen CJ. Revisiting the rosiglitazone Story—Lessons Learned. N Engl J Med. 2010 Jul 21. [Epub ahead of print]

	ROSI	1.1 (0.5, 2.3)	1.2 (0.5, 3.3)
Sulfonylurea	PIO	1.2 (0.7, 2.0)	1.6 (1.0, 2.6)
	ROSI	1.2 (0.5, 2.8)	1.2 (0.5, 3.3)
Metformin	PIO	0.6 (0.3, 1.3)	0.9 (0.2, 3.0)
	ROSI	0.4 (0.0, 7.6)	-

*This value is different than the AC briefing document as the briefing document had an erroneous value

From the data above, it would appear that when one looks at MACE, the point estimate for pioglitazone for two groups (placebo, active) is less than for rosiglitazone, while the point estimate for one group (sulfonylurea) is identical and greater for another (metformin). The confidence intervals do not reveal elevated risks as all include unity (1). A similar exercise for CHF reveals that the point estimate for pioglitazone for one group (placebo) is less than rosiglitazone, but is greater for two groups (active, sulfonylurea). This would not support the assertion of some that pioglitazone causes less CHF than rosiglitazone. These results do not seem to warrant a radical change in FDA's regulatory direction with regard to rosiglitazone and actually provide some reassurance that there may not be differences between these two PPAR agents.

Retrospective cohort study of Medicare claims (CMS study)

I agree with Dr. Parks that this study has many strengths and warrants further investigation as a hypothesis generator. I also agree with Dr. Parks that this study has weaknesses, and it is perplexing that the results demonstrate that the original signal that started the rosiglitazone controversy, myocardial infarction, was not demonstrated to be different between rosiglitazone and pioglitazone in this study. Although Dr. Graham explains this by asserting that there were MI cases embedded within the mortality results, this is speculative and fragile at best. The remaining results, hazard ratios of 1.27 for stroke, 1.25 for heart failure, 1.14 for all-cause mortality and 1.15 for acute MI, stroke or death are all less than two and would represent a relatively low magnitude of association.[2] In nonexperimental research, bias can never be entirely eliminated and therefore the association should be large relative to any plausible biases.[1]

In observational studies, there are good reasons why a hazard ratio less than 2 is considered a low magnitude of association and it is worth reviewing the mathematical exercise that Shapiro went through to explain this.[1] In his paper, Shapiro considered a hypothetical exercise from a case-control design study comparing 100 controls to 100 cases and two forms of bias, informational and selection. In the exercise, an information bias of 2 controls and selection bias of 2 exposed cases resulted in a relative risk of 1.14 (similar to some of the point estimate results in the CMS study), demonstrating the fragility of estimates less than 2. Although the CMS PPV% ranged from 85-100% depending on category, this exercise demonstrates that it takes little bias (2% of categorizations-well within the PPV) to account for changes less than 2 and in a very large comparative cohort study like the CMS, modest bias could dominate and account for the observed relative risk of the magnitude observed.

Therefore, reliance on the magnitude of point-estimates demonstrated in the CMS study is problematic and should not be used as a basis for making regulatory decisions. Instead, its utility is in generating hypotheses for further study. Also, this is a very new use of this database and we have not performed any sensitivity analysis to try to determine what level of point estimate may give robust results. In making a regulatory decision such as the one here that could have profound impact on future actions, we should use methods with which we have experience and comfort with the validity of the results.

[2] Shapio S. Bias in the evaluation of low-magnitude associations: An empirical perspective. Am J Epidemiol. 2000 May 15;151(10):939-945

Although I will not discuss it in detail, we are in possession of an abstract of a study by WellPoint that seems to be of the same design as the CMS study that we commissioned. This study compared the risk of myocardial infarction and cardiovascular death among pioglitazone and rosiglitazone-treated patients in a managed care population. The draft manuscript claim that there is not a significant difference between rosiglitazone or pioglitazone treated groups for the risk of acute MI/CV death. This warrants further investigation, particularly in light of the limited magnitude of effect seen in the CMS study. It may also demonstrate that relatively weak association point estimates can easily be biased in either direction.

Review of the RECORD trial

During the 2007 AC, preliminary results of RECORD were presented. The data that formed these results had not been reviewed by the agency at that time, but did offer some reassurance that rosiglitazone did not have increased cardiovascular events compared to agents in different classes (mainly sulfonylureas and metformin) and might actually have a better profile for some individual endpoints. These preliminary data probably gave panel members some reassurance that rosiglitazone, compared to sulfonylurea and metformin, did not have the signal that was seen in the FDA meta-analysis (where the main comparators were also sulfonylurea and metformin), as, despite being open-label, RECORD was a long-term, randomized, controlled trial.

For the 2010 AC, we performed a thorough review of the RECORD data. The review findings and how much reliance can be placed on RECORD have proven to be quite controversial. As part of the review, DMEP placed a consult with the Division of Cardiovascular and Renal Products (DCRP), which was performed by Dr. Marciniak. During his review, Dr. Marciniak originally identified eight cases that he felt represented cases that should have been sent to the independent panel for adjudication and were not. This understandably caused him concern that reporting bias or even manipulation of cases by the sponsor may have occurred. Dr. Marciniak also had several issues with the trial design and endpoints, however, it must be recognized that this trial was designed between the sponsor and the EMEA to answer EMEA specific concerns and not as part of a request by the FDA.

During our preparation for the AC and as part of the review, Dr. Marciniak's eight cases were thoroughly investigated by the Division of Scientific Investigation (DSI) in conjunction with an independent medical reviewer from DRCP. Seven of the eight cases were determined to have had appropriate handling and were in compliance with the protocol. The eighth case was not originally sent for adjudication. Upon review of the SAE by the sponsor, they requested the investigator to submit the case for adjudication. The investigator complied with this request, but apparently filled out the incorrect form, so the case was sent back. Further, careful evaluation by DSI did not reveal any evidence of misconduct.

Dr. Marciniak was not reassured by the findings of DSI for reasons that were unclear and also did not seem to accept their findings regarding these eight cases of concern. His presentation at the 2010 AC meeting focused on his concerns about RECORD's potential bias and probably undermined the panel members' confidence in RECORD thus influencing some of the voting. He also presented his own unblinded readjudication of random cases applying a different set of definitions for cardiovascular events from those stipulated by the RECORD protocol. His review revealed higher rates of cardiovascular events than that reported by the sponsor for rosiglitazone compared to non-rosiglitazone treatment. Finding of important differences for adverse cardiovascular events associated with rosiglitazone use is concerning, and I agree that there are obvious flaws with RECORD (open label being the greatest). There is, however, great concern with a reviewer going into a database that he already believes may have problems, using different definitions of the endpoints for those originally used and in an unblinded fashion searching for further evidence to support their own concerns. This is a practice that we are careful to assure does not occur among investigators or sponsors in analyzing trial data because it is fraught with its own biases.

Dr. Unger, Deputy Director of the Office of Drug Evaluation I, in his review and presentation at the 2010 AC acknowledged concern for potential bias in the open-label nature of RECORD, but also noted the flaws with Dr. Marciniak's approach regarding readjudication. Dr. Unger expressed confidence that the mortality data for the trial are likely secure, as mortality is an objective endpoint less prone to bias by the open-label design.

With the conflicting views of the RECORD database, except (perhaps) for the mortality data (which wasn't concerning and favored rosiglitazone use) without an impartial third party looking at blinded data, it is hard to know what the truth is regarding the data collected for RECORD. However, our review of the data is new since 2007, and the impact of the data integrity controversy in AC panel members thinking was probably great and therefore warranted discussion. Except for the mortality data, at this point RECORD provides limited confidence regarding the results and the controversy surrounding data integrity probably had a greater impact on the voting by panel members for the 2010 AC meeting compared to the 2007 AC meeting.

2. **What do we need to do, if anything, with the current evidence (i.e. RECORD, CMS) to increase or decrease our reliance on the results?**

In order to make a fully informed decision, we need to have a clear picture of what each piece of data adds to the body of evidence. In order to do this, I believe that RECORD should be readjudicated. This could be done in a step-wise fashion, starting first with mortality, then hospitalizations and then the rest of the data. The readjudication should be done by an independent third party in accordance with usual agency procedures. The readjudication should mirror the original intent of the study (although other analyses could be add in for further hypothesis generation), using the definitions for endpoints that were used in the final protocol.

I also believe that we need to perform sensitivity evaluation of the CMS database to understand what level of magnitude correlates with an association. What type of analyses we perform should be undertaken with OBS guidance, but examples are well described in the literature, such as those described by Austin[3], and other exercises such as randomizing the pioglitazone subjects based on even/odd birth date and comparing them to each other to see what level of association may be generated on items that clearly should not have an association. It would also be useful to compare different statin therapies based on the same endpoints to determine if there is a rank ordering as well as perhaps different hypertensive agents or NSAIDS or sulfonylureas. One could wonder if we see rank ordering of these different agents of the magnitude that was demonstrated for the PPARs, if we would take a regulatory action.

Finally, I believe that we should obtain and evaluate the WellPoint database. To make a final decision without this data would be a demonstration of lack of understanding of the nuances of evidence and could be seen as sacrificing scientific process for political expediency.

3. **If further evaluation of existing data is warranted, what actions should be taken while it is being conducted?**

I believe that it is prudent, due to the uncertainty surrounding the cardiovascular adverse event profile, to fully inform practitioners and patients to the potential risks which should serve to limit the exposure of patients to rosiglitazone to those felt appropriate. I would contend however, that this is probably already happening. Sales for this product are flat, suggesting a great deal of selection in prescribing.

[3] Austin PC, Mamdani MM, Juurlink DN, Hux JE. Testing multiple statistical hypotheses resulted in spurious associations: a study of astrological signs and health. Jo Clin Epidem. 59 (2006) 964-969.

The scientific data do warrant labeling changes for rosiglitazone, including additional information in the box warning, and Warnings and Precautions sections to update the meta-analysis information. I would not include data from the CMS study at this point, because our understanding of the value and dependability of this database is in its infancy, especially for relative risks ratios that are under two. Consideration should be given to whether labeling should indicate that rosiglitazone be used in those who have failed other drugs of the class. We have had other examples where we have employed this mechanism while awaiting additional safety data, such as biologic products for rheumatoid arthritis. However, if labeling of this sort were to occur, I would limit the wording to saying something in regard to a consideration of other agents should be given before starting rosiglitazone due to unresolved cardiovascular safety issues.

It is important to note that that there is not any randomized clinical trial data comparing rosiglitazone to pioglitazone to support specific labeling of using one product over another should we move in this direction. The support would be that trials have not indicated that pioglitazone has evidence of a concern for cardiac ischemia while this issue remains unresolved for rosiglitazone. It should also be kept in the back of our minds that there is an unresolved issue regarding the bladder cancer potential for pioglitazone. So in effect, we could be supporting the channeling of patients (I say supporting because it has already happened without a labeling change) from rosiglitazone to pioglitazone and a potential for increased bladder cancer risk. I also believe we should use the CMS database to compare cancer, and bladder cancer risks between rosiglitazone and pioglitazone.

Finally there is the question of whether we should continue the TIDE, or a similar trial, to make definitive conclusions regarding any cardiovascular adverse event rate. Making appropriate scientific and regulatory decisions in a highly charged environment such as this can be difficult, takes dedication to principles and in most cases, courage, perseverance and thick skin. I have concerns that the degree of negative press surrounding rosiglitazone may make it untenable for local IRBs and other oversight bodies (both domestic and foreign) to continue to support a randomized trial. This may be more indicative of a reluctance to face some of the very vocal critics of rosiglitazone than a true concern about acceptability of such a trial. It is worth noting that up until recently, 39 countries and 816 independent sites had felt that TIDE was an ethical study and were allowing enrollment.[4]

The recent IOM letter report[5] requested by the FDA to examine ethics and scientific issues in studying the safety of approved drugs suggests that a trial such as TIDE can be ethically performed. This report states that the risk-benefit balance should be judged to be acceptable by FDA, participating IRBs, and the DSMB before initiation and throughout the course of the trial. The original decision to begin TIDE fulfilled all these criteria: we required the study, most potential study site IRBs judged it to be ethical, and the DSMB judged it to be ethical. It is now critical to examine what if anything has occurred since initiation (or what new data do we have) that calls its continuation. I believe that we have the same degree of uncertainty and, based on the variety of scientific opinions voiced at the 2010 Advisory Committee Meeting, equipoise as we had in 2007 when we began the process of requiring what ultimately became the TIDE trial.

To further elaborate, the IOM letter report, as part of their conceptual framework, discusses the Public Health Context stating that 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." This is a policy decision of great magnitude in that it is determining the body of evidence necessary to make regulatory safety decisions. It is important to realize

[4] Gerstein H. TIDE presentation, Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee. July 14, 2010

[5] Ethical Issues in Studying the Safety of Approved Drugs: A Letter Report. Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs. July 9th, 2010

that the 'body of evidence' criteria for a safety decision is not likely to ever be as well-defined as what we have for efficacy evidence (Two or more well-designed randomized trials demonstrating substantial evidence) and is likely to be different to the eye of each beholder. However, like law, regulatory science is built on prior precedents and this decision will be an important, perhaps pivotal, 'case' that will be referenced for future decisions.

The IOM conceptual framework also states under Design Considerations that it is appropriate to require a randomized controlled trial when "uncertainty about the risk-benefit balance is such that a responsible policy decision cannot be made based either on the existing evidence or on evidence from new observational studies." Observational studies in this case have very small effect sizes (odds ratios less than 1.5-2.0, frequently cited as the minimal necessary for an association) that clearly could be influenced by bias. As the IOM conceptual framework states, "If the estimated relative risks are small, selection bias, confounding, and measurement error may be alternative explanations for associations found in an observational study". I submit that we clearly are in an environment of insufficient evidence to make an appropriate policy determination from observational studies. We are also at equipoise, again demonstrated by the voting opinions from the recent Advisory Committee panel members where the majority felt that if rosiglitazone were to stay on the market that the TIDE study should continue. Further evidence of equipoise can be seen by the opposing stances of various professional organizations and societies regarding the marketing and continued study of rosiglitazone. It is important to consider that TIDE has a DSMB so that differences in adverse effects can be closely monitored and, if detected, the trial can be terminated early. It is also interesting to note that the most fervent critics of TIDE seem mute on the PRECISION trial, which is similar in hypothesis and design (i.e. evaluate potential for excess cardiovascular harm from celecoxib compared to naproxen or ibuprofen).

Dr. Parks has observed that TIDE may not be feasible due to recruitment problems and we also heard at the AC that there has been low recruitment. I do not find this unusual given our environment and it is very similar to what occurred at the early stage of the JUPITER trial for rosuvastatin (Crestor). At that time, harsh public criticism and a well publicized Citizen's Petition asking for rosuvastatin's withdrawal from the market due to unsubstantiated safety concerns hampered recruitment. However, once the agency denied the Citizen's Petition, recruitment increased and the trial was able to be performed and completed. It is interesting to note, that JUPITER was performed in subjects that, at the time, were too 'healthy' to qualify for statin therapy so an ethical argument could have been made about exposing such a healthy population to a drug that some felt had greater harm than other available agents. However the final results indicated that rosuvastatin did not have the theoretical adverse events of concern and Jupiter has been considered by some a revolutionary study, expanding the patient population that may receive benefit from statin therapy. It is concerning that studies like JUPITER that have clearly advanced public health may not conducted should there be widespread adoption of the viewpoint of what constitutes an ethical study that some have advanced during this debate.

Finally, despite the unprecedented negative publicity that has surrounded rosiglitazone, the sponsor has determined that approximately (b) (4) patients still use this medication. It is important that we do know if there is a cardiovascular risk for this population.

4. What sort of timeline should we do this under?

We can take fairly quick action in implementing the labeling changes recommended in Dr. Parks and my review. However, it will take some time to resolve other issues such as re-adjudication of RECORD and sensitivity analysis of the CMS database. The FDA Office of the Commissioner has set a goal for resolving rosiglitazone by the end of August. If by resolve it is meant that a path forward is charted, that can be accomplished. I am not confident that a definitive conclusion about the drug's risk and a decision that it should be removed from the market is possible in that time frame simply because the data remain incomplete and inconclusive needing further refinement as described above.

Our action on this drug must take into account the precedence of the decision and how factors such as the enormous publicity, often devoid of balance, might weigh in on the process. We must consider unintended consequences of whatever action is taken and how they may affect the next drug with an inconclusive safety signal, and there are many inconclusive safety signals for many drugs. We must ensure that FDA's decision rests on scientific underpinnings, something that is difficult to do in the environment we find ourselves in with rosiglitazone. To do otherwise risks undermining our statutory responsibility and our scientific and regulatory objectivity.

CONCLUSIONS AND RECOMMENDATIONS

There is evidence, mostly through meta-analyses and observational studies, of a higher risk for some ischemic cardiovascular events of rosiglitazone, but not others, compared to other diabetic agents in different classes. There is not evidence of increased mortality of rosiglitazone compared to different classes of diabetic agents (and perhaps there is an advantage). This creates cognitive dissonance for understanding what the true effect may be as one would expect these two outcomes to track together. This is the hallmark of equipoise: we simply do not have robust, confidence-inspiring data that informs us as to whether there is a true risk.

Some have concluded that the data suggesting a potentially increased risk for ischemic events with rosiglitazone along with the absence of such evidence for pioglitazone, should lead FDA to withdraw rosiglitazone from the market. Understanding how drugs compare to one another is always desirable, but employing this type of logic along with the scientific treachery of cross study comparison is extremely problematic. Taking action on the basis of such a strategy would set a precedent that 'suspicion' should translate into immediate regulatory action. It is a narrow perspective that does not give full consideration to quality of data and risks erroneous conclusions, as history has already shown us. Dr. Gerstein, the lead investigator for the TIDE trial was correct to point out at the 2010 AC meeting that if we were to apply this paradigm (acting on 'suspicion' generated by meta-analysis or observational studies and not looking for more definitive evidence), we would still be routinely using hormone replacement therapy for cardiovascular benefit, a myth propagated by observational studies but dispelled by the Women's Health Initiative randomized trial[6] (WHI). The WHI trial is an example of how incorrect observational studies and biological plausibility can be as there was a large body of observational studies showing cardiovascular benefit and there was biological plausibility support as hormone replacement has a positive effect on lipid profiles. Yet, the WHI randomize trial demonstrated that all this was incorrect and there was actually cardiovascular harm from hormone replacement therapy. We should also realize that the WHI was delayed many years as the proponents of observational studies felt it was unethical to place women on placebo, denying them what they felt was clear evidence of cardiovascular benefit from hormonal therapy.

The WHI is not an isolated example. We would also still be suppressing ventricular pre-mature beats after myocardial infarction as the evidence from observational studies indicated this improved mortality, but was ultimately soundly refuted with randomized trials. For both of these examples, if we were to allow the concept that observational or meta-analysis revealed 'truth' that would make any control trial impossible due to ethical reasons associated with placebo exposure. While these two examples were of using randomize trials to further define 'benefit' of therapy, there are examples where randomized trials have been used to explore whether there is possible 'harm' from drug use. Meta-analysis or observational studies (and theories of 'biologic plausibility') demonstrated cardiovascular harm with the use of digoxin, calcium channel blockers and tiotropium. All of these examples were proven to be quite wrong when adequately design randomized trials were performed. There have been, and will continue to be false

[6] Rossouw JE et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002 jul 17;288(3):321-33.

‘dogmas’ that arise from meta-analysis and epidemiologic data with small magnitude of effects and we should always explore these with more definitive data. It is also important to keep in mind that pioglitazone itself may have a cancer adverse effect not seen with rosiglitazone which needs to be further explored and weighed in any decision.

The evidence that we have regarding the potential for rosiglitazone to cause ischemic events is concerning but tenuous and does not support removal at this point. I recommend continued marketing, the labeling changes outlined by Dr. Parks, and continuation of the TIDE trial and further analysis of existing data as outlined above.

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/

CURTIS J ROSEBRAUGH
08/23/2010