Introduction
Following publication of the December 2008 FDA Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, assessment of cardiovascular safety has become a critical focus during the development of new antidiabetic therapies for Type 2 diabetes mellitus (T2DM). The importance of this guidance document, referred to from here on as “the Guidance,” was evidenced by a September 2009 conference, Cardiovascular Safety and Development of Type 2 Diabetes Mellitus Medications: Current State of the Art and Opportunities to Advance the Science, sponsored by the Drug Information Association, the US Food and Drug Administration (FDA), and the Cardiac Safety Research Consortium. This White Paper provides a brief historical perspective on the evolution of the Guidance, reviews its central tenets, and discusses their implications for the development of new antidiabetic therapies for T2DM.
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Evolution of the Guidance
The seminal influence in this process was a paper entitled *Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes.* This meta-analysis focused on the thiazolidinedione drug rosiglitazone, an agent used in the treatment of diabetes mellitus. The published result of note was an odds ratio for myocardial infarction in the rosiglitazone group compared with the control group of 1.43 (95% confidence interval: 1.03 to 1.98, p = 0.03). Turner and Durham reviewed the intense governmental, regulatory (FDA and the European Medicines Agency), and media activity in the days and months following the paper’s e-publication on 21st May 2007. Given the already voluminous published literature concerning, for example, the validity or otherwise of the result, the RECORD trial, and the drug’s current therapeutic use, this paper focuses specifically on the Guidance and its evolution.

Related FDA Meetings
A joint meeting of the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee and its Drug Safety and Risk Management Committee was held on 30th July 2007. The FDA and rosiglitazone’s Sponsor gave presentations, which were followed by presentations from selected members of the general public. Discussion among the members of the advisory committees followed, and two votes were taken. First, the committees’ members voted 20-3 (Yes-No) that rosiglitazone increases the cardiac risk in patients with T2DM. The Summary Minutes from this meeting noted several related caveats:

- Some committee members voting “Yes” qualified their vote by adding that the current data could be categorized as ischemic risk for rosiglitazone;
- Many members qualified their “Yes” answer by identifying subgroups at increased risk, noting the limitations of comparison to placebo, and noting the increased risk in patients taking insulin;
- Many members expressed reluctance to draw conclusions comparing the risk level of rosiglitazone versus other available therapies until additional data had been reviewed.

Second, the committees’ members voted 22-1 that rosiglitazone should not be removed from the market, and should therefore remain an available treatment option for physicians and their patients. Most of the committee provided recommendations for labeling changes regarding ischemic risks, although differing recommendations were voiced.

Subsequently, a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee was held on 1st and 2nd July 2008 to address potential new regulatory guidance concerning cardiovascular assessments, both pre- and post-approval, for drugs and biologics for the treatment of T2DM. The committee voted 14-2 that, even for drugs and biologics that do not display a concerning cardiovascular safety signal during Phase II/III development, there should be a requirement to conduct a long-term cardiovascular trial, or to “provide other equivalent evidence to rule out an unacceptable cardiovascular risk.”

The Guidance resulted from discussions at this meeting.
Related FDA Guidelines
In February 2008 the FDA released a draft guidance document entitled Diabetes Mellitus — Developing Drugs and Therapeutic Biologicals for Treatment and Prevention. This document, which addressed both Type 1 diabetes mellitus and T2DM, provided guidance “on issues related to trial design, endpoints appropriate for different phases of development, and eligible populations.” Assessment of cardiovascular safety was not addressed in detail in that draft. Therefore, to address this issue in the interim, the Guidance was issued in December 2008 in final form for immediate implementation to ensure that “relevant issues related to minimizing cardiovascular risk are considered in ongoing drug development programs.” The Guidance also noted that the FDA “will address cardiovascular risk assessment for currently marketed antidiabetic therapies in a separate guidance.”

When the February 2008 draft guidance document is finalized, information from the Guidance will be folded into its final text such that the final document will indeed address cardiovascular safety assessment in detail.

Central Tenets of the Guidance
When designing a development program for a new antidiabetic agent, Sponsors should first consider whether the Guidance is applicable to their drug. Generally, the thresholds of regulatory concern, discussed in a subsequent section, do not apply to most injectable insulin or fixed-dose combination products, provided that the individual components do not increase the risk of cardiovascular disease and that there is no pharmacological basis for an interaction between the components. However, in most cases concerning T2DM drugs the Guidance will be applicable. Several central tenets are reviewed here in turn.

Trials to be Conducted
Historically, a preapproval clinical development program for an investigational drug for T2DM typically included small, short (12-week) Phase II studies, a 12- to 24-month Phase III study in which the subjects were healthier than the eventual target population, and uncontrolled extensions followed the completion of the ‘efficacy portion’ of the study. The Guidance makes clear this will change. Going forward, likely studies include:

> Small, short dose finding early Phase II trials;
> Larger, longer, and cardiovascular event-adjudicated later Phase II trials;
> Larger and longer Phase III trials that are cardiovascular event-adjudicated and include subjects at high risk for cardiovascular events.
Additionally, the development program may require a dedicated large simple cardiovascular trial, depending on the result of the meta-analysis to be conducted upon completion of the planned trials within the development program. This meta-analysis, discussed in due course, will incorporate data from most of the Phase II and Phase III studies conducted.

Study Design Considerations
Given that a meta-analysis will be conducted once the (initially planned) studies in the drug’s development program are completed, it is important these studies are planned with similar designs, durations, eligibility criteria, and cardiovascular endpoints (an issue discussed in due course).

Choice of Type of Study
In addition to traditional (fixed design) trials, the Guidance provides the opportunity to explore possible benefits of adaptive clinical design. An adaptive clinical design is a trial that uses accumulating data to decide on how to modify aspects of the study as it continues without undermining the validity and integrity of the trial. Since the Guidance requires more meaningful cardiovascular outcomes data to be collected for submission for approval, an adaptive design may be an economically beneficial way to accomplish this. However, no matter how development programs are designed, it is not acceptable to perform multiple data analyses without controlling for a Type I error. A type I error occurs when a researcher rejects a null hypothesis that is actually true. In a typical research situation, a Type I error means the researcher concludes a treatment does have an effect when in fact it has no effect.

Subject Selection
A clear goal set forth by the Guidance is to obtain clinical trial data that are more directly applicable to the patients likely to be prescribed a drug after marketing approval. One option on how to do this is to not restrict the inclusion criteria by certain drug treatments, but rather open enrollment to all patient populations that would be reflected in the approved drug’s label. These could include subjects that are drug naive, on monotherapy, or on multiple oral and/or injectable therapies. To ensure that no one population is over-represented, the trial could be designed such that different strata are tracked based on drug therapy. When a certain predefined number of subjects are enrolled from a certain stratum (e.g., subjects on metformin only), that stratum could be closed for further enrolment.

A second consideration is the inclusion of high risk subjects. The Guidance states that, “...phase 2 and 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment.” These subjects are likely to be on other drugs to treat co-morbidities, such as other manifestations of metabolic syndrome. To obtain a full picture of the study drug, it would be ideal if all subjects received and took medicine for their co-morbidities, e.g., hypertension, dyslipidemia, and heart disease. However, when multi-country development programs are employed, it is of relevance that, in countries that do not have mandated health coverage, many subjects cannot afford these medicines and hence go without them. In fact, free healthcare, medicines, and diabetes supplies are all reasons why subjects enroll in diabetes studies. It is standard for pharmaceutical companies to offer drugs, such as metformin, if it is a requirement that it must to be taken throughout the study. However, although tight blood pressure and low density lipoprotein (LDL) cholesterol control are recommended as standard of care by various diabetes organizations, these drugs are not routinely supplied to subjects in diabetes trials and many subjects have trouble procuring them.
If a Sponsor’s clinical development program is global in nature, it is advisable to discuss with the appropriate FDA review team what percentage of subjects should come from North America. A typical proportion is around 30%. As discussed above, the characteristics of an ideal subject enrolled in a diabetes trial have been shifted to be more in line with the type of patient that will use the drug post approval. Because of this, the FDA is interested in ensuring the ethnicities that are affected most by T2DM are well represented in the trials. This can lead to a change in recruitment strategies for antidiabetes studies.

**Choice of Cardiovascular Endpoints**

There is currently considerable discussion of this topic, with the “final word” likely being some way off. The traditional Major Adverse Cardiovascular Events (MACE) composite endpoint includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. (A composite endpoint is useful since the number of individual events in a trial may be too low to meaningfully compare those occurring in the test drug treatment group with those in the comparator treatment group.) At the recent DIA/FDA/CSRC-sponsored meeting FDA representatives noted that this endpoint will receive a ‘green light,’ and hence be acceptable to the agency. An expanded MACE endpoint might include hospitalization for unstable angina and urgent percutaneous coronary intervention / coronary artery bypass graft surgery. Other possible secondary endpoints include carotid revascularization and lower extremity amputations / revascularization. It should be noted that a growing list of secondary endpoints requires increasing attention to issues of multiplicity: it is not acceptable to perform multiple analyses of the data without controlling for the possibility of a Type I error. The FDA warns against choosing endpoints that are too broad. The more MACE outcomes as endpoints that are chosen, the less confidence there is in the data. Complex endpoints, such as cardiogenic shock, stent thrombosis, heart failure, or non-cardiovascular death, may be appropriate secondary or tertiary endpoints. When monitoring cardiovascular events, Sponsors may find it worthwhile to open a dialog about requesting a waiver for expedited Serious Adverse Event reporting for components of the primary endpoint with the specific review team from the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research assigned to their drug.

**Endpoint Adjudication**

The Guidance noted that Sponsors should establish “an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.”

Description and discussion of the complexities of obtaining long-term commitment from adjudication committee members, precisely defining the endpoints of interest at the outset of the development program and mapping all potentially used event terms across all (likely international) sites to them, and providing a secure and remotely accessible computer system to facilitate the committee members’ work would require a separate article.

> Suffice it to say here that endpoint adjudication will require significant time and energy during planning and implementation.
The Required Meta-Analysis
Like ICH Guideline E14, which addresses the Thorough QT/QTc Trial as a preapproval clinical assessment of an investigational drug’s QT/QTc interval prolongation liability, the Guidance takes the approach of prospectively excluding unacceptable risk by the employment of a threshold of regulatory concern and associated statistical methodology employing confidence intervals (see also Brass et al). However, there are two differences here. First, given that multiple trials are of interest, a meta-analysis is conducted. Second, since the cardiovascular safety of the test drug is judged against that of a comparator, a risk ratio is of interest.

A risk ratio point estimate (calculated as the number of events for the test drug as the numerator and the number of events for the comparator drug as the denominator) is available from each trial included in the meta-analysis, as is an estimate of the variance associated with it, as represented by the associated confidence interval. The meta-analysis yields a risk ratio point estimate and associated confidence interval over all studies included. As in the case of experimental studies, a strict methodology must be defined for meta-analyses. Before conducting the meta-analysis a decision must be made concerning whether to employ a fixed effects model or a random effects model (see Whitehead). The relevance of this decision is that a fixed effect model generally results in narrower confidence intervals around the point estimate than a random effects model.

In the statistical theory underpinning meta-analysis, an assumption is made that the point estimates from the individual studies included are relatively homogeneous. Heterogeneity arises from differences in studies, such as differences in subject populations, study length, and reporting conventions. A test for heterogeneity can be conducted, and, if the result is not statistically significant, it is often argued by authors that it is acceptable to proceed on the grounds that the studies are not heterogeneous, i.e., that a fixed effects model is acceptable. Turner and Durham discussed the fragility of this argument, i.e., regarding the absence of statistically significant evidence of heterogeneity as a statement of its complete absence, and it is noteworthy that the FDA prefers to see results from a meta-analysis using a random effects model even if the test for heterogeneity is nonsignificant.

When calculating the relative risk as described earlier, a point estimate greater than unity (represented here as 1.0) indicates a greater number of events observed for the test drug. Primary interest in the Guidance falls on the upper bound of a two-sided 95% confidence interval (CI). Three scenarios are described:

> **If this upper bound is equal to or greater than 1.8 (that is, it is possible to state with 95% certainty that the drug may have an 80% or greater excess risk compared with the comparator drug), the drug would be deemed to have an unacceptable risk. In this case, “an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper bound before NDA/BLA submission.”**

> **If the upper bound is equal to or greater than 1.3 and also less than 1.8, and the overall risk-benefit analysis presented at submission supports marketing approval, “a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3.”**

> **If the upper bound is less than 1.3 and the overall risk-benefit analysis presented at submission supports marketing approval, “a postmarketing cardiovascular trial generally may not be necessary.”**
Once the meta-analysis has been conducted, and a threshold of regulatory concern satisfied, two additional issues are noteworthy. First, while the thresholds of regulatory concern are the main criteria of interest, the Guidance does note that the magnitude of the point estimate will be considered. That is, an upper bound of 1.7 (satisfying the 1.8 criterion) associated with a point estimate of 1.6 would be viewed less favorably than the same upper bound associated with a point estimate of 1.3.

Second, a lingering question concerning cardiovascular events remains: What comprises an “adequate” number of events even when the upper bound criterion of 1.8 or 1.3 has been met? The Guidance does not give insight on this issue. In previous recent meetings, some members of the Endocrinologic and Metabolic Drugs Advisory Committee have expressed concern that, even though a specific cardiovascular threshold had been met, there were few actual events, making it difficult to rely on this result as a judgment of safety.

Next Generation Diabetes Drug Development and Therapeutic Care
Traditionally, antidiabetic agents have been judged solely on the degree of hemoglobin A1c (HbA1c) reduction achieved. Endocrinologists and other diabetes care providers are taught that lowering HbA1c to near normal levels is paramount for the health of the patient. However, this may not be the complete story for cardiovascular disease in patients with diabetes. Cardiovascular disease is the most common diabetes-related healthcare issue.

In 2004, heart disease was noted on 68% of diabetes-related death certificates among people aged 65 years or older, and stroke was noted on 16% of them. Both heart disease death rates and risk of stroke are about 2 to 4 times higher in adults with diabetes than adults without diabetes.

Accordingly, several major randomized controlled trials have been designed to test the hypothesis that lowering HbA1c would reduce cardiovascular death. These trials include VADT (Veterans Affairs Diabetes Trial), ACCORD (Action to Control Cardiovascular Risk in Diabetics), ADVANCE (Action in Diabetes and Vascular disease: Preterax and Dimicron Modified Release Controlled Evaluation), and UKPDS (United Kingdom Prospective Diabetes Study). Notably, none of these trials reduced CVD events significantly. A recent meta-analysis of these studies concluded that targeting more-intensive glucose lowering modestly reduced major macrovascular events in the short-to-medium term, although all-cause and cardiovascular mortality were not benefitted. Because of the lack of clear benefit of lowering HbA1c with respect to cardiovascular disease, some experts question the importance placed on this biomarker and advocate for antidiabetes drug trials to be more based on clinical outcomes.
Microvascular conditions, such as a nephropathy, neuropathy, and retinopathy, also need to be considered when evaluating new antidiabetes therapies. Lowering HbA1c levels has been shown to delay their development. Furthermore, the February 2008 FDA draft guidance states “For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control.”

Concluding Remarks
This White Paper has reviewed the FDA’s Guidance addressing cardiovascular safety assessment during the development of new antidiabetic therapies for T2DM. It is hoped that this review will prove useful to all involved in the development of such drugs that will provide additional treatment options for a rapidly-increasing population of diabetic patients.

Notes
1. A condensed version of this paper was published in the December 2009 Issue of the DIA Global Forum.
2. The authors contributed equally to the writing of this paper. They acknowledge presentations and discussions at the DIA/FDA/CSRC-sponsored “Cardiovascular Safety and Development of Type 2 Diabetes Mellitus Medications: Current State of the Art and Opportunities to Advance the Science” conference held in Washington, DC, on 23-24th September 2009. They also note that this paper has not been sanctioned or approved by any representative from the FDA, and Sponsors are encouraged to establish dialog with the agency as appropriate.
References
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Previously, in the field of cardiovascular behavioral medicine, Dr. Turner’s innovative behavioral genetic research investigated inherited and environmental influences in cardiovascular responses to psychological and behavioral stressors. He has published 50 peer-reviewed papers and five books in this field, and received two international research awards. Dr. Turner has spoken before two FDA advisory committees on cardiovascular safety issues, given numerous presentations at international conferences and published many articles on topics within the field of integrated cardiac safety. He is also a Senior Fellow, Center for Medicine in the Public Interest.
Introduction
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Understanding the FDA Guidance on Assessing Cardiovascular Risks for new Antidiabetic Therapies.
A Review of FDA Guidance
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