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**Regulatory Landscapes for  
Future Antidiabetic Drug  
Development (Part1)**  
FDA Guidance on Assessment  
of Cardiovascular Risk

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# Regulatory Landscapes for Future Antidiabetic Drug Development (Part I): FDA Guidance on Assessment of Cardiovascular Risk

Diabetes mellitus is a serious disease that is rapidly assuming epidemic proportions. Huang et al. [1] recently observed that the number of individuals in the United States with diagnosed and undiagnosed diabetes will increase from 23.7 million to 44.1 million between 2009 and 2034. Additionally, the lifetime risk of developing diabetes for those born in the year 2000 is 35% [2]. The need for pharmacologic therapies for this population is therefore considerable. However, the development of such therapeutic agents has recently attracted additional regulatory interest and, arguably, hurdles. An FDA Guidance for Industry [3] now requires sponsors to demonstrate that a new agent does not have an unacceptable cardiovascular risk. Following a brief overview of the evolution of this guidance and the resulting new regulatory landscape in the US, potential implications for the future development of antidiabetic drugs are discussed.

This article is the first in a series. At the time of writing, the EMEA is preparing an updated version of their 2002 Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus [4]. A 2008 EMEA Concept Paper discussed the need for this revision, and indicated that guidance on cardiovascular outcome studies is among the main topics likely to be addressed [5]. The updated guidance is expected in the near future, and, shortly thereafter, the second article in this series will provide a similar review of the European regulatory landscape. As and when other regulatory agencies release guidance documents in this area of drug development, they will also be reviewed.

## Evolution of the FDA Guidance addressing Evaluation of Cardiovascular Risk

The FDA guidance Diabetes Mellitus—Evaluation of Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, was published in December 2008 [3]. The seminal influence in a series of events leading to this guidance was a paper that was e-published by the New England Journal of Medicine on 21st May 2007 [6]. This paper presented a meta-analysis focusing on the thiazolidinedione drug rosiglitazone. The result of note was an odds ratio for the occurrence of 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 [7] reviewed the intense governmental and regulatory (both FDA and EMEA) activity in the days and months following the paper's e-publication, and also the controversy revolving around the scientific legitimacy or otherwise of this result. Given the already voluminous literature on this topic, this paper focuses on the evolution of the guidance and its impact on the US regulatory landscape.

On 6th June 2007, the US Committee on Oversight and Government Reform held a hearing to discuss the FDA's role in evaluating the safety of rosiglitazone (failure to adequately do so being the position of some protagonists at the hearing). Subsequently, 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. While the committees' members eventually voted 20-3 that rosiglitazone increases the cardiac risk in patients with Type 2 diabetes mellitus (T2DM), they also voted 22-1 that rosiglitazone should not be removed from the market, therefore remaining an available treatment option for physicians and their patients. On 19th November 2007, the FDA announced that rosiglitazone's sponsor had agreed to add new information to the existing boxed warning on the drug's label about the potential increased risk for myocardial infarction. Part of the new text read as follows, and finished with a noteworthy statement:

A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing Avandia to some other approved oral antidiabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

Nonetheless, on July 1st and 2nd 2008, the Endocrinologic and Metabolic Drugs Advisory Committee met to address potential new regulatory guidance concerning cardiovascular safety assessments for all 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 alternative evidence to rule out an unacceptable cardiovascular risk. The guidance resulted from discussions at this meeting. It is of note that the final version of the guidance was published quickly. It was felt that the February 2008 draft guideline on the general development of drugs for diabetes did not address cardiovascular risk in sufficient detail, and that there was need for additional guidance in this realm. The final version of the general guidance will incorporate information on the identification of unacceptable cardiovascular risk and supersede the December 2008 guideline.

#### Central Components of the Guidance

Demonstration is required that a new agent to treat T2DM is not associated with an unacceptable increase in cardiovascular risk. Clinical endpoints of interest include, but are not limited to, non-fatal myocardial infarction, non-fatal stroke, and cardiovascular mortality (events which comprise the Major Adverse Cardiovascular Events [MACE] composite endpoint), acute coronary syndrome, and urgent revascularisation procedures. A composite endpoint can be advantageous when the number of individual events may be too low to meaningfully compare those occurring in the test drug treatment group with those in the comparator treatment group. The guidance also makes clear that endpoints now require independent adjudication. Additional changes to development programmes going forward include the length of trials to be conducted and the nature of the subject population employed. Larger and longer late Phase

II trials are called for, as are larger and longer Phase III trials that include subjects at high risk for cardiovascular events. The approach to excluding unacceptable risk can be represented by a three-component model incorporating clinical science (clinical judgments concerning absolute and relative risks), regulatory science (benefit-risk judgments at the public health level and choice of thresholds of regulatory interest), and statistical science (determining whether or not regulatory thresholds have been breached) [8]. Upon completion of a planned preapproval clinical development programme, a meta-analysis exploring the investigational drug's MACE liability is to be conducted (see Caveney and Turner [9] for a more detailed statistical discussion). Since the cardiovascular safety of the test drug is judged against that of a comparator, a risk ratio point estimate and associated confidence intervals (CIs) are of interest. Primary interest falls on the upper limit of a two-sided 95% CI placed around the relative risk ratio point estimate generated by the meta-analysis (see Turner [8] for more detailed statistical discussion).

Three scenarios are discussed in the guidance:

- If the upper limit of this CI is equal to or greater than 1.8, a drug is 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 [limit of the CI] before NDA/BLA submission." [3]
- If the upper limit is equal to or greater than 1.3 but also less than 1.8, and the overall benefit-risk analysis presented at submission



supports marketing approval, a subsequent step will generally be necessary. A postmarketing trial is required to definitively show that the upper limit of the CI is actually less than 1.3. Thus, for drugs that are not deemed to have an unacceptable risk at this point in time, later studies must show that a more comprehensive assessment yields a risk ratio less than 1.3. If the upper limit 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." [3]

### Intent and Possible Unintended Consequences of the Guidance

The intent of the guidance is to ensure that new antidiabetic drugs do not unacceptably increase the risk for cardiovascular events of regulatory interest. The importance of this intent is underscored by observations that diabetes greatly increases the risk of heart disease and stroke [10], and that the majority of patients with T2DM die from cardiovascular disease and not from their hyperglycemia per se. Traditionally, HbA1c has been used as a biomarker to judge long-term glycemic control. While compelling data from the UKPDS study showed that lowering HbA1c in patients with T2DM reduces the risk of microvascular disease [11], similarly convincing evidence for a reduction in macrovascular disease has not been provided. This has led to ambiguity concerning the exact relationship between hyperglycemia, anti-hyperglycemic medications, and cardiovascular disease. Type 2 diabetes mellitus and metabolic syndrome clearly have a complicated pathogenesis. Widely different elements and pathways have been implicated, e.g., glycerol-sn-3-phosphate acyltransferase, plasminogen activator inhibitor-1, intermittent hypoxia, and eating a high fat diet. An interesting hypothesis was provided by Stern [12], who proposed the "common soil" hypothesis as an answer to the association between T2DM and cardiovascular disease. Unlike classical microvascular complications, large-vessel atherosclerosis can precede the development of diabetes, suggesting that rather than atherosclerosis being a complication of diabetes, both conditions have common genetic and environmental antecedents. However, a unifying explanation has not yet been found. In 1990 there were only three classes of drugs for diabetes: metformin, sulfonylureas, and insulin (animal or human). Now nine classes are available [13]. These drugs attack hyperglycemia using different mechanisms of action, including modification of insulin sensitisation, insulin production, and glucose absorption blockage. Nevertheless, only one third of patients diagnosed as having diabetes achieve the American Diabetes Association goal of an HbA1c level less than 7% [2]. Even fewer reach the target level of 6.5% advocated by other professional organisations, e.g., the American Association of Clinical Endocrinologists and European Association for the Study of Diabetes.

The need for the continued development of new antidiabetic drugs is therefore clear. The evidence that lowering HbA1c reduces microvascular disease argues for the continued use of this biomarker in clinical trials of such drugs. In addition, regulatory requirements now also address macrovascular factors explicitly in the form of demonstrating that the drug does not unacceptably increase the risk of such disease: as already noted, this is the intent of the new guidance. However, there may be unintended consequences. The mandate of the new guidance may add tens of millions of dollars to the cost of bringing a new antidiabetic drug to the US market. While the full story is not necessarily captured by these data alone, especially given the global economic recession, inspection of relevant data on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) reveals a general increase in

the number of diabetes trials between 2005 and 2008, followed by a levelling off in 2009. Additionally, late 2008 and 2009 saw several smaller biotech companies abandon their diabetes programmes because of the cost increase. One could speculate that the new mandates are leading all involved pharmaceutical companies, regardless of size, to re-examine their diabetes pipelines and reforecast their predicted return on investment. With so many patients suffering with diabetes, the unclear pathogenesis of the disease, and patients not meeting professional goals for optimal care, the field is ripe for more research discoveries and the market is open for further drug developments. Regulators, policy-makers, and industry leaders will need to be vigilant and work together to ensure that the new regulatory guidance does not stifle the development of antidiabetic agents. ■

### References:

- Huang ES et al., 2009, *Projecting the Future Diabetes Population Size and Related Costs for the US*, *Diabetes Care*, 32:2225-2229.
- Brownlee MD, Hirsch, IB, 2006, *Glycemic Variability: A Hemoglobin A1c-Independent Risk Factor for Diabetic Complications*, *Journal of the American Medical Association*, 295:1707-1708.
- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>
- <http://www.emea.europa.eu/pdfs/human/ewp/108000en.pdf>
- <http://www.emea.europa.eu/pdfs/human/ewp/17634808en.pdf>
- Nissen SE, Wolski K, 2007, *Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes*. *New England Journal of Medicine*, 356:2457-2471 [e-published ahead of hard print].
- Turner JR, Durham TA, 2009, *Integrated Cardiac Safety: Assessment Methodologies for Noncardiac Drugs in Discovery, Development, and Postmarketing Surveillance*. Hoboken, NJ: John Wiley & Sons.
- Turner JR, 2010, *Integrated Cardiovascular Safety: Expanding our Assessment Horizons for Prospectively Excluding Unacceptable Cardiovascular Risks*. *Applied Clinical Trials*, in press.
- Caveney E, Turner JR, 2009, *Understanding the FDA Guidance on Assessing Cardiovascular Risks for new Anti-diabetes Therapies*. *Quintiles Point of View Document*, available from [erica.caveney@quintiles.com](mailto:erica.caveney@quintiles.com) or [rick.turner@quintiles.com](mailto:rick.turner@quintiles.com).
- Centers for Disease Control and Prevention, 2007, *National Diabetes Fact Sheet*: [http://www.cdc.gov/diabetes/pubs/pdf/ndfs\\_2007.pdf](http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf)
- UK Prospective Diabetes Study (UKPDS) Group, 1998, *Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)*. *Lancet*, 352:837-853.
- Stern MP, 1995, *Diabetes and cardiovascular disease. The "common soil" hypothesis*. *Diabetes*, 44:369-374.
- Gale EA, 2009, *Collateral damage: the conundrum of drug safety*, *Diabetologia*, 52:1975-1982.



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