BIOBUSINESS BRIEFS

REGULATORY WATCH

FDA issues guidance for cardiovascular risk assessment of novel antidiabetic agents

Cardiovascular disease associated with type 2 diabetes (T2DM) has become a major issue in the development of novel T2DM therapies. Now, the US Food and Drug Administration (FDA) has issued a final guidance for industry on how to use clinical trials to show that a new T2DM treatment is not associated with an unacceptable increase in the risk of cardiovascular events (http://www.fda.gov/Cder/Guidance/8576fnl.pdf). The FDA will continue to allow blood glucose control, as measured by glycated haemoglobin (HbA1c) levels, as the primary efficacy end point.

The prevalence of T2DM is increasing rapidly, and patients face a substantially greater risk of heart disease than do non-diabetics. None of the currently approved antidiabetic agents has convincingly been proven to reduce this risk of CV disease, and some may actually increase the risk. As T2DM often requires life-long treatment, collation of more information regarding how T2DM treatments can affect cardiovascular events is vital.

The guidance, effective immediately, provides a detailed approach for acquiring, analysing and reporting the necessary safety information from all Phase II and III trials of a novel drug. "These guidelines represent a major adjustment by the FDA in response to mounting concerns about cardiovascular risk," says Clifford Rosen, Director of Clinical and Translational Research, Maine Medical Center, and member of the FDA Endocrinologic and Metabolic Drug Advisory Committee. "The most important of these are the establishment of a separate and independent cardiovascular end-point committee to adjudicate cardiovascular events, and the inclusion of high risk individuals including elderly and renally impaired patients in Phase II and III studies," he adds.

Following trial completion, a meta-analysis of all data should be performed. "I think this is an extremely wise, reasoned, balanced and scientific approach to evaluating the cardiovascular safety of drugs newly developed for use in diabetes. It always makes sense to make maximal use of all the data available on the safety of a drug," says Brian Strom, Chair of the Department of Biostatistics and Epidemiology at the University of Pennsylvania School of Medicine. "In this case, it is important to realize that the meta-analysis is not independent information, but simply an objective way of integrating all of the data available to date. Then, judgments are made based on that integrated information, whether more data are needed, and if so whether those data are needed premarketing or postmarketing." Indeed, Rosen notes that the new guidance also includes upper boundaries for confidence intervals to determine increased risk relative to the need for postmarketing studies.

It is recognized that the new challenges accompanying this guidance could reduce industry interest in the development of novel T2DM therapies. "While it will be easier for adjudicators to define cardiovascular risk, difficulties will be faced in terms of patient recruitment and elevated costs for industries to conduct such trials," concludes Rosen.