The Diabetes Pandemic: Responding to FDA Guidance on Cardiovascular Risk in Type 2 Diabetes Treatment

Diabetes is increasing at a disturbing rate both in the US and Europe, and in China. In America approximately 4000 people are diagnosed with type 2 diabetes each day. In recognition of this alarming growth and the ongoing research and development of both preventive and palliative diabetes treatment, in December, 2008 the FDA released guidance on new anti-diabetic drugs. This guidance recommends that sponsors demonstrate that new anti-diabetic therapies for the treatment of type 2 diabetes are not associated with increased cardiovascular risk. This article will discuss the implications of the FDA guidance recommendations and how sponsors can respond in order to ensure compliance.

The Growing Threat of Diabetes
Type 2 diabetes has been described as an emerging global pandemic, presenting a serious public health problem on an international level. There are approximately 280 million people with diabetes mellitus worldwide; 90% of these have type 2 (non-insulin dependent) diabetes. In the US alone there are currently 24 million diabetics, with steadily increasing numbers. This seems to track with the rising prevalence of obesity.

The sequelae of diabetes are severe and often fatal. Diabetes is currently the leading cause of blindness, kidney failure and limb amputation, and is a major contributor to myocardial infarction and stroke. Approximately 70% of diabetes mellitus-related deaths occur as a result of cardiovascular disease. As a result, diabetes now accounts for a substantial proportion of healthcare expenditure. There are currently many medications used for the treatment of diabetes, and these have had a great impact on many of the immediate consequences of elevated blood sugar, as well as on the development of diabetic blindness, kidney failure and peripheral neuropathy. However, the rate of cardiovascular complications remains high in diabetics, making the continued development of safe and effective new agents for the treatment and prevention of diabetes a high priority.

FDA Guidance
Concerns related to the cardiovascular risk incurred by treatment for type 2 diabetes has heightened in recent years, as some approved drugs appear to actually increase the risk of cardiovascular events. On a broader level, regulators are becoming more stringent regarding the need to ensure the cardiovascular safety of all non-cardiovascular drugs. Highlighting these concerns, in 2008 the FDA released the guidance document: ‘Guidance for Industry – Diabetes Mellitus – Evaluating Cardiovascular Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes’. The FDA Guidance on Diabetes provides non-binding recommendations to ensure that new medications for treating diabetes are demonstrated to be safe (from a cardiovascular standpoint) as well as effective at treating elevated blood sugar.

The release of the FDA guidance on the treatment of type 2 diabetes reflects the growing regulatory consensus that the lack of a preclinical signal and a lack of cardiovascular events in early trials are not sufficient evidence to demonstrate the cardiovascular safety of a new agent. As such, the guidance recommends that Phase II/III must be adequately powered to demonstrate cardiovascular safety compared to current therapies. As assessment of cardiovascular safety has become such a priority, the FDA recommended that pharmaceutical companies should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all Phase II and Phase III trials.

Further, it is recommended that ‘to obtain sufficient endpoints to allow meaningful estimate of risk, the phase II and phase III 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.’ The FDA guidance document makes explicit recommendations about the statistical tests which will be required to demonstrate cardiovascular safety, and have provided estimates of the number of subjects required for these safety studies. It is estimated that the late phase trials to demonstrate cardiovascular safety will require upwards of 2500 subjects, with at least 1300 – 1500 subjects exposed to investigational product for one year or more, and at least 300 subjects exposed for 18 months or more. This is a marked contrast to the far smaller size and shorter duration of previous trials for new anti-diabetic agents.

Centralisation of ECGs
Part of the assessment of a new drug’s short- and long-term cardiovascular effects can be assessed by performing serial electrocardiograms (ECGs). However, the quality of the data generated by a test is only as good as the quality of the interpretation of the test itself. In order to ensure the value of ECG data for evaluating cardiovascular safety, sponsors are encouraged to use a centralised approach to their ECG programme in order to achieve a standardised and consistent database. When a decentralised model is employed, ECGs are performed at the investigator sites using local ECG machines, which may be of many different makes and models. As a result, the automated measurements and interpretations may be very inconsistent.

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due to different types of instruments using a variety of different computer algorithms for calculations. In contrast, a centralised approach overcomes this issue of inconsistency by digitally collecting high quality data in a standardised format for assessment, with the use of consistent and validated systems. All interval duration measurements (IDMs) are assessed by a qualified individual, and every ECG is evaluated by a qualified cardiologist who is trained to follow standardised procedures which are continually validated through a quality control programme. As a consequence, more consistent and cleaner data will be generated. Additionally, centralisation facilitates proactive data monitoring and tracking, with demography and missing visits noted automatically, thereby enabling the collection of valuable data as studies progress.

Accurate and comprehensive capture of cardiovascular events requires an instrument that can detect even the most inconspicuous of indicators. For example, myocardial infarction (MI) does not always have a classic presentation, since as many as 40% of MIs are “silent”, and are associated with either no symptoms at all, or with atypical symptoms which are not recognised by the patient. These “silent” MIs may be detected on the serial ECGs collected during the trial. The capture of these otherwise unrecognised events may help to reduce the duration and cost of these large cardiovascular safety trials. However, the capture of this data requires that ECGs be evaluated in a consistent manner such that analysis of the database can reliably identify these subjects for adjudication by the cardiovascular events committee. Decentralised ECG reading, with interpretations generated by ECG machines or by a wide variety of non-cardiologist physicians, may yield databases with so much noise that new events cannot be reliably resolved.

Another advantage to the use of a centralised cardiac safety core lab is the enhanced availability of ECG data for review by the sponsor and cardiovascular review committee. When ECGs are analysed locally, the paper ECG remains at the site. In contrast, a centralised core lab stores all of the ECG data in a central repository, and can provide online access to ECG data via a centralised portal. The ability to evaluate data across a specific patient and across all patients globally may be invaluable.

Cost-Effective Compliance
Upon its initial release, the FDA Guidance on the development of treatment for type 2 diabetes produced some controversy. The recommendations for extended trial periods with higher numbers of subjects translate into increased expense for sponsors. The use of a centralised cardiac safety core lab will improve the quality of ECG data generated, but is often thought to be more costly than use of decentralised ECG reading. In reality, however, the use of a core lab may actually be more cost-effective than having multiple individual sites perform
ECG evaluations. Contracting with a core lab reduces fees paid to each site for technical support and ECG reading (often by unskilled readers). Additionally, by eliminating errors in collection and transcription of ECG data, sponsors can minimize the amount of retesting that must be carried out. In addition, recent technological innovations have led to the introduction of new, highly compact ECG instrumentation, providing the same industry-leading performance as conventional systems at a lower cost, and making a centralized approach easier to implement. In a recent comparison of cost compiled by a leading provider of technology services, it was shown that the use of centralized ECG provides an overall cost reduction of 34.6%.3

Conclusion
In order to comply with the FDA Guidance on the development of new anti-diabetic drugs, sponsors must now demonstrate that a new agent does not increase cardiovascular events. It is recommended that trial endpoints be clearly designed, that independent cardiovascular endpoint committees be established, and that sponsors prepare to enroll higher-risk subjects in longer and larger cardiovascular safety trials. Trial periods should be extended up to two years, and trials must be adequately powered to detect the requisite number of cardiovascular events in order to satisfy the statistical requirements outlined in the FDA guidance.

To comply with these recommendations and avoid inconsistency, inaccuracy and unnecessary extra cost, the use of centralized ECGs is crucial. As a result of centralized ECG collection and evaluation, data management quality and consistency is improved. With improved quality, greater consistency and ultimately more accurate data, false positive and negative ECG findings can be avoided. The overall duration, size and cost of the drug development programme can be decreased, while still ensuring compliance with the new, more stringent regulatory requirements.

References