



FEATURED ARTICLE

BRAVING THE NEW WORLD OF DIABETES DRUG DEVELOPMENT

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Diabetes drug developers have seen significant regulatory upheaval over the past few years, so much so that many sponsors - and investors - have abandoned the field altogether. While there's no avoiding the new regulatory hurdles, there are ways to make them somewhat more manageable.

The changes in the diabetes field began in mid-2007, when Dr. Steven Nissen and Kathy Wolski of the Cleveland Clinic published a meta-analysis in the *New England Journal of Medicine* linking GlaxoSmithKline's type 2 diabetes drug Avandia (rosiglitazone) to an increased risk of myocardial infarction and cardiovascular-related death.¹

The study set off a firestorm of scientific and political debate, prompting lawmakers and consumer groups to pressure the FDA for higher cardiovascular safety standards for diabetes drugs. In 2008, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee agreed that diabetes drug developers should be required to conduct cardiovascular safety studies prior to gaining approval. The agency took the advice of its experts, issuing new guidelines for cardiovascular safety in diabetes drug development.²

Historically, diabetes drugs have been approved based on their ability to lower blood glucose levels as measured by glycosylated hemoglobin (HbA1c). Lower HbA1c in landmark studies, such as the NIH's Diabetes Control and Complications Trial (DCCT), led to a decrease in microvascular complications of diabetes including retinopathy, nephropathy and neuropathy. But diabetes as a disease increases the risk for macrovascular complications, including myocardial infarct and stroke, both conditions with high morbidity and mortality. Regulators wanted to be sure that the diabetes drugs patients were taking to help avoid microvascular complications weren't simultaneously raising macrovascular risks.

Thus the new FDA guidelines require sponsors of clinical trials for type 2 diabetes drugs to gather cardiovascular safety data prior to approval. Such a study requires enrolling about 4,000 patients, which adds at least two to three years and more than \$100 million to the clinical trial program.

Because of the guidelines, issued in late 2008, many companies and investors backed away from the diabetes field and once viable drugs in the highly competitive diabetes space became obsolete. The ramifications of the 2008 guidelines are still being felt throughout the industry.

Last September, rosiglitazone was pulled from the market in Europe. While the drug remains available in the U.S., the FDA restricted access to it, with new patients allowed to take it only if they cannot control their blood glucose levels using other medications and cannot tolerate Actos (pioglitazone), a similar drug marketed by Takeda Pharmaceuticals.

The FDA has remained focused on cardiovascular safety as it evaluates new drugs and re-evaluates old ones. Meridia (sibutramine), a drug for the treatment of obesity, was pulled from the market in 2010 based on the results from the SCOUT trial, which showed an increased risk for cardiovascular complications in subjects with pre-existing cardiovascular conditions. Also, last October, the agency issued a complete response letter to Amylin Pharmaceuticals and Eli Lilly for their once-weekly diabetes drug Bydureon (exenatide extended release), asking for a cardiovascular safety study focusing on QTc risks at high doses.

Balancing Cost and Benefit

There is no avoiding the FDA's stringent cardiovascular safety requirements for diabetes drugs, but there are steps sponsors can take to shift the cost-benefit pendulum in their favor.

The most effective way to minimize the costs of a cardiovascular safety study is to run the smallest trial possible. One way to achieve this is to negotiate with the FDA on the number and type of permissible major adverse cardiovascular events (MACE). Endpoints with a higher event rate - such as coronary revascularization and unstable angina rather than just the "classical" MACE of myocardial infarction, stroke and cardiovascular death - will require fewer patients in the cardiovascular safety study to generate statistically meaningful data.

Sponsors can also potentially reduce their trial size by enrolling patients with higher cardiovascular risks, thus conducting a "real life" study that is more meaningful than a study in highly selected, relatively low risk subjects. While conducting a trial solely in high risk patients could result in a limited label, incorporating a significant number of high-risk patients into a subset of a large and well-rounded trial is a viable strategy.

To facilitate enrollment in a cardiovascular safety study, sponsors can also focus their enrollment efforts. Rather than enrolling diabetes patients from a standard general practitioner or endocrinologist, sponsors can enroll at cardiovascular and renal clinics, which are likely to have a higher percentage of diabetes patients with higher cardiovascular risk factors.

There are other strategies a sponsor can employ as well, such as taking advantage of adaptive trial designs and, in some situations, focusing on a niche subset, such as acutely ill patients.

Despite these best practices, the costs of running a clinical trial program for type 2 diabetes are significant. In addition to the preapproval cardiovascular safety requirements, there are post-approval studies: in many cases an even larger cardiovascular safety study is needed, as well as head-to-head efficacy trials against competitors and a variety of combination studies.

However, with worldwide sales of \$25 billion in 2009, and a patient population expected to exceed 350 million by 2030, the payoff offered by success in even a small portion of the market can be well worth the investment.³

INC Research is a global contract research organization with expertise in specific therapeutic areas including endocrinology. Our team has conducted more than 75 trials for indications such as diabetes, obesity, metabolic syndrome, dyslipidemia,

atherosclerosis, arterial hypertension, dyslipidemia and more. In the type 2 diabetes space, we have helped sponsors deal with changing regulatory requirements across the globe, overcoming regulatory-induced delays in study start-up and completing enrollment and data delivery on-time.

For more information on INC Research's experience in diabetes and endocrinology, contact Hans-Peter Guler at hpguler@incresearch.com.

About the Author

Hans-Peter Guler, MD, has over 20 years of experience in clinical research. Prior to joining INC Research, Dr. Guler served as Chief Medical Officer/VP Clinical Development at Phenomix. Prior to that, he held positions of increasing responsibility with Regeneron Pharmaceuticals Inc., Chiron Corp. and Ciba-Geigy Corp. His work in clinical research included studies at all stages from first-in-man to large registration trials. Indications studied included diabetes mellitus, obesity, rheumatoid arthritis, hepatitis C, asthma, sepsis, cardiovascular disease and renal failure. Prior to accepting his first job in industry, he conducted some of the early studies with recombinant insulin-like growth factor I in academia. He is an author of over 30 peer reviewed articles. Dr. Guler trained in Switzerland and received his MD from the University of Zurich.

References

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²<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>

³<http://www.prlog.org/10568516-brand-new-report-world-diabetes-market-analysis-2010-2025-by-visiongain.html>