



New FDA Guidances On Anti-Diabetes Therapies Change the Landscape of Drug Development

How Quintiles Can Help You Navigate
the Guidances and Successfully
Develop Pipeline Drug Candidates

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Executive Summary/Introduction

Successful research and development efforts have yielded new agents and new classes of drugs that are now available for the treatment of diabetes mellitus. For type 2 diabetes, sulphonylureas and metformin are now joined by thiazolidinediones, DPP4 inhibitors and GLP1 analogues in the therapeutic armamentarium. Many more drugs in these latter classes are currently in development, as well as SGLT2 inhibitors, next generation PPAR modulators, glucokinase inhibitors, HSD11B1 inhibitors and many others. The persistent urgent medical need for newer and better treatments for diabetes is testament to the rapidly increasing prevalence of the disease on a global scale, from 171 million cases in 2000 to a projected 366 million cases by the year 2030.

Did you Know?

Quintiles has conducted 112 diabetes trials since 2006 including:

- *89,000 patients*
- *10,500 sites*
- *50 countries*

While research for diabetes has always been strong, the complexity and cost of drug development for diabetes indications has now become more complex and costly than ever before. The new FDA guidelines, *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*, issued in March 2008 and *Diabetes Mellitus: Evaluating Cardiovascular Risks in New Antidiabetic Therapies to Treat Type 2 Diabetes*, issued in December 2008 will increase the complexity and thus the cost of further developing diabetes drugs. In addition to the previous safety testing, the guidelines now require an in-depth safety review for all type 2 diabetes drugs with a specific focus on cardiovascular outcomes such as stroke, myocardial infarction, and cardiovascular mortality.

According to the *Pink Sheet*, Venture Capitalists are reevaluating whether or not they will invest in type 2 diabetes drugs knowing how these draft guidelines will drive the cost and length of clinical trials for their investments. On average the cost for a single patient in a diabetes trial can range from \$15,000 to \$30,000 depending on therapeutic class and type of diabetic patient. The FDA Guidelines could increase the cost per patient as much as 25 percent to 50 percent. Many companies however still see the benefits of developing diabetes drugs, not only for patients, but for a solid return on investment. According to IMS MIDAS data in 2007 global pharmaceutical sales, diabetes ranks at number five with annual US sales of \$24.1B in 2007 representing a year-over-year growth of 10.7%.

Like many business investments, there are always risks and the potential benefits received in pursuing the risks. In the case of diabetes drug development the risk of developing these drugs is a higher investment in both dollars and man power. Forming a working relationship with a knowledgeable service provider who understands not only diabetes drug development, but who has the experience you need to ensure your success. We believe Quintiles is that provider.

Quintiles has been involved with diabetes research for nearly 35 years beginning in 1975 with our Founder and Chairman, Dr. Dennis Gillings' investigation into then West Germany, where 56 deaths associated

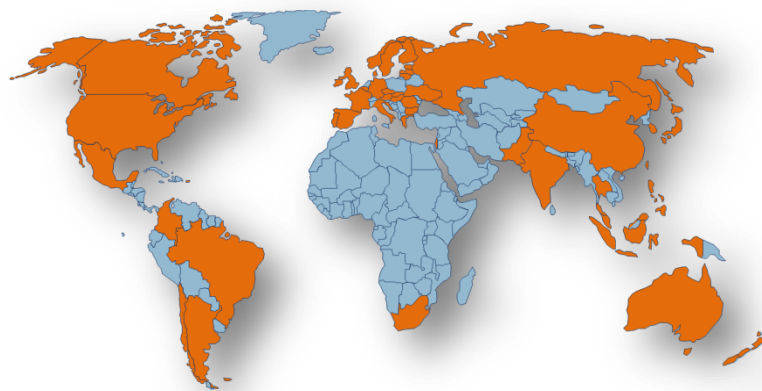


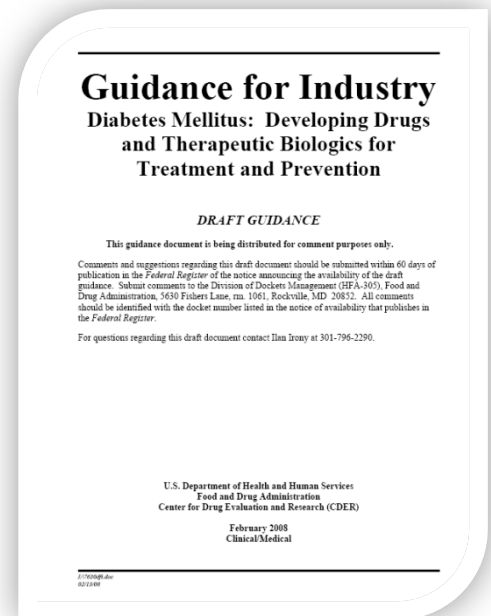
Figure 1 – Quintiles has conducted diabetes studies in over 50 countries as highlighted in orange.

with glyburide occurred in geriatric populations. There was considerable concern in the US that a drug from West Germany was being inappropriately submitted to the FDA for marketing approval.

Dr. Gillings' findings led to appropriate label changes for the drug and, once the UGDP cardiovascular issues had been satisfactorily resolved, glyburide was approved for marketing in the United States. More recently our experience from 2006 to the present includes a total of 112 studies in Diabetes and Diabetes complications enrolling over 89,000 patients from nearly 10,500 sites in over 50 countries as highlighted in Figure 1.

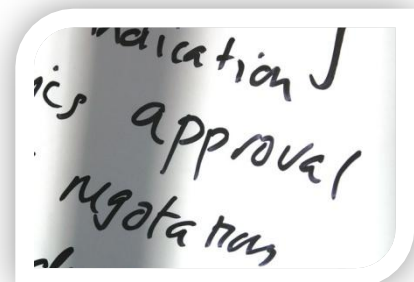
The Guidance

In 2008, the U.S. Food and Drug Administration released two guidance documents that will have profound impacts on the development of drugs for diabetes [Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. U.S. DHHS, FDA, CDER. February 2008. Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. U.S. DHHS, FDA, CDER. December 2008]. The guidance on cardiovascular risk reflects input from FDA's Endocrinologic and Metabolic Drugs Advisory Committee, which in July, 2008 called for studies of the cardiovascular risks of new antidiabetic drugs. This guidance is controversial, with prominent diabetes specialists, advocates, and educators challenging the guidance, arguing that the new standards are excessive and threaten to stifle drug discovery at the expense of patients who need more treatment options. However, as a practical matter, it is highly unlikely that the FDA will rescind or revise the published guidance over the next several years.



Study Design, Endpoints, Study Population

The general guidance document from February, 2008 reinforces much of what has become standard practice in the conduct of diabetes drug development programs over the last decade. A 6-8 week run-in period is recommended for phase II studies in order to allow for education, optimization of compliance with treatment regimens, and stabilization of metabolic parameters. In addition, a placebo run-in period for phase III studies can help screen out noncompliant subjects. Hemoglobin A1c remains the



surrogate outcome measure of choice in diabetes trials, although significant reductions in the need for concomitant anti-diabetes drug therapy or improvements in diabetes-related morbidity or mortality may be important as well. For the treatment of type 2 diabetes (to which most pipeline drugs are targeted), efficacy and safety may be evaluated with placebo-controlled monotherapy trials, placebo-controlled add-on trials, and active-controlled trials. Over the course of the development program, the investigational drug should be assessed as monotherapy and in combination with other approved drugs. Active-controlled and combination therapy trials will assume even greater importance as government agencies in the U.K., and now the U.S. will be assessing value based on comparative effectiveness research. Anticipating the relevant assessments and optimizing the positioning of a drug during the development program will be an important strategy in this regard.

The new FDA guidances have important implications for the selection of appropriate study populations during drug development programs. Attempts should be made to include ethnic populations in which diabetes is disproportionately prevalent, such as Latinos, African Americans and Native Americans. When older patients are included, protocols should specifically address decreased renal function, autonomic dysfunction, poor glucose counter-regulatory responses, hypoglycemia unawareness and interactions with commonly used drugs. These considerations are important to protecting patient safety as well as to building a valuable and robust data set.

Evaluating Cardiovascular Risk

The guidance on evaluating cardiovascular risk in new antidiabetic therapies presents novel challenges in selecting appropriate study populations. Improved long-term glycemic control in patients with type 2 diabetes is associated with a reduced risk of both macrovascular and microvascular complications. The results of the UKPDS, Kumamoto, and ADVANCE trials showed intensive therapy improved the outcome of microvascular disease in those with type 2 diabetes mellitus. Likewise, epidemiologic analyses (observational studies or secondary analyses of trials) suggest a correlation between higher rates of cardiovascular disease and chronic hyperglycemia. If new drugs intrinsically increase cardiovascular risk, then the cardiovascular outcomes benefit of improved glycemic control may be dampened or even reversed, depending on the magnitude of the effect. In order to convincingly demonstrate what impact an experimental drug itself has on cardiovascular outcomes, studies will need to include large numbers of patients at higher risk of cardiovascular events, for long periods of time. Thus, inclusion of patients with advanced disease, elderly patients, and patients with renal impairment will be essential.

For new studies in the planning stage, cardiovascular events such as cardiovascular mortality, myocardial infarction, stroke, and possible others (e.g. hospitalization for ACS, urgent revascularization procedures) will need to be tracked across phases II and III of the development program. An independent cardiovascular endpoints adjudication committee will be needed to appropriately classify events. Phases II and III study designs must be appropriate in order to allow a meta-analysis of cardiovascular events at the time of completion of the studies. Depending on the numbers of patients at higher cardiovascular risk entered into the studies, study durations of 1.5 years or more could replace 3-6 months as the norm. Phase III trial data should be available for at least 2,500 subjects exposed to the investigational product, with at least 1,300 to 1,500 of these subjects exposed to the investigational

product for 1 year or more and at least 300 to 500 subjects exposed to the investigational product for 18 months or more. Extensions of 6- to 12-months may be necessary in order to obtain enough events and to provide data on longer-term cardiovascular risk.

It is now necessary to examine the incidence of important cardiovascular events in the investigational agent and control groups. Approvable drugs will have an upper bound of the two-sided 95% confidence interval for the estimated risk ratio of less than 1.8. If this result is in the 1.3-1.8 range and the risk-benefit analysis otherwise supports approval, a post-marketing trial will be necessary to demonstrate that the actual upper bound of the 95% confidence interval for the estimated risk ratio is less than 1.3.

Cardiovascular Endpoints Committee Management

The Clinical Endpoint Validation and Adjudication (CEVA) department within Quintiles' Pharmacovigilance unit is dedicated to the management of clinical trial oversight groups, such as Cardiovascular Endpoints Committees. We have managed over 90 Endpoint Adjudication Committees (over 50% of which were responsible for adjudicating cardiovascular endpoints), and have processed over 115,000 endpoint dossiers for multiple therapeutic indications and event types, including all of those mentioned in the December, 2008 FDA guidance on evaluating cardiovascular risk in new anti-diabetes therapies. Our experience spans phase I through phase IV clinical trials, and includes support of endpoint adjudication committee processes on 18 mega-trials (defined as trials with 1,000 – 18,000 endpoints requiring adjudication). One of the most recent examples includes a 13,000+ patient registration trial in which more than 4,000 cardiovascular events were adjudicated.

About CEVA

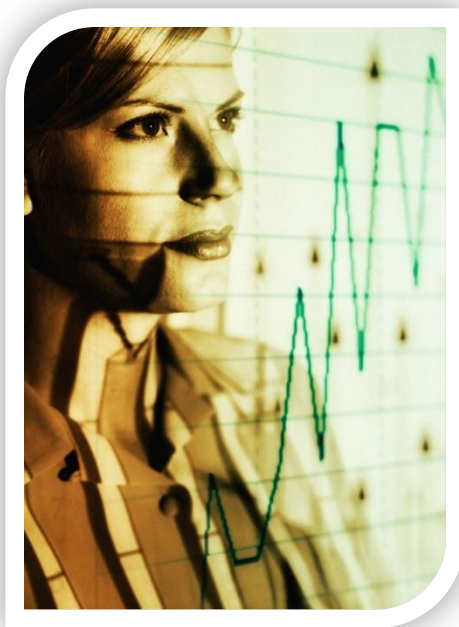
The Quintiles CEVA department consists of specialists from scientific, clinical and administrative backgrounds who offer a high quality, cost efficient and effective approach to oversight group management. We have over 100 trained CEVA staff in 8 offices across 6 regions: North America, South America, Europe, South Africa, Asia and India. We use globally accessible endpoint systems to support, automate and integrate processes in all Quintiles CEVA offices.

Our CEVA group assists with multiple aspects of the Cardiovascular Endpoints Committee process and management, including the following:

- Identification, screening, qualification and selection of committee members
- Process design including development of charter, workflows and endpoint site manual
- Endpoint reporting and adjudication CRF design
- Endpoint tracking and reconciliation
- Endpoint dossier compilation and submission for adjudication
- Collection and data cleaning for final, completed Adjudication CRFs
- Endpoint status reporting
- Committee meeting planning and coordination, including logistical arrangements, agendas and minutes of open sessions
- Committee member contracts, payments and reimbursements

Biostatistical Considerations

The FDA advises sponsors to craft their development program to ensure that phase II and phase III clinical trials are designed and conducted so that meta-analysis can be performed at the time of completion. As long as this goal is met, sponsors can decide the best way to achieve this. Quintiles understands that different companies will have varied goals and objectives that will need to be met. When planning the size and duration of the different phase II and III studies that comprise a diabetes program, the overall objective of the meta analysis is certainly not the only consideration. Crafting these various studies to reach the goal in the most economically prudent way is important. We understand that it is equally important to review the data from the trials to make sure efficacy and non-cardiac safety are also being met. Thus a balance must be struck between conducting short term early phase trials with longer early phases trials. Over the life of a program, it will be economically advantageous to gather at least 6 months of cardiovascular outcomes data from all subjects enrolled in all trials. However, many companies will need 12 week efficacy data in order for funding to continue. As discussed below, adaptive clinical design and interim analysis may be two ways to achieve this.



Given that safety information is accrued at a slower rate than for efficacy, one could consider taking more than one dose into phase III. In this case, a decision to discontinue one of the arms can be made at an interim analysis during the confirmatory stage when more safety data are available. The decision to discontinue one of the arms at this stage can be based on safety information only, or on combination of safety and efficacy. While this would increase the cost of the development, it would at the same time improve the probability of success for the program. The assessment of associated costs and benefits of such an approach can be made through simulations.

Another approach would be to combine phase IIb and phase III in one “seamless” adaptive design trial, with a more robust phase IIb stage. Depending on how many doses have been studied in phase II, the safety and efficacy estimates may be derived by fitting a model to safety and efficacy dose response respectively, rather than being based on observations for each individual dose. Based on these estimates, a dose with an optimal combination of safety and efficacy would advance into phase III.

Because safety information collected during phase II is relatively limited, considerable uncertainty exists at the end of phase II regarding the expected risk ratio. This, in turn, dictates uncertainty regarding the required size of the phase III program. To address this uncertainty, a sample size re-assessment can be proposed for confirmatory trial(s). The sample size re-assessment would be based on the meta-analysis estimate of the cardiovascular risk ratio. This maneuver can avoid the need to initiate another safety trial because the target safety result has been “just missed”.

Medical and Pharmacovigilance Considerations

Therapeutic and drug safety expertise will play increasingly significant roles in executing safe and effective anti-diabetes drug development programs. The Quintiles Global Medical & Scientific Services staff is comprised of more than 80 physicians representing the entire spectrum of medical specialties and subspecialties. Two of these physicians are board certified endocrinologists. Drs. Erica Caveney and Loukas Gourgiotis, in addition to the knowledge they bring from their clinical care of diabetes patients, both are experienced in monitoring diabetes trials and understand the unique challenges of conducting these types of studies. Also, 8 physicians with special expertise in drug safety work within Quintiles Pharmacovigilance. The Quintiles Drug Safety Physicians work in concert with Therapeutic Medical Monitors to provide expert safety case evaluation and signal detection services across multiple protocols for the same product or as a stand-alone service. Safety Physicians can provide the full spectrum of safety oversight during clinical development and beyond.



Dr. Erica Caveney, MD

- Associate Director, Medical & Scientific Services
- Board Certified in Internal Medicine (2001-2011)
- Board Certified in Endocrinology, Diabetes, and Metabolism (2005-2015)
- 5-year clinical experience at tertiary care centers for a variety of endocrinological disease and diabetes (Duke University Medical Center and University of North Carolina Hospitals)
- Main clinical research areas: Type I and Type II Diabetes Mellitus, Osteoporosis, Obesity, Thyroid Dysfunction, Thyroid Cancer, Pituitary and Adrenal Diseases, Calcium Abnormalities
- Laboratory Experience in Obesity Research



Dr. Loukas Gourgiotis, MD

- Associate Director, Medical & Scientific Services
- Qualified Endocrinologist
- 6-year clinical experience at a tertiary referral center for a variety of endocrinological diseases and diabetes (National Institutes of Health, USA)
- Main clinical research area: diabetes, clinically aggressive thyroid cancer, osteoporosis
- Master in Clinical Research (Duke University)
- Author of 18 articles and 3 book chapters
- Pharmaceutical Company experience in Phase III trials for diabetes

DEDICATED DRUG SAFETY MEDICAL ADVISORS KEY SERVICES

Clinical Trial

- Medical review of SAEs
- Writing and coordination of regulatory reports:
 - Analysis of similar events for FDA
 - US IND Annual Report
 - EU Annual Safety Report
- Critical review of safety section of investigator brochures, protocols
- Creation of expectedness list
- Coding conventions
- Customized SAE form design

Peri-approval

- Company Core Safety Information
- Risk Management Plans

Post Approval

- Medical Review of AEs & SAEs
- Writing and coordination of regulatory reports:
 - Periodic Reports
 - Periodic Safety Update Reports
- Risk Management activities:
 - Risk Management Plans
 - Risk Minimization Action Plans (RiskMAPs)
- Qualified Person
- Labelling review

Signal Detection

Advantages of Quintiles Dedicated Group of Drug Safety Medical Advisors

Combination of medical and drug safety expertise

Physical proximity to processing hubs:

- In the first 6 months of 2007 the group reviewed >5000 SAEs with 100% of deadlines met
- Instantaneous medical support for project

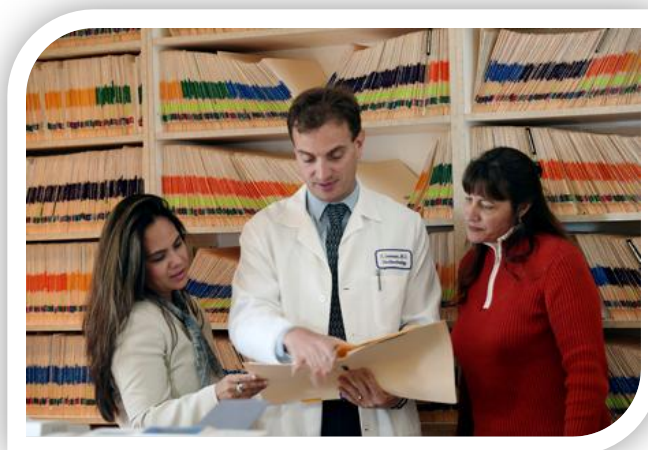
Continuous coverage - each project is assigned a lead and back-up medical advisor

Consistency - internal guidelines facilitate consistent medical coverage when handing over projects

Signal detection services range from prompt evaluation of all individual serious cases and adverse events of special interest as they are processed to composition of case reports for internal analysis to large safety database statistical assessment throughout the lifecycle of the product. Quintiles Medical Advisors will review periodic aggregate data in the form of line listings of new and cumulative events to detect any shift in the risk/benefit analysis. Additionally, they will participate in regular safety meetings with the Sponsor to review the summarized data. Consultation during communication with regulatory authorities, creation of safety evaluation committees or label change committees, composition of additional label warnings or dear doctor letters, or other important steps in the safety lifecycle of products can be provided.

Post-Marketing Considerations

The Food and Drug Amendments Act of 2007 (FDAAA) highlights the importance of risk evaluation and mitigation strategies (REMS) and post-marketing drug safety activities. These areas are very much in play during the development of anti-diabetes drugs. Sponsors can leverage Quintiles therapeutic, risk management, pharmacogenomic, safety, and regulatory experts to pursue options that best match the profile of the product to the risk management program to help ensure safe use and market longevity.



As noted, the recently published FDA Guidance makes it clear that if the pre-marketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk of the product (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a post-marketing trial generally will be necessary. This may be achieved by conducting a single trial that is adequately powered or by combining the results from a pre-marketing safety trial with a similarly designed post-marketing safety trial. This clinical trial will be a required post-marketing safety trial.

A strong recommendation in the current climate would be to plan a global drug registry. By utilizing our web portal and other options in our proactive risk management suite of services, we can promote a direct-to-consumer platform for education and outreach, including the registry, which allows real-time, real-world data on both the safety profile and appropriate use of the drug. The registry can also accommodate a subset that could be identified for special laboratory parameters which may be of interest such as liver function tests and pancreatic enzymes.

Quintiles can also advise on and provide post-marketing pharmacovigilance and signal detection services for the new drug. We can provide these services not only to meet regulatory requirements, but with the

goal of proactive signal detection that is crucial to ensuring product longevity. This signal detection can be applied simply to the proprietary drug safety database or, using the Galt signal detection tool, it can be applied to many disparate large databases. Quintiles can provide both the data mining tool and the repository to hold this safety information.

Given the increasing emphasis on benefit-risk balance, any risk management program should emphasize methods to enhance the known, quantifiable benefit of the product to offset the elucidation of risk. Thus, a program to further enhance the benefits of the product should also be seriously considered. This could be folded into the proposed registry, but should also include some small phase IV studies specifically designed to investigate quality of life and other patient outcomes. Quintiles has the expertise to help develop protocols to include various patient types.

Long-term observational studies, reporting out frequently (i.e., every 6 or 12 months), could be considered to demonstrate sponsor investment in any safety concern. Evidence to demonstrate value (e.g., impact on longer term clinical and economic outcomes) should then be collected in such a study. This would balance reporting on safety with reporting on benefits.

Finally, iGuard is an internet patient community started by Quintiles in the fall of 2007 and has over a million members, many of whom are diabetic and taking a variety of anti-diabetic drugs. iGuard allows for the collection of patient reported outcomes (PRO) and can provide the sponsor company with information directly from patients who are taking the new drug, or indeed allows comparison with PRO data which can be elicited from patients who are taking other similar competitor drugs.



Concluding Statement

Thank you for taking the time to review the information provided in this document. The recent FDA guidelines related to managing risk associated with diabetes drug development will undoubtedly increase both cost and complexity of conducting clinical trials for diabetic drugs in development. With over 35 years of diabetes research experience and over 112 studies in the past 3 years, Quintiles has the experience you need to feel comfortable conducting your diabetes research to meet and exceed the requirements of these new guidelines. In particular, Quintiles offers full clinical trial support as well as critical services needed to meet the guidelines such as:

- Consulting
- Clinical Trial Design
- Clinical Endpoint Validation and Adjudication (CEVA) Services
- Pharmacovigilance Services
- Biostatistics Services With Experience in Developing Adaptive Clinical Trial Protocols
- Experience Medical Staff
 - Dr. Erica Caveney, MD
 - Dr. Loukas Gourgiotis, MD
- Risk Management Services
- IGuard
 - Access to patient reported health outcomes and clinical trial opt-in for patient recruitment

Should you have any immediate questions or comments, please feel free to call John Nicosia, Global Sales Director at 919-998-7877 or john.nicosia@quintiles.com . We look forward to discussing this and other research needs with you soon.