Guidance for Industry

Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

DRAFT GUIDANCE

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For questions regarding this draft document contact Ilan Irony at 301-796-2290.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical/Medical

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Rockville, MD 20857
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment and prevention of diabetes mellitus. The intention of this guidance is to serve as a focus for continued discussions among the review divisions, pharmaceutical sponsors, academic community, and the public.[2] The organization of the guidance parallels the development plan for a particular drug or biologic. In the following discussion, we briefly describe type 1 and type 2 diabetes mellitus and treatment goals, discuss issues relevant to preclinical development, and then provide guidance on issues related to trial design, endpoints appropriate for different phases of development, and eligible populations. These issues are addressed for both type 1 and type 2 diabetes mellitus.

Although this guidance focuses more on the development of drug and therapeutic proteins to target the metabolic control of blood glucose in patients with diabetes, it also provides guidance on the development of products intended to prevent diabetes mellitus in high-risk individuals. Since the development of products for the prevention of diabetes is a relatively novel area, it is possible that specific guidances will be developed in the future for this topic as regulatory experience accrues. Therapeutic approaches to mitigate or reverse other clinical or pathophysiological hallmarks of what is often termed the metabolic syndrome are not addressed in this guidance.

[1] This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of diabetes drug or biological products. The FDA/NIH Joint Symposium on Diabetes, held on May 13 and 14, 2004, in Bethesda, Maryland, gathered relevant perspectives from academia and industry on issues covered in this guidance.

In addition, we recognize other important topics surrounding the treatment and prevention of diabetes mellitus. However, the following discussions are beyond the scope of this guidance.

- A comprehensive treatment strategy involves dietary changes and interventions other than medications.

- Highly desirable treatments specifically targeted to have direct effects in preventing end organ damage and diabetes-associated acute and chronic complications.

- Significant advances in the development of treatments for diabetes have been made through experimental approaches other than drugs or therapeutic proteins, such as transplantation of pancreata, pancreatic islet cells, stem cells that may differentiate into insulin-producing cells, and closed-loop devices (or artificial pancreas) that constantly monitor blood or interstitial glucose and adjust automated insulin delivery via a pump accordingly.

- The expansion of available choices in diagnostic devices that allow accurate and instantaneous glucose measurements, continuous glucose monitoring, and the identification of parameters of glucose metabolism characterizing states of insulin resistance has been significant to patients and health care professionals.

Advice on the development of specific products for preventing or treating complications of diabetes (e.g., diabetic peripheral neuropathy) can be sought from the relevant review division and other existing guidances.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.[3] Instead, this guidance focuses on specific drug development and trial design issues that are unique to the study of diabetes mellitus, as measured by changes in hemoglobin A1c (HbA1c, glycosylated hemoglobin, or glycohemoglobin). Reductions in HbA1c directly reflect improvements in glycemic control. Therefore, HbA1c is considered a well-validated surrogate for the short-term clinical consequences of hyperglycemia and long-term microvascular complications of diabetes mellitus.

The FDA recognizes that diabetes mellitus is associated with an increased risk of macrovascular complications and that reducing long-term cardiovascular complications in patients with diabetes should be an important goal of disease management. However, a premarketing recommendation to demonstrate macrovascular risk reduction in the absence of a signal for an adverse cardiovascular effect may delay availability of many effective antidiabetic drugs for a progressive disease that often requires multiple drug therapy. A reasonable approach may be to conduct long-term cardiovascular studies post-approval in an established time frame. We recommend that the design of such trials be discussed with the FDA and perhaps with clinical

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

trialists and experts in endocrinology and cardiology. This approach is beyond the scope of this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND AND TREATMENT GOALS

Diabetes mellitus has reached epidemic proportions in the United States and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures. Although there are several drug treatments currently available (see Appendix C), the FDA recognizes the need for new agents for the prevention and treatment of diabetes (e.g., development of drugs, therapeutic biologics, and devices).

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Alterations of lipid and protein metabolism also are important manifestations of these defects in insulin secretion or action.

Most patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or type 2 diabetes (with a complex pathophysiology that combines progressive insulin resistance and beta-cell failure and has a heritable basis). Diabetes also can be related to the gestational hormonal environment, genetic defects, other endocrinopathies, infections, and certain drugs.

The treatment goals for patients with diabetes have evolved significantly over the last 80 years, from preventing imminent mortality, to alleviating symptoms, to the now recognized objective of normalization or near normalization of glucose levels with the intent of forestalling diabetic complications. The Diabetes Control and Complications Trial (DCCT)[4] has conclusively demonstrated that tight glucose control in patients with type 1 diabetes significantly reduces the development and progression of chronic diabetic complications, such as retinopathy, nephropathy, and neuropathy. Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study.[5] There are also reasonably strong data in patients with type 2 diabetes supporting a reduced risk of microvascular complications with improved long-term glycemic control, although macrovascular risk reduction in this patient population is less conclusive.[6]

[4] N Engl J Med, 1993, 329:977-986

[5] Diabetes, 2006, 55:3556-3565

[6] Lancet, 1998, 352:837-853 and 854-865

Glycemic control in these studies has been based on changes in HbA1c. This surrogate endpoint reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms) and lowering of HbA1c is reasonably expected to reduce the long-term risk of microvascular complications. In addition, there is a growing recognition that addressing cardiovascular disease risk factors, such as hypertension, smoking, and dyslipidemia, in patients with diabetes is particularly important, as diabetes is now considered an atherosclerotic heart disease equivalent.

III. DIAGNOSING DIABETES MELLITUS

Based on studies that have established a relationship between plasma glucose concentrations, measures of glycemic exposure, and risk of diabetic retinopathy, the following criteria have been adopted for the diagnosis of diabetes mellitus:

- Fasting plasma glucose greater than or equal to 126 mg/dL (7.0 mmol/L)
- Plasma glucose greater than or equal to 200 mg/dL (11.1 mmol/L) at 2 hours following ingestion of 75 g anhydrous glucose in an oral glucose tolerance test
- Random plasma glucose greater than 200 mg/dL (11.1 mmol/L) in a person with symptoms of diabetes

These criteria were recommended by the American Diabetes Association (ADA) and the World Health Organization (WHO) in 1997 and 1998, respectively.

Other important definitions include:

- Impaired glucose tolerance: a plasma glucose equal to or greater than 140 mg/dL (7.8 mmol/L) but less than 200 mg/dL (11.1 mmol/L) at 2 hours in the oral glucose tolerance test
- Impaired fasting glucose: fasting plasma glucose (FPG) equal to or greater than 100 mg/dL (5.6 mmol/L) but less than 126 mg/dL
- Gestational diabetes mellitus (GDM):
  - According to the ADA criteria, GDM is detected based on two or more values meeting or exceeding any of the following threshold values during a 75- or a 100-g oral glucose tolerance test:
    - FPG greater than or equal to 95 mg/dL (5.3 mmol/L)
    - Plasma glucose greater than or equal to 180 mg/dL (10 mmol/L) at 1 hour
    - Plasma glucose greater than or equal to 155 mg/dL (8.6 mmol/L) at 2 hours
    - Plasma glucose greater than or equal to 140 mg/dL (7.8 mmol/L) at 3 hours (the optional 3-hour time point only applies to the 100-g test)
  - GDM is diagnosed by the WHO criteria if FPG is greater than or equal to 126 mg/dL (7.0 mmol/L) or if the 2-hour glucose after a 75-mg oral glucose load is greater than or equal to 140 mg/dL (7.8 mmol/L)

Impaired fasting glucose and impaired glucose tolerance have recently gained importance because they identify groups of people at high risk for developing overt diabetes mellitus over

time, and because recent studies have demonstrated reductions in the progression to overt disease in these groups with specific therapeutic interventions. These individuals, along with women who have had a history of gestational diabetes, have been targeted for clinical evaluation of diabetes prevention.

IV. PRECLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES[7]

Preclinical development often includes pharmacology studies in which efficacy is assessed in animal models appropriate to the diabetes type being targeted for therapy. Toxicology studies for antidiabetic therapies generally should be conducted in the standard nondiabetic animal models.

A. Type 1 Diabetes Mellitus

In preclinical models that most closely mimic type 1 diabetes in humans, animals manifest spontaneous insulitis and progressive beta-cell destruction. Non-obese diabetic (NOD) mice and diabetes-prone BioBreeding (BB) rats are the most commonly used rodent models for type 1 diabetes, in which proof-of-concept studies of prospective therapeutic agents can be conducted. Such studies examine parameters relevant to the treatment of human disease, such as preservation of beta cells and insulin secretory function and fasting and postprandial levels of C-peptide and glucose. Streptozotocin-induced diabetes in rats is a predictable metabolic model of human type 1 diabetes, but does not involve an autoimmune mechanism, and, therefore, should not be used in preclinical studies of immune-directed diabetes prevention strategies.

NOD mice develop type 1 diabetes by an autoimmune disease similar to humans. In these mice, approximately 90 percent of females and 60 percent of males become hyperglycemic and develop diabetes by 12 months of age.

Approximately 90 percent of mature diabetes-prone BB rats develop diabetes. Diabetes-resistant BB rats constitute a variant that develop type 1 diabetes after some environmental insult (e.g., Kilham rat viral infection).

B. Type 2 Diabetes Mellitus

Animal models of type 2 diabetes are characterized by insulin resistance, hyperglycemia, and hyperinsulinemia. Some of the most frequently used models of type 2 diabetes are the leptin-deficient mouse (*ob/ob*), the leptin-receptor-deficient mouse (*db/db*), the obese Zucker rat (*fa/fa*), the Wistar Kyoto rat (*fa/fa*), and knockout mice lacking relevant targets, such as insulin receptors or glucose transporter 4 genes.

For all peroxisome proliferator-activated receptor (PPAR) agonists, 2-year carcinogenicity evaluations in rats and mice should be conducted before the initiation of clinical studies longer than 6 months in duration, based on their known carcinogenic potential as a class. Additionally, for PPAR drugs with gamma agonist activity, the maximum tolerated dose for carcinogenicity

[7] See 21 CFR part 58 for the FDA's good laboratory practices for conducting nonclinical laboratory studies.

assessment should be defined as the dose that results in a 20 to 25 percent increase in heart weight in rodents in the 13-week dose finding studies. This recommended dose limitation is designed to prevent excess cardiac mortality in the 2-year bioassay secondary to fluid accumulation and cardiomegaly. Refer to Appendix A for further details on this issue.

C. Insulins and Insulin Analogues

In vitro studies of insulins and insulin analogues can be useful for describing insulin receptor binding affinities and dissociation rates, receptor autophosphorylation, phosphorylation of signaling elements, and promotion of mitogenesis. In addition, for insulin analogues, affinity to the insulin receptor relative to other targets of insulin action, such as the insulin-like growth factor 1 receptor, should be characterized and compared to that found with native-sequence human insulin.

V. CLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES[8]

A. Trial Design and Conduct

1. Optimization of Glucose Control and Diabetes-Associated Comorbid Conditions

Individualization of therapy is essential to optimum control of glycemia in patients with diabetes. Consequently, some studies permit use of other antidiabetic therapies before randomization to ensure enrollment of patients whose diabetes control will be acceptable for clinical investigational purposes. Such studies often allow entry of patients using a specific class of antidiabetic drugs (e.g., baseline metformin therapy in patients with type 2 diabetes), to which either the investigational drug (or biologic) or a placebo will be added during randomization. Addition of new noninvestigational drugs or substantial changes in the dose of permissible baseline drug therapy after randomization may confound the results and interpretability of both efficacy and safety. For the results to be interpretable, any changes to these other therapies should be carefully documented.

When planning exploratory phase 2 studies, we recommend that sponsors include a run-in period before randomization to allow for diabetes education and for optimization of compliance with diet and exercise. This 6- to 8-week run-in period also is intended to allow for stabilization of parameters of metabolic control (e.g., HbA1c, fructosamine), so that the magnitude of the effect of different doses of the product can be most accurately estimated. Absence of this run-in period can result in overestimation of the *real world* treatment effects, given the intensive reinforcement of hygienic measures and compliance during clinical trials that is not reflected in typical treatment settings. In addition, placebo run-in periods in phase 3 studies can help screen out noncompliant subjects. We recommend providing efficacy data with a new product that result from rigorously designed studies.

[8] See 21 CFR parts 312, 50, and 56 for regulations regarding investigational new drug applications and human subject protection, including informed consent.

Adequate control of diabetic comorbidities in accordance with current standards of care should be incorporated in the criteria for eligibility in the study protocol. The addition of therapies to control diabetic comorbidities after randomization should be carefully documented (as should be the use of these therapies at baseline), because these therapies may confound the interpretation of both safety and efficacy of the investigational drug or biologic.

Improvement in HbA1c has become the standard surrogate outcome measure in many trial designs for a variety of therapies. In patients with diabetes, the following situations also can be considered a benefit of therapy: 1) a meaningful reduction of insulin requirements (in either type 1 or type 2 diabetes), or 2) a reduction in the number or doses of oral antidiabetic agents (in type 2 diabetes mellitus), both in the context of stable or improved HbA1c. Even though HbA1c is appropriate as a surrogate endpoint in many study designs, documented improvement in a serious morbidity or mortality related to diabetes (i.e., outcome studies) may be more persuasive evidence of benefit for drugs in which substantial safety issues or questions arise (see sections V.B., Study Assessments and Endpoints, and V.E., Sample Size and Study Duration, for additional considerations).

2. Type 1 Diabetes Mellitus

As stated earlier, insulin is the essential glucose-lowering therapy for the treatment of patients with type 1 diabetes. Therefore, all experimental treatments for type 1 diabetes (and their matching placebos, as applicable) that are not insulin analogues or other insulin receptor ligands should be studied as add-on therapies to insulin.

Preclinical data or knowledge of a particular mechanism of action may indicate that an investigational product has the potential to cause or worsen hypoglycemia, either by binding to insulin receptors or by affecting other aspects of glucose absorption and metabolism. If the investigational product is anticipated to have the potential to lead to hypoglycemia, either directly or through potentiation of insulin effect, the study design should include allowance for insulin dose adjustments to protect trial subjects from hypoglycemia. However, pharmacodynamic interactions with insulin, as well as the need to adjust insulin doses to prevent hypoglycemia, may pose significant challenges for study design, interpretation, and inference of the new drug's efficacy. For example, given the need to titrate insulin to control for glycemia and to guard against hypoglycemia, the blinding of subject and investigator to treatment allocation may not be practical or acceptably safe. Unblinded, controlled trials may be appropriate in some circumstances, particularly for trials incorporating clearly objective endpoints. On the other hand, unblinding can severely limit the interpretability of subjective endpoints (i.e., patient-reported outcomes) that might be incorporated as secondary assessments of efficacy.

In phase 1 and phase 2 trials of products intended to prevent or delay the progression of type 1 diabetes, sponsors are encouraged to conduct randomized, placebo-controlled studies, while investigating early pharmacodynamic markers of effect as well as the safety of the tested product.

3. Type 2 Diabetes Mellitus

Efficacy and safety of new products for the treatment of type 2 diabetes can be evaluated in placebo-controlled monotherapy trials, placebo-controlled add-on therapy trials, and active-controlled trials. Given the progressive nature of type 2 diabetes and the requirement for multiple drug therapy, the clinical development program should involve evaluation of the investigational drug as monotherapy and in combination with many other approved antidiabetic drugs.

In the past, oral agents (i.e., sulfonylureas) to treat type 2 diabetes were approved largely on the basis of placebo-controlled trials with no underlying pharmacological therapy, in which all randomized subjects received only counseling for appropriate diet and an exercise program in addition to the product being tested. As medical care for diabetes has evolved, it may now be difficult to find patients who are appropriate candidates for purely placebo-controlled trials because a large proportion of those diagnosed with diabetes are receiving early pharmacological treatment. Considerations of withdrawal of existing therapy to enroll patients in a placebo-controlled trial of a new agent as initial monotherapy should include informed consent, severity and duration of disease, presence of diabetic comorbidities, and dose of the existing drug therapy. In addition, strict escape or withdrawal criteria for loss of glycemic control should be explicit in the study protocol.

The discontinuation of effective treatment for the purposes of making a patient eligible for inclusion in a placebo-controlled trial of significant duration (e.g., longer than 6 months) raises ethical issues, although placebo-controlled trials of 6 months or less in duration may be appropriate, provided that the protocol contains strict escape or rescue criteria related to hyperglycemia and poor glycemic control. In such trials, the number of patients meeting the escape criteria can be assessed as a measure of efficacy. In any case, we recognize that both placebo-controlled (with or without background therapy) and active-controlled studies can provide the essential safety and efficacy data to support approval.

a. Studies of a test agent as monotherapy

Many patients with type 2 diabetes who are potential candidates for studies of new therapeutic agents are likely being treated with one or more antidiabetic medications. Development of a new investigational product to support its indication as monotherapy in type 2 diabetes can be undertaken in subjects who are drug-naïve and whose diabetes is reasonably well controlled with diet and exercise. These subjects can participate in placebo- and dose-controlled studies for up to 24 weeks, provided that they continue to remain in reasonable metabolic control for the duration of the studies (see below for an example of escape or rescue criteria). Likewise, subjects on low doses of a single antidiabetic medication who are under reasonable glycemic control can discontinue their medications under strict glycemic supervision to participate in placebo-controlled studies of an agent to be used as monotherapy.

There also should be a reasonable expectation that placebo dropouts caused by further loss of glycemic control will be limited, thus enabling controlled assessments of both efficacy and safety.

For either phase 2 or phase 3 studies, regardless of HbA1c at entry, subjects whose hyperglycemia persists or worsens beyond prespecified thresholds should be appropriately monitored and treated throughout the study. In developing these escape or rescue criteria, it is useful to consider that even for drugs that show therapeutic effects only after a matter of weeks (e.g., thiazolidinediones/PPAR agonists), most responders experience a reduction in fasting blood glucose of greater than 20 mg/dL (1.1 mmol/L) by 6 weeks. For agents that lower postprandial rather than fasting glucose levels, a clinically meaningful reduction in HbA1c (e.g., 0.3 percentage units) also usually is evident by 6 weeks. The following are examples of rescue criteria based on thresholds for FPG or HbA1c:

- FPG greater than 270 mg/dL (15 mmol/L) from baseline to Week 6
- FPG greater than 240 mg/dL (13.3 mmol/L) from Week 6 to Week 12
- FPG greater than 200 mg/dL (11.1 mmol/L) or HbA1c greater than 8.0 percent from Week 12 to Week 24

For agents that lower postprandial rather than fasting glucose levels, the sponsor is encouraged to enforce specific rescue criteria based on thresholds of unacceptable postprandial glucose encountered during the first 12 weeks of the study and unacceptable HbA1c encountered thereafter.

Even if the escape criteria related to poor glycemic control result in early discontinuation of a substantial proportion of participating subjects, the trial may still be interpretable, at least from the standpoint of efficacy. (For more details, see section V.G., Important Statistical Considerations.) The rate of meeting withdrawal criteria also can provide an assessment of efficacy using a time-to-event analysis if events are collected or responder analysis based on a binary outcome of treatment success or failure. Subjects meeting glycemic rescue criteria ideally should remain in the study even after receiving the additional or alternative therapy to allow for the assessment of safety of the investigational drug or biologic.

Phase 2 or phase 3 studies investigating the efficacy of a new product as monotherapy in subjects already on active therapy for their diabetes can be more problematic. The majority of these subjects will probably experience significant worsening of glycemic control when their medications for diabetes are discontinued. These subjects require a washout period with careful monitoring of glucose. An unknown, and likely high, proportion of subjects simply will either not qualify for studies because of loss of control before randomization or will discontinue because of worsening glycemia in the initial weeks of treatment with poorly effective doses of the investigational drug or with placebo. The washout period should take into account the pharmacokinetic properties of the existing treatment (e.g., 5 half-lives) and the fact that HbA1c reflects mean glycemic control over 2 to 3 months. The length of treatment with the test agent before endpoint ascertainment should account for the duration of the pharmacodynamic effects of previous treatments and the expected timing of a pharmacodynamic effect (e.g., plasma glucose, HbA1c) of the test agent.

A difference between active drug and placebo (or between two active treatments such as a lower and higher dose of the test agent) in the proportion of subjects meeting criteria for glycemic rescue therapy can be used as a measure of efficacy.

b. Studies of new agents on a background of existing therapy

For subjects taking two or more antidiabetic agents to control glycemia, a potential approach in phase 2 or phase 3 can be a randomized study in which the investigational product or matching placebo is substituted for one of the drugs being taken. Sponsors can conduct extensive dose titration and dose exploration in phase 2 studies of this type, typically 12 to 16 weeks in duration.

For phase 3 studies of investigational agents as add-on therapy, the typical design is not that of substituting the investigational agent for an existing medication, but rather to add the investigational agent to the existing therapy. Typically, these studies are designed as placebo-controlled superiority or active-controlled noninferiority trials. In these studies, patients inadequately controlled on optimal or near-optimal doses of approved therapies should be randomized to one of several doses of the investigational agent or to placebo as add-on to the existing medications (or, in the case of active-controlled trials, to a therapy previously approved for such add-on use). Subjects should be on optimal or near-optimal doses of approved therapies for two reasons: 1) most practicing physicians titrate the dose of one therapeutic agent before considering addition of another antidiabetic agent to improve glycemic control; and 2) this approach allows for more rigorous assessment of the investigational product's efficacy by avoiding a confounding effect of any upward dose titration of the approved medication during the trial.

Another design less commonly used in studies directed at assessing efficacy is the randomized withdrawal. For example, all subjects can be treated with the test agent either as monotherapy or in addition to existing therapy. After a treatment period sufficient to reach pharmacodynamic steady state, subjects can be randomized, in double-blind fashion, either to continue test therapy or to switch to placebo for an additional period (e.g., 12 to 16 weeks). Subjects whose glycemic control deteriorates to the point of meeting escape criteria and requiring additional therapy may create a bias in the assessment of efficacy if the efficacy endpoint is defined as change of HbA1c from randomization to the study endpoint. The primary endpoint for the withdrawal design should be the time to therapeutic failure if event times are collected or, if not, the proportion of HbA1c treatment failures in each treatment group.

B. Study Assessments and Endpoints

1. General Considerations

Throughout development of new molecular entities, particularly within novel classes of therapeutic products, thorough safety evaluations are critical even in the early phase clinical studies. These early studies should be designed with conservative approaches to testing, initially in smaller numbers of subjects, with single doses, and with appropriate safety monitoring not only for glycemia-related parameters, but also for potential hazards identified based on

preclinical or in vitro study results or on known effects seen with other members of the drug class (if available).

a. Pharmacokinetics

In general, pharmacokinetic parameters of noninsulin therapeutics should be evaluated in phase 1 studies. These studies can be performed in healthy volunteers to determine the basic pharmacokinetic parameters (e.g., absolute bioavailability, area under the curve (AUC), C_{max}, T_{max}, $T_{1/2}$). Additionally, pharmacokinetic studies also may be appropriate in the intended patient population. We recommend that exposure-response data be obtained during the phase 2 dose-finding studies. (See the guidance for industry *Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications*.)

In patients with diabetes, the high prevalence of altered glomerular filtration rates, delayed or deficient gastrointestinal transit and absorption, and the potential for interactions with commonly used medications usually dictate the need for the evaluation of the pharmacokinetics of new agents in the target population, beyond investigations in healthy volunteers. It is important to evaluate the in vivo and in vitro mechanisms of drug absorption and disposition. This information will provide the basis for the design of the drug interaction studies addressing the class effects of oral antidiabetic drugs (e.g., addressing the induction potential of CYP enzymes by thiazolidinediones, CYP2C-based interactions with sulfonylureas, and interactions with renal tubular secretion of metformin). We also recommend interaction studies with drugs that have a narrow therapeutic index and with drugs likely to be co-administered in the diabetic population. (See the draft guidance for industry *Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling* for details.)[9]

Effects of food on pharmacokinetics should be evaluated in the development of therapeutic products that are intended to be administered orally in temporal proximity to meals (e.g., agents designed to exert effects on glycemia peri- or postprandially, such as meglitinides). Because patients with diabetes may be a particularly sensitive population in terms of polypharmacy and underlying, often subclinical, cardiac disease, we also encourage sponsors to address the effect of the drug on the QT interval by conducting a thorough QT study.[10]

b. Pharmacodynamic endpoints and biomarkers

Products whose pharmacodynamics, by design, are restricted to effects on postprandial glucose (e.g., meglitinides) should be tested in dose-finding, proof-of-principle, short-term, oral glucose challenge studies. However, such demonstrations of pharmacodynamic activity are not sufficient evidence of efficacy for new drug application (NDA) approval,[11] because the link between a modifying effect on postprandial glucose excursions to clinical outcomes is not sufficiently

[9] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[10] See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.

[11] See 21 CFR part 314 for regulations regarding NDAs.

strong to consider the use of this pharmacodynamic endpoint as a surrogate for efficacy. Such products should be shown to be safe and effective in improving overall glycemic control based on reduction in HbA1c. That said, description in labeling of the effects of the agent on excursions in postprandial serum glucose concentrations, thereby effecting reductions in overall glycemic exposure (as manifest by reductions in HbA1c), may be warranted in some cases to provide physicians with an understanding of the mechanism of action of the agent and its implication for method of use.

Glycated endogenous proteins with turnover rates faster than hemoglobin, such as fructosamine, can be used as preliminary indicators of a product's effects on integrated glycemic exposures in early phase studies of limited duration. Demonstration of reductions in HbA1c, with a concomitant meaningful decrease in mean daily insulin requirements in relevant patients, is desirable but not necessary for the preliminary inference of efficacy from these early studies. Changes in FPG, plasma glucose level after a standard meal, plasma glucose level after oral administration of 75 g of glucose, average blood glucose (mean of seven home measurements obtained before and after each meal and at bedtime), and fructosamine can be used as primary measures of efficacy in phase 2 studies. They also can be used as secondary, supportive measures of efficacy in phase 3 studies.

c. Efficacy endpoints

For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control. Superiority or noninferiority hypotheses may be appropriate depending on the trial design. Refer to section V.G., Important Statistical Considerations, for a discussion of issues related to noninferiority trials and choice of noninferiority margins as they relate to studies in diabetes. Also see the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.

d. Effects on markers of insulin resistance and diabetes comorbidities

Treatment-associated reduction in endogenous hyperinsulinemia (in type 2 diabetes) or improvement in insulin sensitivity are arguably salutary health effects, but do not alone provide sufficient support of a new agent for approval purposes. Effects of antidiabetic agents on blood pressure and serum lipids are of obvious importance and can be described in labeling with disclaimers commensurate with the limitations of the trials regarding extrapolation of findings to conclusions about ultimate drug effects (i.e., on mortality or irreversible morbidity).

e. Effect of weight loss on diabetes

In recent years, the FDA has recommended to sponsors of weight loss products seeking an indication for the treatment of type 2 diabetes that they should demonstrate that the product's effect on glycemic control is independent of weight loss. The FDA has reconsidered the necessity of this recommendation. The FDA's current thinking is that a sponsor can gain approval for the treatment of type 2 diabetes for a drug or biologic whose principal mechanism

of action appears to be weight loss by showing a clinically meaningful and statistically significant improvement in glycemia.

The development program to support a diabetes indication for these products should be comparable to the development programs used for antidiabetic products not intended for weight loss. For example, the product would need to be studied in subjects with a wide range of body mass indices (from lean to obese), different duration of diabetes (new onset to long-standing), and under different conditions of use (monotherapy and combination therapy). Sponsors interested in the development of weight loss products for the treatment of type 2 diabetes should discuss their plans with the Division of Metabolism and Endocrinology Products.

2. Insulins

In the case of a new insulin with perhaps unique pharmacokinetic characteristics dictating a specific method of use (i.e., dosing interval, timing relative to meals), efficacy can be assumed based on pharmacodynamic (e.g., clamp) studies. However, studies of clinical safety and efficacy usually will be necessary to demonstrate that the method of use leads to effective diabetes management and that the treatment is not associated with undue hypoglycemia (e.g., relative to an approved insulin and standard regimen). (See Appendix B for a discussion on hypoglycemia). These studies should be directed at achieving actual reductions in glycemia (as opposed to simple maintenance of pretrial levels of control) from baseline to end of study. Test and comparator groups should be treated to similar goals. Similar degrees of glycemic control (test noninferior to reference) should be achieved so that comparisons among groups in frequency and severity of hypoglycemia will be interpretable in ultimate risk-benefit assessments.

a. Insulin mixes

When seeking approval of a new formulation of premixed short- and long-acting insulins, the sponsor should establish the distinctiveness and usefulness of the premixed products compared to each individual insulin component. We recommend that the premixed product's pharmacokinetic and pharmacodynamic profiles have a target difference of at least 20 percent from each of its single components (e.g., NPH and regular/rapid insulin) and also from each adjacent product within its product line. Such differences can be established by the maximum concentrations (C_{max}) and the various partial AUCs (e.g., $AUC_{0\text{-}4\ hr}$ and $AUC_{4\text{-}12\ hr}$) from insulin plasma exposure versus time profiles. From a pharmacodynamic perspective, the maximum glucose infusion rate (GIR) and the various partial AUCs (e.g., $AUC_{GIR0\text{-}4\ hr}$ and $AUC_{GIR4\text{-}12\ hr}$) from glucose infusion rate versus time profiles can be used. In addition, the bioavailability of the new premixed product should remain comparable to the total bioavailability of the short-acting insulin product.

b. Insulin use in pumps (continuous subcutaneous insulin infusion)

Endpoints to be used in the development of insulins for use in pumps should include ascertainment of compatibility between the insulin or analogue and the pump and infusion sets. Likewise, the stability, sterility, and appearance of insulin under laboratory conditions simulating

the conditions and stresses of actual use should be assessed. Assuming the use of approved pumps and approved insulins, clinical studies *per se* are not usually necessary for approval of the use of a particular insulin in a pump. However, glycemic control may need to be evaluated in a short-term clinical study for novel delivery systems. To clarify expectations for development and approval, additional discussion is encouraged between the FDA (including the Office of Combination Products) and sponsors of particular insulin pumps or insulins.[12]

c. New insulin analogues or insulin receptor binding agonists

In the development of new insulin analogues or insulin receptor binding agonists, sponsors should address the following three fundamental issues in randomized, controlled trials:

1. The risk of hypoglycemia under conditions of use ultimately recommended in labeling, relative to approved insulin products and regimens. In this regard, both test and control groups should achieve improved and similar glucose control as assessed by HbA1c.

2. Pharmacokinetic variability should be evaluated, according to injection site, thickness of fat layer, and other parameters known to affect absorption, distribution, metabolism, and excretion characteristics. Additionally, pharmacodynamic characteristics should be carefully studied to direct dosing interval (for long-acting products) and timing of dosing relative to meals (for short-acting products). Assessment of insulin receptor binding (affinity and dissociation rates), receptor autophosphorylation, phosphorylation of signaling elements and promotion of mitogenesis may add important data to the characterization of new insulin analogues.

3. As a complex biological protein, insulin has the potential to be immunogenic. Adequate assays should be developed that measure antibodies to the test product before the submission of an application. Antibody titers, the timing of their detection and disappearance (if applicable), and correlation with pharmacological effects should be ascertained. The potential for any of the antibodies to neutralize the effects of a new insulin should be assessed, particularly in the presence of high titers of antibodies, and in the presence of allergic reactions or suspicion of immune-complex deposition, or apparent loss of clinical effectiveness.

d. Inhaled insulins

Investigations of insulin delivered by inhalation should include preclinical safety, pulmonary safety, pharmacokinetics, pharmacodynamics, dose proportionality, and hypoglycemic risk. The extent of preclinical studies needed depend, in part, on the novelty of the formulation (e.g., what excipients are used) for the inhaled route. Typically, the minimum preclinical program should be comprised of two 14-day inhalation studies focusing on the histopathology of the respiratory tract, followed by a 6-month bridging study in the most appropriate species. The pharmacokinetics (including bioavailability), pharmacodynamics, and hypoglycemic risk of

[12] It should be noted that proposed labeling may affect the design of trials using a particular insulin with a particular pump.

inhaled insulin in humans should be compared to that of subcutaneously administered insulin. Intrasubject pharmacokinetic variability should be evaluated.

We encourage sponsors of inhaled insulin products to enroll at least some patients with underlying pulmonary disease, such as chronic obstructive pulmonary disease and asthma, to assess not only effects of inhaled insulin on their pulmonary function, but also the effects of their disease on insulin kinetics. Cigarette smoking affects inhaled insulin bioavailability, and airway status may lead to alterations in drug delivery to the absorption site. Therefore, sponsors should investigate the potential effect of cigarette smoking and inhalational drugs for pulmonary disease on the efficacy and safety of the inhaled insulin product, including assessments of the effects on insulin pharmacokinetic and pharmacodynamic endpoints and the rates and timing of hypoglycemia.

Sponsors developing inhaled insulin products should evaluate the pulmonary safety of these inhaled insulin products (including excipients). Safety assessments should include pulmonary function as measured by the full battery of pulmonary function tests, including spirometry, lung volumes, and diffusion capacity. Serial pulmonary function tests should be performed and the long-term effects of the inhaled insulin product on pulmonary function should be established. Additional safety assessments include high resolution computed tomography of the chest at baseline and on treatment. Because of the potential effects of diabetes mellitus on the pulmonary system, a comparator group is recommended for these safety assessments. In addition, assessment of anti-insulin antibody responses is essential in the overall safety assessment of the inhaled insulins, because the inhaled route may lead to a different propensity toward immune responses. Pre-use storage and in-use handling conditions during these studies should be designed to mimic actual use of the products. Accuracy of use and dosing should be assessed and documented.

3. Noninsulin Products

A reduction in insulin dose is not sufficient stand-alone evidence of efficacy for approval or labeling of a noninsulin product. In addition to showing a meaningful reduction in the insulin dose, the drug should be shown to independently reduce HbA1c, or at least show that no increase in HbA1c accompanies the insulin reduction. In this context, the elimination of the need for insulin entirely in patients with type 1 diabetes or simplification of the insulin regimen while maintaining or improving glycemia (i.e., optimum control with a nonintensive insulin regimen resulting in reduced hypoglycemic risks) is considered clinically meaningful.

Novel approaches to the treatment of type 2 diabetes, such as the use of gastrointestinal neuropeptides or products that inhibit degradation of these peptides, have been shown to have effects beyond the control of insulin secretion and insulin action, such as rate of gastric emptying, food intake, and glucose counterregulation. Nonetheless, the recommended endpoints for approval of such products specifically for the treatment of diabetes will be the same as the traditional approaches used in the development of currently approved insulin secretagogues or insulin sensitizers (i.e., change from baseline in HbA1c).

Products intended for the treatment of diabetes can be developed for use as monotherapy and for use in combination therapy regimens with other drug classes with different mechanisms of action.

A fixed-dose combination (FDC) of a new agent and an established agent should be studied in a manner that demonstrates that each of the individual components makes a contribution to the claimed effects of the FDC, and that the combination is acceptably safe. If the FDC consists of two currently approved and marketed drugs, and will be labeled for the same indications and patient populations as the separately approved therapies, and the safety and efficacy of these drugs have been established in co-administration, a full factorial efficacy trial may not be necessary to demonstrate the contribution of each FDC component to the claimed effects. In this setting, pharmacokinetic data defining any drug-drug interactions between the components generally should be sufficient. There are exceptions to this approach, such as situations where there are potential safety concerns with the co-administration of the two components. In addition, we recommend nonclinical toxicity studies for certain FDC products, even when the components are previously marketed drugs or biologics. For details, see the guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

4. Prevention of Type 1 Diabetes Mellitus or Preservation of Beta-Cell Function in Patients Newly Diagnosed with Type 1 Diabetes Mellitus

Studies of products aimed at the prevention of type 1 diabetes in high-risk subjects, or at preservation of beta-cell function in recent-onset type 1 diabetes with remaining endogenous insulin reserve, should evaluate metabolic outcomes, such as the following:

- Fasting and postprandial glucose and glycemic excursion
- Frequency and severity of hypoglycemic events
- Fasting and stimulated C-peptide levels
- Daily insulin requirements in the subjects with diabetes, expressed in international units (IU) per kilogram of body weight

These studies also should evaluate the variations in serum or plasma levels of immune markers, such as anti-insulin, antiglutamic acid decarboxylase 65 and 67, ICA512, and IA-2 beta antibodies. Other markers of cellular immune response (T-cell subpopulations, cytokines) also can be used. In phase 2 studies for the prevention of type 1 diabetes, genotyping and assessments of specific populations of pathogenetically relevant T-cells are encouraged. In particular, the correlation between genotypes and immunoreactive T-cell subpopulations, biomarkers related to glycemic control, and response to treatment may lead to more successful phase 3 studies.

Phase 2 and phase 3 studies of immunosuppressive products or immunomodulators for the prevention of type 1 diabetes also should evaluate their effects on general immune responses, including T-cell proliferation in response to conventional antigens, immunoglobulin subclasses, and titers of antibodies in response to primary antigens and recall responses. Depending on the known or suspected mechanism of action, as well as findings from previous clinical and nonclinical studies, other endpoints should be considered in the overall safety evaluation. These

assessments should be conducted in patients with diabetes, and not borrow substantially from other patient populations, such as populations with neoplasia or post-transplant patients treated concomitantly with other immunosuppressants.

Phase 3 studies of investigational products intended for the prevention of type 1 diabetes mellitus in high-risk individuals typically will designate a delay in the diagnosis of type 1 diabetes as the criterion for defining efficacy. An appropriate endpoint to support efficacy can be the proportion of subjects in the treatment groups who develop frank diabetes after a prespecified period of time (the period being at least 1 year) compared across treatment groups.

Preservation of beta-cell function in patients recently diagnosed with type 1 diabetes is being actively pursued by the pharmaceutical industry and in government and academic collaborations. We acknowledge the evidence from the DCCT and other studies that have demonstrated clinical benefits in patients who achieve better glucose control, in terms of delaying the chronic complications of diabetes. Similarly, we acknowledge that patients who had greater preservation of endogenous insulin secretory function (as assessed by C-peptide in the serum) at baseline were more likely to have lower HbA1c with fewer hypoglycemic events over time.

Phase 3 development of investigational products intended to preserve endogenous beta-cell function in patients with newly diagnosed type 1 diabetes can designate a measure of C-peptide (e.g., AUC following a standardized mixed meal tolerance test) compared to control at 1 year as the primary efficacy endpoint. Sponsors should analyze the change from baseline to the study endpoint (typically 1 or 2 years) in both treatment groups, and demonstrate maintenance of C-peptide or an attenuation in the rate of decline compared to the control group. For this endpoint to provide convincing evidence of preserved endogenous beta-cell function, the trials should demonstrate a clinically meaningful reduction in mean daily insulin requirements accompanied by similar magnitude of glycemic control compared to the control arm. A favorable effect on these endpoints should be balanced against the risks of the particular intervention being tested. Subjects should continue to be monitored for an extended period (2 to 4 years or longer) to investigate both the durability of the effect and whether they experience a lower frequency of hypoglycemia, diabetic ketoacidosis, and long-term complications of diabetes.

As with most prevention claims, we generally will accept fewer risks for treatments intended to prevent type 1 diabetes compared with treatments that preserve endogenous beta-cell function in patients already diagnosed with type 1 diabetes.[13] This distinction is made because some individuals exposed to prevention strategies have no chance for benefit, as they are not inexorably destined to develop diabetes. Therefore, some patients (who presumably cannot be pre-identified) would be subject to the risks of the treatment with no hope of benefit.

5. Prevention of Type 2 Diabetes Mellitus

In phase 3 studies for products intended to prevent the development of type 2 diabetes in high-risk individuals (such as individuals with impaired glucose tolerance, impaired fasting glucose, or with a history of gestational diabetes), potential endpoints supporting approval include delay in type 2 diabetes diagnosis or reduction in the proportion of patients diagnosed with type 2

[13] See 21 CFR 56.111(a)(1)(i) regarding the unnecessary exposure of subjects to risk.

diabetes by ADA criteria, relative to placebo. These study designs should include a follow-up (washout) period to assess whether the tested agent truly delays progression to diabetes or only masks diabetes during the treatment period. Such studies will likely be of substantial duration (years) and size. The FDA cannot *a priori* define the magnitude of a clinically meaningful effect size.

For prevention studies of drugs with a pharmacological action of improving glycemic parameters (e.g., approved treatments used in the prevention setting), improvement in clinical parameters beyond those that would be expected from glucose lowering alone should be demonstrated, since the forestalling of a biochemical diagnosis of frank diabetes from the prediabetic state may not itself be a sufficiently tangible benefit against which one can appropriately judge the risks. Such supportive evidence can include a demonstration of a durable delay in the onset of type 2 diabetes after the prevention therapy is stopped, or can show that the delay in progression to type 2 diabetes mellitus is accompanied by other indicators of clinical benefit (e.g., delay or lessening in microvascular or macrovascular complications). That said, the more modest the treatment effect, the higher the standard for safety and the more restricted (e.g., to subjects at highest risk for near-term conversion to frank type 2 diabetes) the indicated target population.

C. Metabolic Syndrome

The term *metabolic syndrome* represents a cluster of laboratory and clinical findings that serve as markers for increased risk for cardiovascular disease and type 2 diabetes, and, depending upon the definition used, is prevalent in as much as 25 percent of the adult American population. A host of therapies now exist to address individual or multiple components of the syndrome (e.g., lipid-altering agents, antihypertensives, insulin sensitizers). A therapeutic product intended to treat the metabolic syndrome ideally should normalize or improve all components of the syndrome and ultimately be shown to prevent the development of type 2 diabetes and reduce cardiovascular morbidity and mortality. As mentioned in the Introduction section, a full discussion of this syndrome is beyond the scope of this guidance.

D. Study Population Considerations

In general, premarket study populations should be representative of the population for which the product, once approved or licensed, is intended. Two specific considerations with regard to study populations are listed below.

1. Pediatric Populations

Under the Pediatric Research Equity Act (PREA), section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 355c), as amended by the Food and Drug Administration Amendments Act of 2007 (Public Law No. 110-85), sponsors must study a product in all relevant pediatric populations when submitting an application under section 505 of the Act (21 U.S.C. § 355) or section 351 of the Public Health Service Act (42 U.S.C. § 282) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. However, the PREA requirements may be waived or deferred in certain

794 circumstances. Although a detailed discussion of how sponsors may comply with the PREA
795 requirements is beyond the scope of this guidance, several relevant points are addressed below.
796
797 In the case of new molecular entities, particularly for new classes of therapeutic products with
798 novel mechanisms of action, the early studies should enroll adult subjects only, reserving
799 pediatric exposure until the metabolism, pharmacodynamics, and safety of the agent are
800 reasonably well-defined. The same precaution can be applied to already approved agents with
801 known toxicities in nondiabetic populations, such as immunosuppressive or immune modulatory
802 products. Because many of the general aspects of the clinical pharmacology and safety profiles
803 of an approved therapeutic are better understood, it may be appropriate to dose pediatric patients
804 earlier in the development programs of approved versus unapproved investigational products.
805
806 In the initial development of insulins and other agents with potential to cause hypoglycemia, we
807 recommend that subjects with particularly labile glucose control and a substantial history of
808 recent hypoglycemia be excluded. Because of the high representation of children and
809 adolescents in the population with type 1 diabetes, patients in these demographic subsets usually
810 should be included early in the clinical development of treatments for type 1 diabetes. However,
811 it is not appropriate to study all products for type 1 diabetes in children before approval. For
812 example, inhaled insulins, which represent simply an alternate route of administration for a well-
813 established active ingredient, should be developed for adult use initially because of uncertainties
814 in the safety of new inhalation dosage forms. After additional safety data are developed, these
815 products can be studied in children, including during the postmarketing period. In such cases,
816 the initial approved labeling should specifically address dosing and administration in adults.
817 Labeling for pediatric use can be developed and approved after additional studies are conducted
818 in pediatric patients.
819
820 Given the increasing representation of children and adolescents with type 2 diabetes, studies of
821 therapeutic products intended for the treatment of type 2 diabetes should at some point include
822 patients younger than 18 years of age, assuming no obvious contraindications to such use (e.g.,
823 hypothetical effects on growth and development based on mechanism of action).
824
825 Sponsors may contact the review division for further information with regard to meeting the
826 PREA requirements.
827
828 *2. Other Study Populations*
829
830 Type 2 diabetes occurs more frequently in Latino, African American, and Native American
831 patients relative to patients of northern European descent. Therefore, attempts should be made to
832 enroll representative numbers of individuals from these ethnic groups during the clinical
833 development program, particularly during the phase 3 trials. Attention also should be paid to
834 considerations in geriatric patients, including decreased renal function, autonomic dysfunction,
835 poor glucose-counterregulatory response, hypoglycemia unawareness, and potentially dangerous
836 interactions with other commonly used drugs. It is desirable to determine whether demographic,
837 genetic, metabolic (e.g., C-peptide, body mass index, previous antidiabetic therapy), or other
838 factors predict responses to a new antidiabetic agent, predispose patients to certain toxicities, or
839 otherwise affect tolerability and compliance.

E. Sample Size and Study Duration

The ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* recommends a total exposure of at least 1,500 subjects (300 to 600 for 6 months, 100 for 1 year) for the safety assessment of chronically administered drugs developed for the treatment of non-life-threatening conditions. However, exposures exceeding these recommendations should be used for products developed for the treatment of type 2 diabetes, given the large and growing size of the population with type 2 diabetes and the increasing complexity of treatment regimens. At the time of submission of the marketing application (either a biologics license application (BLA) or an NDA) for products intended for the treatment of type 2 diabetes mellitus, we recommend that phase 3 trial data 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.

These investigational products should be tested as monotherapy and in combination with antidiabetic medications with which they likely will be co-administered in clinical practice. As treatment of type 2 diabetes mellitus frequently requires combination therapy, overall exposures and length of duration should be weighted more in trials evaluating the investigational product with other antidiabetic medications. The guidance for industry *Premarketing Risk Assessment* also anticipates situations where larger numbers of exposures for longer periods might be needed, including for diseases where many sufficiently safe alternative treatments already exist or for a preventive treatment. Therefore, we encourage long-term extensions of 6- to 12-month controlled trials and anticipate that the safety information relevant for approval will be provided at the initial submission of an application.

Development of products intended to preserve beta-cell mass and function in type 1 or type 2 diabetes can be considered in enriched populations, where genetic or immunologic markers predicting the natural history of the disease exist. Testing the investigational product in high-risk populations enriched for such markers enhances power to detect an effect of the intervention (if one exists), as compared to testing the product in the general diabetic population. Even in enriched populations, pivotal studies may still need to be relatively long (e.g., 2 or more years) to show a meaningful effect, given the natural history of the decline in beta-cell function in the target populations and also recognizing the need for long-term safety information.

For all new development programs for drugs to treat diabetes, phase 3 studies should be sized to allow meaningful evaluation of the consistency of effects across subgroups based on sex, age, ethnic background, duration and severity of the disease (e.g., based on categories of HbA1c at baseline), interactions with other likely concomitant medications as combination therapies, and other relevant factors specific to the product and indication sought. Randomized treatment groups should be well balanced for these factors, and to fully ensure balanced assignment, randomization stratified for a limited number of factors may be desirable, with particular emphasis on those baseline variables hypothesized to affect either safety or efficacy.

Most patients taking products intended to treat diabetes are titrated to achieve a particular effect on serum or plasma glucose or on HbA1c. The primary efficacy parameter should be assessed substantially after the end of the titration period (e.g., 3 months) to better reflect the steady-state effect of the dose regimens studied.

Regardless of the choice of control used in phase 3 studies, the duration of the controlled phase in an efficacy trial is an important issue. In studies of recently approved products that lasted more than 1 year, sponsors have typically conducted a randomized, controlled study lasting at least 6 months, followed by an extension phase lasting 6 months or longer. Sponsors should weigh the advantages and disadvantages when deciding between a controlled and uncontrolled extension phase, and should ensure that the chosen design will provide interpretable long-term data.

Although uncontrolled extensions still allow for an expanded safety database (both in numbers exposed and duration of treatment), interpretability of both efficacy and safety data in an uncontrolled study period is limited by lack of a control group.

Since diabetic populations are prone to certain morbidities (such as cardiovascular disease and renal dysfunction), only longer term comparative safety data would allow for an assessment of the relative rates of these common, but important morbidities in subjects assigned to the investigational agent versus the control. Studies lasting longer than 1 year that employ an appropriate active comparator with adjudication of safety endpoints of interest by an endpoint committee blinded to treatment are strongly encouraged and may be needed if preclinical or phase 2 or phase 3 studies reveal a safety signal. Longer term controlled data also allow for better assessments of the comparative durability of effects on glycemia. Such studies, however, may have high rates of dropouts; therefore, treatment algorithms for maintenance of adequate glycemic control should be considered in the study design.

Of note, all drugs currently approved for the treatment of diabetes are indicated to improve glycemic control. The FDA currently bases approval of these drugs and biologics on HbA1c. We recognize that reducing long-term macrovascular complications in patients with diabetes should be an important goal of disease management. Although a recommendation to demonstrate macrovascular risk reduction premarketing may delay availability of many effective antidiabetic drugs for a progressive disease that often requires multiple drug therapy, sponsors should conduct large outcomes trials before submission of marketing applications for drugs in development that show nonclinical or clinical evidence of increasing macrovascular risk. Therapies that have not demonstrated a deleterious effect on cardiovascular outcome during extensive premarketing evaluation may need further post-approval assessment for their effects on long-term macrovascular disease. Interpretation of data resulting from such studies may be complicated by the need to identify conclusively the effect of a single drug within a multidrug regimen that usually is part of an adequate treatment for a complex, progressive condition such as type 2 diabetes and its associated comorbidities.

Phase 3 studies with a 6-month, placebo-controlled phase can be extended into a rigorously controlled, randomized, double-blind active-controlled phase that employs double-dummy agents.

Before submitting a marketing application, assessment of the immunogenic potential of therapeutic proteins, including insulins and insulin analogues, and of monoclonal antibodies, should be performed over a period of at least 6 to 12 months in study subjects reasonably representative of the intended population. If adverse events characteristic of allergic or immunologic reactions are identified, we may ask for additional studies, with durations longer than 12 months. These additional studies may need to be conducted before submission of a marketing application or as a postmarketing commitment, based on the overall analysis of the risks and benefits of the product. The appropriate timing of additional studies in these circumstances can be discussed with the FDA at a pre-BLA meeting, pre-NDA meeting, or other similar advice meeting.

A licensed monoclonal antibody used only in allogeneic transplantation, where patients are immunosuppressed through multiple modalities, should be newly evaluated for immunogenic potential in the diabetic or high-risk prediabetic population.

F. Premarketing Safety Evaluation

The safety evaluation of a new drug is, in the end, directed by the findings of preclinical investigations, by concerns arising based on the mechanism of action of the drug, by known toxicities of agents with a similar chemical structure or mechanism of action, and by the findings of previous clinical trials. In other words, ultimately, the safety evaluation is an iterative process based on prior experience.

Additionally, new antidiabetic agents, used alone or in combination with approved agents, should be assessed for their tendency to cause or augment hypoglycemia, an event that is part of diabetes management. Acceptable hypoglycemic risk, although not defined in absolute terms, usually is risk that is comparable to existing therapies, to which the new drug is directly compared, when both drugs are used in trials in which subjects are treated to identical glycemic goals with comparable glycemic outcomes (e.g., ADA guidelines). Furthermore, patients with diabetes often use multiple medications, not only to control glycemia, but also to address cardiovascular disease risk factors, such as hypertension and hyperlipidemia, and microvascular and neuropathic complications of diabetes. Interactions between the new investigational product and these other medications can result in adverse events that should be considered, documented, and reported. Finally, worsening of comorbid conditions other than diabetes should be ascertained, reported, and analyzed in comparison to the rates of similar adverse events in the control group.

Findings of specific safety signals with a product or related product (whether cardiovascular or otherwise) during any development phase should be investigated further in controlled studies enriched with the population at risk for the signal. The timing of this investigation (pre-approval or post-approval) depends on the strength and nature of the signal and whether the treatment offers a major advance over existing therapies.

For general issues related to risk assessment, pharmacovigilance, and risk minimization plans, refer to the following guidances:[14]

- Guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*
- Guidance for industry *Development and Use of Risk Minimization Action Plans*
- Guidance for industry *Premarketing Risk Assessment*
- ICH guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and addendum
- ICH guidance for industry *E2E Pharmacovigilance Planning*

G. Important Statistical Considerations

Standard statistical considerations apply to programs for drugs or biologics intended to treat diabetes. However, the following discussion highlights a few specific areas that are important to consider specifically for these therapeutic products.

1. Sample Size

Sample size calculations for superiority trials with HbA1c change from baseline as the primary endpoint should be based on two-sided tests of significance at the 5 percent level and at least 80 percent power. Effect sizes should represent clinically meaningful differences.

Sample sizes for noninferiority trials should be based on one-sided significance levels of 2.5 percent and at least 80 percent power. Because the calculations depend on the noninferiority margin, the sponsor should provide a rationale for the choice of margin and should be guided by the concept that this margin should not represent a clinically meaningful loss of efficacy relative to the active control. Typically, we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials. For additional guidance on noninferiority studies, refer to ICH E9 and ICH E10.

2. Preventing Missing Data from Subjects Who Prematurely Withdraw from Treatment

We encourage sponsors to obtain HbA1c measurements in all subjects, including those who withdraw prematurely or receive rescue medication because of poor glycemic control, near the calendar date at which they were scheduled to complete the trial. Complete data collection can facilitate the desired goal of a true intent-to-treat analysis (i.e., the analysis of all randomized subjects) and also serve as a measure of good clinical trial conduct.

[14] See http://www.fda.gov/cder/guidance/index.htm.

3. Analysis Methods

We recommend that the analysis of HbA1c change from baseline adjust for differences between groups in HbA1c at baseline (e.g., ANCOVA with baseline HbA1c as a covariate in the model). Factors in addition to treatment can be included in the model as appropriate, particularly variables with substantial correlation with the outcome and independence from the treatment, and variables used to stratify the randomization.

Although every reasonable attempt should be made to obtain complete HbA1c data on all subjects, dropouts are often unavoidable in diabetes clinical trials. The resulting missing data problems do not have a single general analytical solution. Statistical analysis using last observation carried forward (LOCF) is easy to apply and transparent in the context of diabetes trials. Assuming an effective investigational therapy, it is often the case that more placebo patients will drop out early because of a lack of efficacy, and as such, LOCF will tend to underestimate the true effect of the drug relative to placebo providing a conservative estimate of the drug's effect. The primary method the sponsor chooses for handling incomplete data should be robust to the expected missing data structure and the time-course of HbA1c changes, and whose results can be supported by alternative analyses. We also suggest that additional analyses be conducted in studies with missing data from patients who receive rescue medication for lack of adequate glycemic control. These sensitivity analyses should take account of the effects of rescue medication on the outcome.

The full analysis set as described in ICH E9 should be the primary analysis population for both superiority and noninferiority analyses. Supporting analyses in one or more subsets of the full analysis set also can be conducted and are encouraged in noninferiority analyses.

Analyses of data from studies using withdrawal designs depend on the type of primary endpoint. Survival analysis methods should be used if therapeutic failure times are collected. If the endpoint is therapeutic success or failure, categorical methods should be used.

If statistical significance is achieved on the primary endpoint, secondary assessments of efficacy can be considered. Type 1 error should be controlled across all clinically relevant secondary efficacy endpoints that may be intended for product labeling to provide statistical support for their inclusion in the label.

The sponsor should report least-square mean treatment differences and associated 95 percent confidence intervals from the primary statistical model for all continuous efficacy endpoints.

Rates of hypoglycemia should be compared statistically between groups. If count data are analyzed, the sponsor should use robust statistical methods that take account of the dependence of events within individual patients.

4. Graphical Methods

Graphical methods showing treatment effects over time for study completers should be presented. Additional graphical presentations of the data to illustrate the effect of the drug are

encouraged. For examples, see the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

APPENDIX A: PRECLINICAL CONSIDERATIONS FOR PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS

Because of the effects of PPAR agonists on glucose and lipid metabolism, many compounds are being developed for the treatment of type 2 diabetes and/or dyslipidemia which activate PPARα, PPARγ, PPARα and γ (dual agonist), or PPARα, γ, and δ (pan agonist).

Recommendations for the Duration of Chronic Toxicology Studies

The ICH guidance regarding the duration of chronic toxicity studies in rodents and nonrodents has been adopted,[15] and for the nonrodent chronic toxicity study, a 9-month duration generally is appropriate for supporting chronic human use. However, since the no observed adverse effect levels for some of the toxicities associated with PPAR agonists can be adequately defined only after chronic administration, a 1-year study in nonrodents is recommended for drugs in the PPAR class.

Because of the prevalence of positive carcinogenicity findings with PPAR agonists, 2-year carcinogenicity evaluations in mice and rats are recommended. Since heart weight increases of 25 percent or greater after 13-week treatment with PPAR agonists have been predictive of excess cardiac mortality with longer-term chronic dosing (greater than or equal to 12 months) in all animal models, a dose that results in 20 to 25 percent increases in heart weight is considered to define the maximum tolerated dose for use in the 2-year carcinogenicity study for agonists with gamma activity.

Recommendations for the preclinical evaluation of PPAR-related toxicities are as follows:

- **Cardiac Effects.** The effects on the heart should be characterized by reviewing electrocardiograms, clinical chemistry, and cardiac histopathology in rats and nonrodents. QT prolongation potential should be thoroughly evaluated in multiple dose nonrodent toxicity studies. For compounds with PPAR alpha or delta agonist activity, biomarkers of direct cardiac toxicity such as Troponin I and T should be monitored in animal studies.

  Additional evaluations are recommended as follows:

  - Correlation of heart weights with thickness of ventricular free wall and ventricular septum in chronic toxicology studies in rats and nonrodents.
  - Morphometric measurements of ventricular myocardial hypertrophy in nonrodents.
  - Presence of karyomegaly in myocardium of ventricles.
  - Pattern and distribution of myocardial fibrosis.
  - Characterization of myocardial inflammatory infiltrates.
  - Determination of composition of serous effusions.
  - Presence of fatty changes detected by stained heart tissue. The sections can be stained with Sudan IV or Oil Red-O.

[15] See the ICH guidance for industry *S4 Duration of Chronic Toxicology Testing in Animals (Rodent and Nonrodent Toxicity Testing).*

  - Characterization in animals and humans of the potential for plasma volume expansion.

- **Hepatic Effects.** The cause of any liver enlargement observed should be determined (peroxisome proliferation, mitochondrial proliferation/swelling). Liver tissues should be stained to detect the presence of fatty changes. The sections can be stained with Sudan IV or Oil Red-O. Liver enzyme levels and biochemical markers of peroxisome proliferation (Acyl CoA and CYP 4A) should be analyzed in rodents and nonrodents.

- **Bone Marrow Effects.** Bone marrow smears from femur and sternum should be quantified to assess for effects on cellularity.

- **Renal Effects.** Drug-related increases in urothelial tumors have been observed in rodent carcinogenicity studies with PPAR agonists. If such tumors are observed, mechanistic studies (e.g., urinalysis assessing crystalluria, urine pH, urinary electrolytes) are recommended.

- **Muscle Toxicity.** Skeletal and/or cardiac muscle degeneration have been commonly observed for agonists with PPAR alpha or PPAR delta activity. Creatine kinase and troponin evaluations should be performed in preclinical studies for these subtypes. Histopathological evaluations of skeletal muscle should include multiple sites to evaluate effects on both type I and type II muscle (e.g., diaphragm, gastrocnemius, soleus, intercostals muscles).

- **Other Known Toxicities.** Thymic and lymphoid atrophy, reproductive organ toxicity, adipose proliferation, and infiltration are toxicities commonly associated with the administration of PPAR agonists in preclinical studies. Preclinical study designs should include adequate assessments for these potential toxicities.

- **Electron Microscopy.** Electron microscopy evaluations should be conducted on established target organs for PPAR agonists (liver and heart mandatory) and on other compound specific target tissues, as identified (e.g., renal proximal tubules, skeletal muscle).

APPENDIX B: HYPOGLYCEMIA

Severe episodes of hypoglycemia are often encountered when patients implement a program of intense glycemic control. These adverse occurrences are often the limiting factor in achieving improvements in metabolic control and reductions in HbA1c. There are often substantial differences in the interpretation and reporting of the severity of hypoglycemic episodes among investigators, studies, and clinical programs because of the diversity of the definitions used in clinical studies. To help in the interpretation of this important safety attribute of a new diabetes treatment that may cause hypoglycemia, we recommend standardization of definitions in individual protocols and across protocols within the development program. One recommended approach for such standardization is to use classifications of severity from well-accepted sources, such as the ADA.

The ADA Workgroup on Hypoglycemia classifies hypoglycemia as follows (Diabetes Care, 2005, 28: 1245):

- **Severe hypoglycemia.** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

- **Documented symptomatic hypoglycemia.** An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L).

- **Asymptomatic hypoglycemia.** An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L). Since the glycemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline is normally 65 to 70 mg/dL (3.6 to 3.9 mmol/L) and since antecedent plasma glucose concentrations of less than or equal to 70 mg/dL (3.9 mmol/L) reduce sympathoadrenal responses to subsequent hypoglycemia, this criterion sets the lower limit for the variation in plasma glucose in nondiabetic, nonpregnant individuals as the conservative lower limit for individuals with diabetes.

- **Probable symptomatic hypoglycemia.** An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is important to recognize these events as probable hypoglycemia. Such self-reported episodes that are not confirmed by a contemporaneous low plasma glucose determination may not be suitable outcome measures for clinical studies that are aimed at evaluating therapy, but they should be reported.

- **Relative hypoglycemia**. An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration greater than 70 mg/dL (3.9 mmol/L). This classification reflects the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels greater than 70 mg/dL (3.9 mmol/L) as plasma glucose concentrations decline toward that level. Though causing distress and interfering with the patient's sense of well-being, and potentially limiting the achievement of optimal glycemic control, such episodes probably pose no direct harm and, therefore, may not be a suitable outcome measure for clinical studies that are aimed at evaluating therapy, but they should be reported.

At a minimum, hypoglycemic events should be reported in each of the first three classifications: severe hypoglycemia, documented symptomatic hypoglycemia, and asymptomatic hypoglycemia.

Currently, there is no standardized convention for reporting the frequency of hypoglycemia in clinical studies. The ADA Workgroup recommends that both the proportion (percentage) of subjects affected and the event rates (e.g., episodes per subject-year or 100 subject-years) for each of the classifications of hypoglycemic events be reported. These data provide complementary information. In addition, we anticipate that the distribution of subjects having a specific number of hypoglycemic events will be reported (see also section V.G., Important Statistical Considerations). For the hypoglycemic episodes, sponsors should include information on potential precipitants (e.g., missed meal, exercise) and patterns (e.g., timing of the event during the course of the day or night).

APPENDIX C: CURRENTLY AVAILABLE DRUG TREATMENTS

A. Insulin Products

A variety of recombinant human insulins and insulin analogues are available and these products serve as the primary basis for treating the glucose metabolic defects in type 1 diabetes. Insulin and its analogues also have an important role in the treatment of type 2 diabetes, particularly as the disease progresses. These products are used in different combinations according to the pharmacokinetic profile of each insulin type, and some are available in premixed combinations of different proportions of short- and long-acting agents. These insulins also can be used in conjunction with oral agents (described below) to achieve control of blood glucose. There has been tremendous interest and some success in developing noninjectable insulins (e.g., inhaled insulin). However, current development of these products has been aimed at supplementing or replacing short-acting insulin only and would not represent a full alternative to injectable insulin and its analogues.

B. Oral Agents for Type 2 Diabetes

The first oral products for the treatment of diabetes mellitus were the sulfonylureas, which are long-acting insulin secretagogues. The meglitinides constitute another class of insulin secretagogues that are taken with meals and have short-term effects, primarily on the postprandial elevations of plasma glucose. Metformin exerts its effect on endogenous hepatic glucose production. PPAR agonists enhance insulin sensitivity. Alpha glucosidase inhibitors prevent intestinal glucose absorption and have primary effects on the excursion of postprandial glucose.

C. Newer Classes of Therapeutic Products

More recently, an analogue of human amylin, pramlintide, was approved for the treatment of type 1 or type 2 diabetic patients as an adjunct to mealtime short-acting or rapid-acting insulin. Amylin, a neuroendocrine hormone that is co-secreted with insulin from pancreatic beta cells, slows intestinal carbohydrate absorption through decreased gastric emptying and suppresses hepatic gluconeogenesis by inhibiting glucagon secretion postprandially. Additionally, exenatide, a glucagon-like peptide 1 (GLP-1) analogue (belonging to the new class of incretin mimetics) has been approved for type 2 diabetes, in combination with other oral antidiabetic agents. In response to nutrients in the lumen of the gut, GLP-1 is secreted from the intestinal L cells. Similar to amylin, GLP-1 decreases gastric emptying and glucagon secretion. In addition, GLP-1 stimulates insulin secretion. Because the effects of GLP-1 are glucose-dependent, GLP-1 mediates glucose homeostasis without causing hypoglycemia. Both pramlintide and exenatide are injectables.

There is a newer class of oral drugs known as dipeptidyl peptidase 4 (DPP4) inhibitors that has been the focus of intense development. DPP4 is a serine protease responsible for the rapid metabolism of endogenous GLP-1. By inhibiting this enzyme, DPP4 inhibitors prevent the rapid catabolism of endogenous GLP-1, thereby potentiating the incretin effect of GLP-1.