

**DEPARTMENT OF HEALTH & HUMAN SERVICES**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

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**BACKGROUND INTRODUCTORY MEMORANDUM**

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**Forum:** Endocrinologic and Metabolic Drugs Advisory Committee meeting  
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**Topic:** The role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus

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**INTRODUCTION**

All drugs that are approved by the Food and Drug Administration (FDA) for the treatment of diabetes mellitus are indicated to improve glycemic control. FDA has been basing approval of antidiabetic drugs on the surrogate of hemoglobin A1c (HbA1c), which is a well-validated measure of glycemia. However, questions have been raised as to whether long-term cardiovascular trials should be part of the approval process for pharmacological therapies developed for the treatment of diabetes. There are 2 categories of cardiovascular trials, one that evaluates whether a treatment has cardiovascular benefit (i.e., reduces cardiovascular events) and another that evaluates whether a treatment is likely to increase cardiovascular risk. A requirement for demonstrating cardiovascular benefit will likely have major implications on the availability of new treatments for type 2 diabetes, because conclusive evidence of a reduced risk of macrovascular complications in type 2 diabetes has not yet been established for any of the currently available antidiabetic medications, including insulin. In addition, a requirement for long-term cardiovascular benefit would prompt questions as to why currently marketed therapies (all lacking evidence of such benefit) should remain available.

Establishing a hurdle of long-term, costly trials to exclude cardiovascular harm may also affect drug development for type 2 diabetes, particularly if this mandate applies to every product, even those that have no suggestion of cardiotoxicity.

To further explore these complex issues, we have convened the current advisory committee meeting to discuss the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus. The purpose of this briefing document is to provide introductory material to prepare the advisory committee members for the scheduled presentations and ensuing discussion.

The advisory committee meeting is scheduled for 2 full days. The panel will be populated by the Endocrinologic and Metabolic Drugs Advisory Committee, diabetologists, cardiologists, statisticians, and members of the Drug Safety and Risk Management Committee (DSARM). During the first day, experts in the field of diabetes and cardiology will present background information that will lay the foundation for extensive discussion among committee panel members (Table 1). Most of the second day of the advisory committee meeting will be reserved for an extensive discussion among the advisory committee members.

**Table 1. Topics to be Presented to the Advisory Committee Panel**

Introduction, including current basis of approval of drugs/biologics for type 2 diabetes
Natural history of type 2 diabetes and diabetes-related macrovascular complications
Hemoglobin A1c as a surrogate for glycemic control and diabetes-related complications
Cardiovascular outcome trials: Statistical considerations
Clinical macrovascular outcomes with antidiabetic drugs: What we already know
Clinical macrovascular outcomes with antidiabetic drugs: Ongoing studies
Need for cardiovascular assessment during the approval process for antidiabetic drugs
Challenges in designing a cardiovascular outcomes trial in patients with type 2 diabetes

This FDA-prepared document contains:

- Pertinent background information on diabetes and available treatments
- A summary of treatment goals for patients with type 2 diabetes
- A summary of completed and ongoing cardiovascular trials in patients with type 2 diabetes or with impaired glucose tolerance
- FDA's current approach to the approval of drugs and biologics developed for the treatment of type 2 diabetes
- Introductory concepts relating to cardiovascular assessment of drugs and biologics developed for the treatment of type 2 diabetes

. “Points for Discussion” for use during the advisory committee panel’s deliberations (these “Points for Discussion” are not necessarily the questions that FDA will ask the advisory committee panel to vote on) . Appendices with pertinent references

The appendices contain the recently published draft guidance for industry entitled “Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention”, which includes a description of FDA’s current approach to the development of drugs and biologics for the treatment of type 2 diabetes. In addition, the appendices contain reference articles for the clinical trials mentioned in this briefing document. Some of the clinical trials are ongoing or if completed, final study results have not yet been published. For these trials, we have included reference articles describing the study design (if published).

## **TYPE 2 DIABETES MELLITUS**

Diabetes mellitus affects more than 170 million people worldwide and more than 20 million people in the United States. Approximately 90% of patients with diabetes have the type 2 form, which is increasing at alarming rates, in part due to the obesity epidemic and widespread physical inactivity. Chronic complications of diabetes include microvascular disease (retinopathy, nephropathy, and neuropathy) and macrovascular disease (coronary artery disease, stroke, peripheral vascular disease). In the United States, diabetes is the leading cause of blindness, end-stage renal disease, and non-traumatic lower-extremity amputations. Neuropathy can cause chronic pain and involvement of the autonomic nervous system can result in other disabling conditions, such as diabetic gastroparesis.

People with type 2 diabetes and no prior history of myocardial infarction appear to have as high a risk of myocardial infarction as non-diabetic people with a history of previous myocardial infarction. The risk of death from cardiovascular disease is 2-4 times higher among people with type 2 diabetes than among people without diabetes.

Cardiovascular disease and stroke account for approximately two-thirds of deaths in people with diabetes.

## **Pharmacologic Treatments for Type 2 Diabetes**

Type 2 diabetes is characterized by 2 major pathophysiological abnormalities – insulin resistance at the site of insulin action and impaired insulin secretion from the pancreatic beta-cell. Other abnormalities include derangements in hepatic glucose metabolism and dysregulation of gastrointestinal peptides (e.g., incretin hormones). Pharmacologic treatments for diabetes with different mechanisms of action each target one or more of the multiple defects contributing to hyperglycemia. Because type 2 diabetes is a progressive disease, most patients require the use of a combination of different antidiabetic drugs to maintain adequate glycemic control over time. Patients who are unable to control hyperglycemia with oral antidiabetic agents require insulin therapy. Insulin given in sufficient amounts can normalize blood glucose levels. However,

concerns over hypoglycemia, weight gain, and the subcutaneous route of administration often delay the initiation of therapy, prompt discontinuation of therapy, or result in suboptimal dosing. Table 2 summarizes the classes of currently approved treatments for type 2 diabetes with their presumed primary mechanism of action (if known).

<b>Table 2. Classes of Drugs Approved for the Treatment of Type 2 Diabetes</b>	
<b>Drug Class With Examples</b>	<b>Presumed Primary Mechanism of Action</b>
<b>Insulins</b> - Insulin Aspart - Insulin Glulisine - Insulin Lispro	Stimulate peripheral glucose uptake by skeletal muscle and fat and inhibit hepatic glucose production
<b>Sulfonylureas</b> - Glipizide - Glyburide	Stimulate insulin release by inhibiting the ATP-dependent potassium channel on pancreatic beta-cells
<b>Biguanides</b> - Metformin	Decrease hepatic glucose production
<b>Alpha-glucosidase inhibitors</b> - Acarbose - Miglitol	Delay glucose absorption from the gastrointestinal tract by inhibiting enzymes that convert carbohydrates into monosaccharides
<b>Thiazolidinediones</b> - Pioglitazone - Rosiglitazone	Insulin sensitizers Modulate the transcription of genes involved in glucose metabolism
<b>Glinides</b> - Nateglinide - Repaglinide	Stimulate insulin release by inhibiting ATP-dependent potassium channels on pancreatic beta-cells (structurally different to sulfonylureas and exert effects via different receptors)
<b>GLP-1 analogues</b> - Exenatide	Stimulate glucose-dependent insulin secretion
<b>Amylin analogues</b> - Pramlintide acetate	Slow gastric emptying and suppresses the postprandial rise in plasma glucagon
<b>DPP-4 inhibitors</b> - Sitagliptin phosphate	Slow inactivation of incretin hormones (e.g., GLP-1), which stimulate glucose-dependent insulin secretion
<b>Bile acid sequestrants</b> - Colesevelam hydrochloride	Unknown
GLP-1 = glucagon-like peptide 1 DPP-4 = dipeptidyl peptidase 4	

All medications currently approved for the treatment of type 2 diabetes are indicated to improve glycemic control. Treatments that reduce hyperglycemia have merit because a reduction in blood glucose lessens the symptoms of hyperglycemia (e.g., polyuria, polydipsia). FDA has been using HbA1c (also known as glycated hemoglobin) as the

primary measure of glycemia. HbA1c is formed by the non-enzymatic, irreversible attachment of glucose to hemoglobin and is directly proportional to the ambient glucose concentration. HbA1c reflects mean blood glucose over the lifespan of the red blood cell, but correlates best with mean blood glucose over the preceding 12 weeks. In addition, a reduction in HbA1c has been shown to lower the risk for some of the chronic complications of diabetes. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive glycemic control (as assessed by HbA1c) with insulin reduces the risk of onset and progression of retinopathy, nephropathy, and neuropathy in patients with type 1 diabetes. In the United Kingdom Prospective Diabetes Study (UKPDS), patients with type 2 diabetes who were randomized to intensive glycemic control with a sulfonylurea, insulin, or a combination of these agents had a lower risk of microvascular complications than patients randomized to standard glycemic control, which was initially comprised of diet and exercise.

### **Completed Cardiovascular Trials in Patients with Type 2 Diabetes**

Follow-up and analysis of cardiovascular outcomes in the two randomized treatment groups from the Diabetes Control and Complications Trial noted that patients with type 1 diabetes treated with intensive glycemic control who subsequently reverted to less intensive glycemic control after trial completion had lower risk of cardiovascular disease than those originally randomized to conventional glycemic control. A conclusive beneficial effect of glycemic control on cardiovascular disease in patients with type 2 diabetes has not yet been demonstrated. In the University Group Diabetes Program (UGDP), patients treated with the first generation sulfonylurea, tolbutamide had an increase in cardiovascular mortality compared to patients treated with diet alone or diet plus insulin. Although this finding has not been corroborated in other long-term clinical trials with sulfonylureas, the labels for all approved sulfonylureas include a bolded paragraph describing a possible increase in cardiovascular mortality with these agents. In contrast, the UKPDS showed a 16% risk reduction (which did not reach statistical significance) for the composite endpoint of fatal and non-fatal myocardial infarction and sudden death in the intensive group treated with insulin or sulfonylurea compared to the conventional group treated with diet ( $p=0.052$ ). A retrospective analysis of the UKPDS also showed a significant reduction in cardiovascular disease and all-cause mortality in a subgroup of 342 overweight patients who received metformin. However, the subgroup of patients in UKPDS who had inadequate glycemic control on sulfonylurea ( $n=537$ ) and were randomized to add-on metformin ( $n=268$ ) had a 96% increase in diabetes-related mortality ( $p=0.039$ ) compared to patients who continued on sulfonylurea alone ( $n=269$ ). These findings from the UKPDS have not been considered definitive evidence of cardiovascular benefit or harm because of the limitations described above,

The two marketed peroxisome proliferator-activated receptor (PPAR) agonists (rosiglitazone and pioglitazone) increase the risk of congestive heart failure but have inconclusive effects on the macrovascular complications of type 2 diabetes. PROactive (PROspective pioglitAzone Clinical Trial in macroVascular Events) was a blinded, randomized, cardiovascular outcomes trial in approximately 5,200 patients that compared pioglitazone (titrated to 45 mg) to placebo as add-on to background

antidiabetic therapy in patients with type 2 diabetes and cardiovascular disease. Patients were required to have a history of at least 1 of the following: myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or stroke at least 6 months prior to recruitment; acute coronary syndrome at least 3 months prior to recruitment; or objective evidence of coronary artery disease or obstructive arterial disease in the leg. The protocol excluded patients with New York Heart Association Class II-IV heart failure. The patients randomized to pioglitazone add-on therapy had a lower incidence of the composite of all-cause mortality, non-fatal myocardial infarction, and stroke compared to patients randomized to placebo add-on therapy ( $p=0.027$ ). However, this composite was a secondary endpoint added after the last trial visit occurred, and pioglitazone failed to show a significant benefit ( $p=0.095$ ) for the prespecified primary composite endpoint (time to all-cause mortality, myocardial infarction, stroke, acute coronary syndrome, coronary or leg revascularization, or amputation above the ankle). In addition, there was no statistically significant difference between treatment groups for any of the individual components of the primary endpoint. Although investigators were instructed to titrate medications for cardiovascular risk factors to the International Diabetes Federation European Region 1999 guidelines, with a goal HbA1c  $<6.5\%$ , the changes in HbA1c, serum triglycerides, HDL cholesterol, and blood pressure were more favorable in the pioglitazone-treated group relative to the placebo add-on group. Consequently, some have argued that it is difficult to discern whether the favorable trend in PROactive is entirely attributable to pioglitazone or to the better control of established cardiovascular risk factors in that treatment group.

Almost 1 year ago, the Food and Drug Administration (FDA) convened an advisory committee meeting to discuss the risk of myocardial ischemia associated with the use of rosiglitazone. Most of the advisory committee members (20 vs. 3) voiced concern that rosiglitazone was associated with an increased risk for myocardial ischemia based on the results of an FDA meta-analysis of mostly short-term randomized, controlled trials. Three longer-term clinical trials (ADOPT, DREAM and RECORD) have not confirmed or excluded this risk of myocardial ischemia. In addition, an analysis of these three trials did not suggest an increased risk of all-cause mortality associated with rosiglitazone (hazard ratio stratified on study 0.87; 95% confidence interval 0.68, 1.11;  $p=0.25$ ). The advisory committee voted 22 to 1 in favor of keeping rosiglitazone on the market with appropriate changes to the physician and patient product labels. After taking the discussion and votes from the advisory committee meeting into account and carefully deliberating internally, the FDA decided that rosiglitazone should remain on the market but with labeling changes which included an updated Boxed Warning containing the information on increased myocardial ischemic risk and a Medication Guide. The FDA determined that the data on myocardial ischemic risk with rosiglitazone are inconclusive and asked GlaxoSmithKline, the manufacturer of rosiglitazone, to conduct a new clinical trial to more definitively assess the risk of myocardial ischemia with rosiglitazone.

### **Ongoing or Recently Completed Cardiovascular Trials in Type 2 Diabetes**

Ongoing or recently completed cardiovascular trials in patients with type 2 diabetes are summarized below. These trials have a primary cardiovascular endpoint, but only

PROactive (see above) and RECORD (see below) have attempted to evaluate the cardiovascular effect of a single antidiabetic agent. The remainder of these cardiovascular trials in patients with type 2 diabetes is evaluating the effect of intensive glycemic control or different treatment strategies (e.g., insulin sensitizer vs. insulin secretagogues) on cardiovascular outcomes.

### ACCORD

The recommended target HbA1c in nonpregnant adults with type 2 diabetes is <7.0% (or lower in select individuals) according to the 2008 Clinical Practice guidelines issued by the American Diabetes Association and  $\leq 6.5\%$  (as near normal as possible without inducing clinically significant hypoglycemia) according to the 2007 guidelines issued by the American Association of Clinical Endocrinologists. Unexpected preliminary findings from the ongoing ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial have raised the possibility of a HbA1c threshold below which there may be an adverse effect on mortality. ACCORD is a NHLBI (National Heart, Lung, and Blood Institute) sponsored, randomized, double 2 x 2 factorial trial testing 3 treatment approaches in approximately 10,000 patients with type 2 diabetes: intensive vs. conventional glycemic control; intensive vs. conventional blood pressure control; and treatment of lipids by a fibrate+statin compared to a statin alone. Patients enrolled in ACCORD had a mean duration of diabetes of 10 years and were at high risk for cardiovascular events because they were required to either have cardiovascular disease or have  $\geq 2$  risk factors for cardiovascular disease. The primary endpoint is the composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. The glucose substudy was designed to have 89% power to detect a 15% treatment effect of intensive glycemic control compared to standard glycemic control.

The hypertension and lipid portions of the trial continue as planned but the glycemic portion was terminated prematurely based on a recommendation of the Data Safety Monitoring Board because of excess deaths (257 vs. 203) over the average 4-year treatment period in the patients assigned to intensive glycemic control (HbA1c <6%) compared to those assigned to conventional glycemic control (HbA1c 7-7.9%). The investigators stated that this unexpected finding is not explained by hypoglycemia or by any of the antidiabetic drugs used in the trial (including rosiglitazone). The American Diabetes Association issued a statement in response to this announcement advising that patients continue to strive for HbA1c <7% and that treatment still be tailored to the individual patient. The American Diabetes Association also recommended that patients with diabetes and existing cardiovascular disease or multiple cardiovascular risk factors consult with their physician regarding glycemic treatment goals.

## ADVANCE

In contrast to the preliminary results from ACCORD, interim results from ADVANCE (Action in Diabetes and Vascular Disease) were reported to not show increased mortality among intensively treated patients with type 2 diabetes at high risk for cardiovascular events who were followed for an average treatment period of 5 years. These results are based on one of the ADVANCE substudies, which randomized approximately 11,000 patients to a sulfonylurea-based regimen (gliclazide MR) to which other oral agents and insulin could be added, as needed, to achieve HbA1c  $\leq 6.5\%$  or to conventional treatment.

## VADT

The Veterans Affairs Diabetes Trial (VADT), sponsored by the Department of Veterans Affairs, is also evaluating the effect of intensive (HbA1c  $\leq 6\%$ ) vs. conventional (HbA1c 8-9%) glycemic control on cardiovascular events in patients with type 2 diabetes. This 5-year study has enrolled 1,700 patients with inadequate glycemic control on at least 1 oral antidiabetic agent and/or daily insulin injections. Patients with a history of stroke, myocardial infarction, or invasive revascularization within the preceding 6 months or with significant angina or New York Heart Association Class III or IV heart failure are excluded. The study intends that both treatment groups receive equal distribution of therapeutic classes of antidiabetic medications (the dose of insulin is expected to be the only difference between groups) so that the main difference between treatment groups is the intensity of glycemic control. All other cardiovascular risk factors are being treated according to medical guidelines and are intended to be identical in both treatment groups. The primary endpoint is the occurrence of any major cardiovascular event (myocardial infarction, stroke, new or worsening heart failure, amputation for ischemic diabetic gangrene, invasive intervention for coronary artery disease or peripheral vascular disease, and cardiovascular death) determined by an independent endpoints committee blinded to treatment. The sample size is based on an estimated event rate of 40% over an average of 6 years of follow-up in the standard treatment arm. The statistical analysis plan will use survival analysis and the log-rank test to compare complication-free survival between the 2 treatment groups.

Results from ACCORD, ADVANCE, and VADT are being presented at the June 2008 American Diabetes Association Annual Meeting.

## RECORD

RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) is an ongoing, open-label, randomized clinical trial involving approximately 4,000 patients with type 2 diabetes being followed for a treatment period of 5-7 years. An interim analysis of RECORD was published last year after a published meta-analysis (N Engl J Med 2007;356:2457-71) showed an increased incidence of myocardial infarction in patients treated with rosiglitazone. RECORD enrolled patients with inadequate glycemic control on either metformin or sulfonylurea but did not require

patients to be at increased risk for cardiovascular disease. Patients inadequately controlled on metformin were randomized to add-on sulfonylurea or add-on rosiglitazone. Patients inadequately controlled on sulfonylurea were randomized to add-on metformin or add-on rosiglitazone. The primary objective of RECORD is to compare the time to reach the composite endpoint of cardiovascular death or cardiovascular hospitalization in rosiglitazone-treated patients versus patients not treated with rosiglitazone. Both treatment groups have a target HbA1c  $\leq 7.0\%$ . The protocol does not discuss how study personnel should manage other cardiovascular risk factors during the study. Non-inferiority will be concluded if the upper bound of the two-sided 95% confidence interval for the hazard ratio of the primary endpoint in the rosiglitazone group relative to the non-rosiglitazone group falls below 1.20. The power to exclude this non-inferiority margin of 1.20 may be reduced because the interim analyses showed an annual event rate for the primary endpoint lower than predicted and a loss-to-follow-up rate higher than predicted. However, it should be noted that the interim analysis did not show an increased risk of cardiovascular mortality associated with rosiglitazone (hazard ratio 0.80; 95% confidence interval 0.52, 1.24;  $p=0.32$ ).

### BARI-2D

BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) is an NHLBI-sponsored, 2x2 factorial trial comparing coronary revascularization combined with aggressive medical treatment versus aggressive medical treatment alone in approximately 2,400 patients with type 2 diabetes and angiographically documented stable coronary artery disease. In addition, the trial is simultaneously comparing 2 glycemic control strategies: insulin sensitization vs. insulin provision. Patients randomized to the insulin-sensitizing strategy receive thiazolidinediones or metformin. Patients randomized to the insulin-providing strategy receive sulfonylureas, meglitinides (repaglinide, nateglinide), or insulin. Alpha-glucosidase inhibitors can be used by either treatment group. The goal HbA1c is  $<7.0\%$  for all patients and there is to be uniform control of hypertension, dyslipidemia, and obesity following recommended medical guidelines. Patients with persistent HbA1c  $>8\%$  can receive antidiabetic drugs from the opposite treatment arm to bring HbA1c within the 7.0-8.0% range. The primary endpoint is all cause 5-year mortality.

### Cardiovascular Trials in Patients with Impaired Glucose Tolerance

#### STOP-NIDDM

Stop-Noninsulin-Dependent Diabetes Mellitus (STOP-NIDDM) is a double-blind, randomized, placebo-controlled trial that randomized approximately 1,400 patients with impaired glucose tolerance to the alpha-glucosidase inhibitor, acarbose (100 mg three times a day) or placebo. The acarbose treatment arm had a 49% relative risk reduction ( $p=0.03$ ) in cardiovascular events (coronary artery disease, cardiovascular death, congestive heart failure, stroke, and peripheral vascular disease) compared to placebo. However, this endpoint was a secondary objective of the study and the analysis was not adjusted for multiplicity, raising the possibility that the observed effect and nominal

statistical significance could be due to chance. The authors acknowledged that this finding was hypothesis-generating and would need confirmation in another trial.

### NAVIGATOR

NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research), sponsored by Novartis, is a randomized, double-blind, placebo-controlled, 2x2 factorial trial investigating whether nateglinide or valsartan can prevent diabetes and/or cardiovascular events in people with impaired glucose tolerance who are at high risk for cardiovascular events. There are two primary endpoints, one related to the delay or prevention of progression to diabetes and a second related to cardiovascular morbidity and mortality.

### DREAM

DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) is a double-blind, placebo-controlled, 2x2 factorial trial that randomized approximately 5,300 patients to a median treatment of 3 years with rosiglitazone or placebo (and simultaneously ramipril or placebo). Patients were required to have impaired fasting glucose and/or impaired glucose tolerance with no prior history of cardiovascular disease. Although this trial did not have a primary cardiovascular endpoint (the primary endpoint was newly-diagnosed diabetes or all-cause mortality), one of the secondary endpoints was a composite of cardiovascular events (myocardial infarction, stroke, cardiovascular death, revascularization procedures, heart failure, new angina with objective evidence of ischemia, or ventricular arrhythmia needing resuscitation).

### **Treatment Goals in Patients with Type 2 Diabetes**

As mentioned above, conclusive evidence of cardiovascular risk reduction with any of the currently approved treatments for type 2 diabetes has not yet been established. Because type 2 diabetes often coexists with other cardiovascular risk factors (e.g., hypertension and dyslipidemia), current treatment guidelines stress the importance of multifactorial reduction of cardiovascular risk factors (treatment of blood pressure and dyslipidemia, stopping smoking, daily aspirin) in addition to intensive glycemic control (Table 3).

<b>Cardiovascular risk factor</b>	<b>American Diabetes Association (2008)</b>	<b>American Assoc. of Clinical Endocrinologists (2007)</b>
Glycemic control, HbA1c, %	<7.0	≤6.5
Blood pressure, mmHg	<130/80	<130/80
Lipid profile*		
LDL-cholesterol, mg/dL	<100 or <70	<100 or <70
Serum triglycerides, mg/dL	<150	<150
HDL cholesterol, mg/dL	>40 (men); >50 (women)	>40 (men); >50 (women)
Smoking cessation	Yes	Yes
Aspirin therapy	If history of CVD or at increased risk for CVD	Use routinely unless a specific contraindication is present
CVD=cardiovascular disease		
*LDL-C is primary target		

There are clinical data supporting this approach of targeting cardiovascular risk factors in patients with type 2 diabetes. For example, the Collaborative Atorvastatin Diabetes Study (CARDS) was terminated early after atorvastatin 10 mg was shown to reduce the composite primary endpoint of time to first occurrence of acute coronary heart disease events, coronary revascularization, or stroke by 37% (p=0.001) compared to placebo in patients with type 2 diabetes, no prior history of cardiovascular disease, and serum LDL cholesterol ≤160 mg/dL. Also, the Steno-2 Study showed an approximate 50% reduction in the risk of cardiovascular disease (hazard ratio 0.47; 95% confidence interval 0.24-0.73) over nearly 8 years of follow-up in 80 patients with type 2 diabetes and microalbuminuria who were randomized to a multifactorial treatment strategy (goal HbA1c <6.5%, blood pressure <130/80 mmHg, cholesterol <175 mg/dL, triglycerides <150 mg/dL, reduced dietary fat, regular exercise, and smoking cessation) compared to the 80 patients who received conventional care.

When designing cardiovascular trials in patients with type 2 diabetes, the protocol should specify the treatment goals for all known risk factors for cardiovascular disease. An area for discussion concerns whether comparable goals should be achieved in the treatment groups, and if so, how this should be accomplished.

### **APPROVAL PROCESS FOR DRUGS AND BIOLOGICS FOR TYPE 2 DIABETES**

Earlier this year, FDA issued a draft guidance for industry describing our current recommendations to sponsors developing drugs and therapeutic biologics for the treatment and prevention of diabetes mellitus. The pertinent information relevant to the discussion at hand is summarized below. Please refer to the draft guidance for additional information.

## **Phase 2 Development Program**

The Phase 2 program for pharmaceutical products being developed for the treatment of type 2 diabetes typically consists of 1 or 2 dose-finding studies, usually conducted in patients who are not on other anti-diabetic therapy or who are taking a stable dose of metformin. These studies usually randomize a few hundred patients to 12 weeks of treatment with placebo or one of several doses of the investigational agent. The primary efficacy outcome measure for these trials is the placebo-adjusted change in HbA1c from baseline to endpoint. The doses that show the most promising preliminary efficacy and safety profiles are selected for further evaluation in phase 3.

## **Phase 3 Development Program**

The Phase 3 program for pharmaceutical products being developed for the treatment of type 2 diabetes typically consists of several 6-month placebo controlled trials and 6-18 month extensions to these trials.

In general, we ask sponsors to test the investigational agent as monotherapy and in combination with antidiabetic medications with which the product will likely be co-administered in clinical practice. As treatment of type 2 diabetes mellitus frequently requires combination therapy, overall patient exposures in the development program should be weighted more in trials evaluating the investigational product in combination with other antidiabetic medications.

The 6-month monotherapy trial typically enrolls patients with HbA1c 7-10% who are not receiving other pharmacological treatments for diabetes or who have been adequately washed off a single antidiabetic medication. These patients are usually randomized to 6 months of treatment with placebo or 2 doses of the investigational agent.

The 6-month combination therapy trials typically enroll patients with HbA1 c 7-10% despite near-maximal or maximal stable doses of a background antidiabetic medication (e.g.,  $\geq 1500$  mg of metformin daily; at least one-half of the maximum recommended dose of a sulfonylurea). These patients are randomized to 6 months of treatment with placebo or 1-2 doses of the investigational agent as add-on to the background antidiabetic medication(s).

Sometimes, sponsors conduct non-inferiority trials comparing the investigational agent to an already marketed antidiabetic treatment, either in a monotherapy population or as add-on to background antidiabetic therapy.

The primary efficacy outcome measure for the phase 3 trials is the placebo-adjusted (or active control-adjusted) change in HbA1 c from baseline to endpoint. For the non-inferiority trials, we have been requesting non-inferiority margins of 0.25-0.40%, depending on the magnitude of the treatment effect of the comparator agent in previous trials.

Key secondary efficacy outcome measures for the phase 3 trials usually include changes in fasting plasma glucose, changes in parameters related to the investigational product's mechanism of action (e.g., insulin sensitivity, postprandial glucoses), responder analyses (e.g., proportion of patients achieving HbA1c <7.0%), body weight, and lipid profiles.

To obtain long-term data, Sponsors typically perform 6-18 month extensions to several of their 6-month phase 3 trials. Although uncontrolled extensions still allow for an expanded safety database, interpretability of efficacy and safety data in an uncontrolled study is limited by lack of a control group. Therefore, we strongly recommend that at least some of the extension trials be controlled. Sponsors who wish to perform uncontrolled extension trials should explain how they intend to ensure interpretable long-term data.

### **Sample Sizes**

The International Conference on Harmonisation guideline 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 prior to approval of at least 1,500 subjects (300-600 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, we have been asking for exposures that exceed these recommendations for products developed for the treatment of type 2 diabetes, because of the large and growing size of the population with type 2 diabetes and the increasing complexity of treatment regimens as additional antidiabetic therapies have become available. Therefore, at the time of submission of the marketing application for products intended for the treatment of type 2 diabetes mellitus, we recommend that phase 2/3 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. Larger exposures may be required if there are premarketing safety signals in the non-clinical data or in the clinical trials or if there are safety concerns with related compounds or based on the product's mechanism of action.

### **HbA1c as the Primary Efficacy Endpoint**

As mentioned above, all FDA-approved drugs for the treatment of diabetes are indicated to improve glycemic control. Recently, FDA has requested changes to the labeling of all drugs developed for the treatment of type 2 diabetes to accurately and succinctly reflect the basis of approval for these agents. Specifically, the indication section has been simplified so that all the separate indications (e.g., monotherapy, combination therapy, and initial or second-line therapy) are replaced by a single indication: "Drug X is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." In addition, under the "Warnings and Precautions" section of these labels, we have requested that sponsors add the statement "There have been no clinical studies establishing conclusive evidence of

macrovascular risk reduction with DRUG X or any other oral antidiabetic drug” to remind healthcare providers of the limitations of the currently available data. The labels do not contain any wording suggesting an improvement in the long-term sequelae of diabetes.

### **Current Approach to Premarketing and Postmarketing Safety Evaluation**

We typically rely predominantly on HbA1c when assessing the benefit of an antidiabetic drug. However, we could decide that a company must show that the drug has additional benefits beyond HbA1c if the drug has substantial safety issues. As discussed in the draft guidance, we recognize that diabetes is associated with an increased risk of microvascular and macrovascular complications and that reducing these long-term complications is an important goal of disease management. However, because diabetes is a progressive disease that typically requires multiple drug therapy, we also see value in treatments that control day-to-day hyperglycemia and its associated symptoms, particularly treatments that do not cause weight gain or significant hypoglycemia. We consider the need for additional trials beyond those typically required in a type 2 diabetes development program if there are safety concerns that question reliance on HbA1c alone (e.g., if there are important non-clinical or clinical safety signals, concerns related to the mechanism of action of the product, or concerns based on a related product). The timing of this investigation (pre-approval or post-approval) depends on several factors, such as the basis for requesting such a trial and whether the treatment offers a major advance over existing therapies.

### **Challenges with Current Clinical Trials in Patients with Type 2 Diabetes**

Clinical trials in patients with type 2 diabetes have inherent challenges related to the underlying characteristics of the disease. First, most of the phase 3 diabetes trials are placebo-controlled (e.g., placebo add-on to existing background antidiabetic therapy). Some patients may require discontinuation of effective therapy for the purpose of becoming eligible for inclusion in the trial. These patients are likely to experience significant worsening of glycemic control when the antidiabetic medication(s) are discontinued. Also, patients (particularly those randomized to placebo) must be protected from exposure to prolonged hyperglycemia, which may have short-term and long-term ramifications. Several design features protect patients from prolonged hyperglycemia including the upper limit of HbA1c acceptable for enrollment in the trial, the duration of the placebo-controlled portion of the trial, and the use of glycemic rescue criteria that prompt discontinuation from the study or initiation of glycemic rescue therapy (which, thereafter, confounds the assessment of efficacy and safety). The glycemic rescue criteria need to balance the ethics of continued hyperglycemia with the feasibility of the trial if many patients require discontinuation.

Another important and somewhat related challenge pertains to the progressive nature of type 2 diabetes and the expected worsening of glycemic control over time. This is particularly relevant for trials designed to obtain long-term (>6-month) efficacy and safety data. Because patients cannot ethically be exposed to worsening, prolonged hyperglycemia, additional antidiabetic agents are typically needed over time. As a

result, long-term cardiovascular trials will likely need to compare one drug within a multidrug regimen with other available therapies, making demonstration of the efficacy and safety of any single drug a formidable task.

## **CARDIOVASCULAR ASSESSMENT FOR MEDICATIONS FOR TYPE 2 DIABETES**

This section introduces some concepts that relate to the cardiovascular assessment for drugs and biologics developed for the treatment of type 2 diabetes. Additional concepts and important considerations are expected to emerge from the presentations and panel discussion at the advisory committee meeting.

### **Cardiovascular vs. Non-cardiovascular Complications of Diabetes**

Although the current advisory committee meeting will focus on the cardiovascular complications of type 2 diabetes, treatments for type 2 diabetes that positively impact some of the other chronic, disabling complications of diabetes can have merit, even if these therapies have a neutral cardiovascular effect. A more challenging question is whether there is merit in a treatment for type 2 diabetes that has a signal for cardiovascular harm but a beneficial effect on a non-cardiac, but important, complication of diabetes. Perhaps this will depend on the uniqueness of the agent (e.g., if there are other agents that offer the same benefit without cardiovascular toxicity), the degree of cardiovascular harm, and whether a unique patient population could be identified in which the benefits of the drug outweigh the risks.

### **Cardiovascular Benefit vs. Absence of Cardiovascular Harm**

A requirement for cardiovascular assessment of treatments developed for type 2 diabetes can be classified into two categories: (1) evidence that a treatment for diabetes reduces cardiovascular events (i.e., that a treatment has a beneficial effect on the macrovascular complications of diabetes) and (2) reassurance that the treatment is unlikely to increase cardiovascular risk. Requiring demonstration of cardiovascular benefit may have major implications on the availability of new treatments for type 2 diabetes. In addition, because conclusive evidence of a reduced risk of macrovascular complications in type 2 diabetes has not yet been established for any of the currently available antidiabetic medications (including insulin), such a regulatory mandate would need to consider what action is necessary for currently approved and marketed therapies.

Reassurance that the treatment is unlikely to increase cardiovascular risk is, in essence, a large cardiovascular safety trial that establishes a predefined level of risk that must be ruled out. Such a study would be powered by the magnitude of the risk one would like to exclude. The smaller the risk one wishes to exclude, the larger the sample size (which could be somewhat reduced by enrolling patients at very high risk for the event of interest). The magnitude of risk one wishes to exclude would need to be prespecified, and these non-inferiority studies would need to be particularly well-designed and well-

conducted, because a poorly executed trial will bias results toward showing no increase in risk between the treatment arms.

Below, we show example calculations of total sample sizes needed to rule out increased risk in a non-inferiority trial using alpha = 0.05 and 90% power based on various annual event rates in a 5 year trial with a 2-year recruitment period. As the treatment of cardiovascular disease and cardiovascular risk factors continues to improve, the expected event rates are likely to be lower in the future, which will result in larger and longer trials than those shown in the table

<b>Total sample sizes for a range of assumed annual event rates and a range of non-inferiority margins</b>				
<b>Annual Event Rate Investigational Agent</b>	<b>Annual Event Rate Comparator</b>	<b>Total Sample Size Needed to Rule Out an Increased Risk of 1.2, 1.3, or 1.4</b>		
		<b>1.2</b>	<b>1.3</b>	<b>1.4</b>
2%	2%	16,600	8,000	5,000
2%	1.75%	>100,000	38,000	15,000
3%	3%	11,000	5,600	3,300
3%	2.8%	48,000	16,000	6,600
4%	4%	8,700	4,300	2,600
4%	3.6%	>100,000	20,000	7,800
5%	5%	6,900	3,400	2,100
5%	4.5%	>100,000	16,400	6,400
6%	6%	5,900	2,900	1,800
6%	5.2%	>100,000	23,000	7,300

### **Patient Population**

The size and power of a clinical trial are affected by the expected event rate of the endpoint of interest. In some trials, the actual event rates have been lower than the anticipated event rates, unexpectedly lowering the power of the study to achieve its primary objectives.

One option to help ensure a sufficient number of primary events is to enroll patients who are more likely to have the event of interest, such as those at increased cardiovascular risk (e.g., known cardiovascular disease, multiple cardiovascular risk factors, elevated C-reactive protein). Another safeguard could be the design of an event-driven trial (which would terminate only when a sufficient number of events has occurred based on prespecified power calculations) instead of a duration-driven trial.

As mentioned above, glycemic deterioration is one of the challenges encountered in long term clinical trials of patients with type 2 diabetes. Even patients with recent onset type 2 diabetes may develop ethically unacceptable hyperglycemia with monotherapy over the course of a several year trial. ADOPT (A Diabetes Outcome Progression Trial) enrolled patients with type 2 diabetes diagnosed within the preceding 3 years (almost one-half of the patients had been diagnosed with type 2 diabetes within the preceding year) and followed these patients for 4-6 years. However, approximately 10-25% of patients across the monotherapy treatment groups (metformin, sulfonylurea, or rosiglitazone) met the primary endpoint of inadequate glycemic control (e.g., consecutive fasting plasma glucose >180 mg/dL after at least 6 weeks of treatment at the maximum tolerated dose of study medication).

Perhaps enrollment of patients earlier in the spectrum of their disease (e.g., impaired glucose tolerance) may be one option for limiting the extent of glycemic deterioration with monotherapy during a multi-year trial. However, if a cardiovascular trial predominantly enrolls patients with pre-diabetes, there may be a question of generalizability to patients who have overt diabetes or those with longstanding disease. In addition, these patients may have a lower baseline risk for cardiovascular disease than those who are further along in the disease process, which may necessitate a very large sample size or enrollment of patients with other risk factors (e.g., established heart disease) that will reduce the likelihood of futility. As an example, DREAM enrolled patients with pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance) and no prior history of cardiovascular disease. In this low-risk patient population, only 55 (1.0%) of the approximately 5,300 patients randomized to rosiglitazone or placebo experienced myocardial infarction, stroke, or cardiovascular death over a median follow-up of 3 years, an event rate that would be too low for a dedicated cardiovascular trial of similar scope.

### **The Primary Endpoint**

In cardiovascular trials, as in all trials, the primary endpoint should be predefined, justified, and accurately captured and analyzed. Powering the study on an individual type of event (e.g., myocardial infarction) is usually not feasible because of low incidence rates. Therefore, many cardiovascular trials use the MACE (Major Adverse Cardiovascular Event) composite endpoint, which contains all-cause mortality (or cardiovascular death), non-fatal myocardial infarction, and stroke. Some cardiovascular trials include other macrovascular events, such as coronary revascularization and lower-extremity amputation. Use of all-cause mortality as part of the MACE endpoint in a trial with excellent follow-up has the advantage of certainty as to whether the event occurred. However, the cause of death should still be determined in a well-designed trial to ensure that there are no imbalances in particular fatal events (e.g., neoplasms or strokes). Use of cardiovascular death as part of the MACE endpoint may be more relevant but, like myocardial infarction and stroke, requires adjudication by an independent and blinded committee with prespecified case definitions and methodology for ascertaining events (e.g., access to medical records and laboratory data).

If the study is powered on a composite endpoint, there will likely be too few events for the individual components (e.g., acute myocardial infarction) of the composite to provide conclusive evidence of a difference between treatment groups with regard to these individual endpoints. In addition, a difference between treatment groups in the composite endpoint may primarily be driven by one or more of the individual components that comprise the endpoint. As a result, secondary efficacy measures often include analyses of the individual components as initial and total events to determine their contribution to the overall primary efficacy results.

### **The Comparator**

As with all controlled trials, the choice of comparator, whether it be placebo or an active therapy, should be carefully considered and justified. Because type 2 diabetes is a progressive disease and cardiovascular trials are typically many years in duration, it is generally not possible to compare an investigational agent as monotherapy to either placebo monotherapy or a monotherapy active comparator. Instead, it is likely that other antidiabetic agents will need to be added to each of the treatment groups to maintain acceptable long-term glycemic control. However, this practicality related to the natural history of diabetes limits the ability to tease apart the beneficial and detrimental effects of the investigational agent from among those of the other needed antidiabetic agents.

For trials that are designed to rule out an increase in cardiovascular risk relative to an active comparator, the cardiovascular effects of the comparator should ideally be known (which is not the case with the approved treatments for type 2 diabetes) so that the results of the trial can be fully interpreted. For example, if the comparator reduces cardiovascular risk, an investigational agent that appears relatively worse may still have beneficial cardiovascular effects.

### **Glycemic Control and Other Cardiovascular Risk Factors**

As with all clinical trials, factors that affect the outcome of a cardiovascular trial should be comparable across treatment groups to prevent confounding of the results. The protocol should prespecify the treatment goals for the known cardiovascular risk factors and state how comparability of these factors across treatment groups will be assured. Should investigators be encouraged to manage blood pressures, lipid profiles, aspirin use, and other cardiovascular factors to current guidelines (which will not necessarily ensure comparability across treatment groups) or should algorithms be used post-randomization to ensure that these risk factors are equalized across treatment groups? For example, in PROactive the investigators managed cardiovascular risk factors according to current guidelines but were not mandated to equalize these risk factors across treatment groups. However, at the end of the trial, pioglitazone significantly reduced HbA1c, improved serum triglycerides and HDL cholesterol, and reduced the LDL-cholesterol/HDL cholesterol ratio relative to placebo, raising questions as to whether the favorable trend in PROactive is entirely attributable to pioglitazone or to the better control of established cardiovascular risk factors. Management of cardiovascular risk factors can be particularly challenging when the investigational agent affects

metabolic parameters (e.g., blood pressure, lipids) in addition to HbA1c. For example, if an antidiabetic agent also increases low density lipoprotein cholesterol or blood pressure, comparable management of cardiovascular risk factors across treatment groups would be expected to result in more use of lipid lowering drugs (e.g., statins) and blood pressure lowering drugs (e.g., angiotensin converting enzyme inhibitors) in the group receiving the investigational agent (which may confound the results).

As mentioned above, ACCORD has raised the possibility of a HbA1c threshold below which there may be an adverse effect on mortality, although this preliminary finding has not been corroborated by an interim analysis of ADVANCE. Nonetheless, these findings (if confirmed when the trial results are finalized) should be taken into account when deciding on the optimum glycemic target in future cardiovascular trials in patients with type 2 diabetes at high risk of cardiovascular disease. In addition, the protocol should prespecify the HbA1c target for each treatment group and, for placebo-controlled trials, clarify how differing glycemia in the active treatment arm and placebo arm will be handled.

### **Timing and Circumstances of Cardiovascular Assessment**

If the advisory committee panel recommends cardiovascular assessment for agents developed for the treatment of type 2 diabetes, the panel should consider whether all or only some antidiabetic agents should undergo this assessment. Should all agents developed for the treatment of type 2 diabetes undergo cardiovascular assessment because of the underlying increased risk of cardiovascular disease in this patient population? Or, should cardiovascular assessment only be requested if there are concerns for cardiotoxicity based on non-clinical findings, data from clinical trials, the mechanism of action of the drug, or known issues with related compounds? Recently, we required a company to perform a phase 3 cardiovascular outcomes trial because of safety concerns based on data from the non-clinical studies and phase 2 trials. The company decided to halt clinical development of the drug. Some may conclude that establishing this hurdle of long, costly trials for drugs that have no suggestion of cardiotoxicity will stifle drug development for type 2 diabetes.

Consideration should also be given as to whether cardiovascular assessment will be needed for currently marketed antidiabetic drugs. As discussed above, questions regarding cardiovascular safety have been raised with sulfonylureas, the combination of metformin and sulfonylurea, and rosiglitazone (with regard to rosiglitazone, FDA has asked GlaxoSmithKline, the manufacturer of rosiglitazone, to conduct a more definitive cardiovascular trial).

If the advisory committee panel recommends cardiovascular assessment for agents developed for the treatment of type 2 diabetes, the panel should also consider the timing of such an assessment relative to marketing approval (pre-approval vs. post-approval). Some factors that may weigh on this determination relate to the strength and timing of a safety signal (for trials that are being conducted on the basis of a cardiovascular signal), the intent of the trial (whether the trial is designed to show

cardiovascular benefit or cardiovascular harm) and how results may be handled (e.g., if a post-approval trial is designed to show cardiovascular benefit, how will the marketing of the drug be handled if the trial shows neutral effects on the cardiovascular system?). Last year, Congress passed the FDA Amendments Act (FDAAA), which gives FDA new authority to require certain postmarketing studies or clinical trials at the time of approval of a drug or biologic if such studies are necessary to further investigate the safety of the product (in general, FDA cannot require postmarketing studies for efficacy). FDA is in the process of interpreting and implementing this new authority.

## **CONCLUSIONS**

Type 2 diabetes affects millions of people in the United States, causing considerable morbidity and mortality. Cardiovascular disease accounts for most deaths among people with diabetes. Therefore, the question of cardiovascular assessment of drugs and biologics developed for the treatment of type 2 diabetes is of high public health importance. We look forward to a thorough and reasoned discussion of this complex, important matter and your recommendations. Thank you in advance for the vital public health contribution you are making through your participation in this important meeting.

## **“POINTS FOR DISCUSSION”**

1. What specific cardiovascular assessments should be required as part of the approval process for drugs and biologics developed for the treatment of type 2 diabetes, and why?
2. Should these cardiovascular assessments occur prior to approval of new treatments for type 2 diabetes or during the post-approval setting?
3. Should these cardiovascular assessments apply to every new treatment for type 2 diabetes or only to those treatments that have a scientific basis for these assessments?
4. Should these cardiovascular assessments be applied to already marketed treatments for type 2 diabetes?
5. Design considerations for a cardiovascular trial:
  - Should the trial’s objective be to show cardiovascular benefit or rule out an increase in cardiovascular risk? If the objective is to rule out a prespecified magnitude of increase in cardiovascular risk, what is an acceptable magnitude of increased risk?
  - What should the primary endpoint be?
  - What type of patient population should be enrolled?
  - Which treatment comparator(s) should be used?
  - How will deteriorating glycemic control be handled?
  - Should investigators be encouraged to manage blood pressures, lipid profiles, aspirin use, and other cardiovascular factors to current guidelines (which will not necessarily ensure comparability across treatment groups) or should algorithms be used post-randomization to ensure that these risk factors are equalized across treatment groups?
  - Are there other critical features that should be considered when designing these trials?
6. Should cardiovascular endpoints be blindly and independently adjudicated in phase 2 and 3 clinical trials of all treatments developed for type 2 diabetes?

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# **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)**

**February 2008  
Clinical/Medical**

# **Guidance for Industry**

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

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

**February 2008  
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1 **Guidance for Industry<sup>1</sup>**  
2 **Diabetes Mellitus: Developing Drugs and Therapeutic**  
3 **Biologics for Treatment and Prevention**  
4  
5  
6

7  
8 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current  
9 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to  
10 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of  
11 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA  
12 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call  
13 the appropriate number listed on the title page of this guidance.  
14

15  
16  
17  
18 **I. INTRODUCTION**  
19

20 This guidance provides recommendations for the development of drugs and therapeutic biologics  
21 regulated within the Center for Drug Evaluation and Research at the Food and Drug  
22 Administration (FDA) for the treatment and prevention of diabetes mellitus. The intention of  
23 this guidance is to serve as a focus for continued discussions among the review divisions,  
24 pharmaceutical sponsors, academic community, and the public.<sup>2</sup> The organization of the  
25 guidance parallels the development plan for a particular drug or biologic. In the following  
26 discussion, we briefly describe type 1 and type 2 diabetes mellitus and treatment goals, discuss  
27 issues relevant to preclinical development, and then provide guidance on issues related to trial  
28 design, endpoints appropriate for different phases of development, and eligible populations.  
29 These issues are addressed for both type 1 and type 2 diabetes mellitus.  
30

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

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<sup>1</sup> 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.

<sup>2</sup> 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.

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39

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

42

43 • A comprehensive treatment strategy involves dietary changes and interventions other  
44 than medications.

45

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

48

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

55

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

60

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

64

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

74

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

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<sup>3</sup> 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>.

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

85  
86 FDA's guidance documents, including this guidance, do not establish legally enforceable  
87 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should  
88 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
89 cited. The use of the word *should* in Agency guidances means that something is suggested or  
90 recommended, but not required.

91

92

## 93 **II. BACKGROUND AND TREATMENT GOALS**

94

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

101

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

106

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

112

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

---

<sup>4</sup> N Engl J Med, 1993, 329:977-986

<sup>5</sup> Diabetes, 2006, 55:3556-3565

<sup>6</sup> Lancet, 1998, 352:837-853 and 854-865

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

131

132

### **III. DIAGNOSING DIABETES MELLITUS**

134

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

138

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

144

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

147

148 Other important definitions include:

149

- 150 • Impaired glucose tolerance: a plasma glucose equal to or greater than 140 mg/dL (7.8  
151 mmol/L) but less than 200 mg/dL (11.1 mmol/L) at 2 hours in the oral glucose tolerance  
152 test
- 153 • Impaired fasting glucose: fasting plasma glucose (FPG) equal to or greater than 100  
154 mg/dL (5.6 mmol/L) but less than 126 mg/dL
- 155 • Gestational diabetes mellitus (GDM):
  - 156 – According to the ADA criteria, GDM is detected based on two or more values  
157 meeting or exceeding any of the following threshold values during a 75- or a 100-g  
158 oral glucose tolerance test:
    - 159 ▪ FPG greater than or equal to 95 mg/dL (5.3 mmol/L)
    - 160 ▪ Plasma glucose greater than or equal to 180 mg/dL (10 mmol/L) at 1 hour
    - 161 ▪ Plasma glucose greater than or equal to 155 mg/dL (8.6 mmol/L) at 2 hours
    - 162 ▪ Plasma glucose greater than or equal to 140 mg/dL (7.8 mmol/L) at 3 hours (the  
163 optional 3-hour time point only applies to the 100-g test)
  - 164 – GDM is diagnosed by the WHO criteria if FPG is greater than or equal to 126 mg/dL  
165 (7.0 mmol/L) or if the 2-hour glucose after a 75-mg oral glucose load is greater than  
166 or equal to 140 mg/dL (7.8 mmol/L)

167

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

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

174  
175

#### 176 **IV. PRECLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES<sup>7</sup>**

177

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

182

##### 183 **A. Type 1 Diabetes Mellitus**

184

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

194

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

198

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

202

##### 203 **B. Type 2 Diabetes Mellitus**

204

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

210

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

---

<sup>7</sup> See 21 CFR part 58 for the FDA's good laboratory practices for conducting nonclinical laboratory studies.

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

219

### **C. Insulins and Insulin Analogues**

220

221  
222 In vitro studies of insulins and insulin analogues can be useful for describing insulin receptor  
223 binding affinities and dissociation rates, receptor autophosphorylation, phosphorylation of  
224 signaling elements, and promotion of mitogenesis. In addition, for insulin analogues, affinity to  
225 the insulin receptor relative to other targets of insulin action, such as the insulin-like growth  
226 factor 1 receptor, should be characterized and compared to that found with native-sequence  
227 human insulin.

228

229

## **V. CLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES<sup>8</sup>**

230

### **A. Trial Design and Conduct**

231

232

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

233

234  
235 Individualization of therapy is essential to optimum control of glycemia in patients with diabetes.  
236 Consequently, some studies permit use of other antidiabetic therapies before randomization to  
237 ensure enrollment of patients whose diabetes control will be acceptable for clinical  
238 investigational purposes. Such studies often allow entry of patients using a specific class of  
239 antidiabetic drugs (e.g., baseline metformin therapy in patients with type 2 diabetes), to which  
240 either the investigational drug (or biologic) or a placebo will be added during randomization.  
241 Addition of new noninvestigational drugs or substantial changes in the dose of permissible  
242 baseline drug therapy after randomization may confound the results and interpretability of both  
243 efficacy and safety. For the results to be interpretable, any changes to these other therapies  
244 should be carefully documented.

245

246  
247 When planning exploratory phase 2 studies, we recommend that sponsors include a run-in period  
248 before randomization to allow for diabetes education and for optimization of compliance with  
249 diet and exercise. This 6- to 8-week run-in period also is intended to allow for stabilization of  
250 parameters of metabolic control (e.g., HbA1c, fructosamine), so that the magnitude of the effect  
251 of different doses of the product can be most accurately estimated. Absence of this run-in period  
252 can result in overestimation of the *real world* treatment effects, given the intensive reinforcement  
253 of hygienic measures and compliance during clinical trials that is not reflected in typical  
254 treatment settings. In addition, placebo run-in periods in phase 3 studies can help screen out  
255 noncompliant subjects. We recommend providing efficacy data with a new product that result  
256 from rigorously designed studies.

257

---

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

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258 Adequate control of diabetic comorbidities in accordance with current standards of care should  
259 be incorporated in the criteria for eligibility in the study protocol. The addition of therapies to  
260 control diabetic comorbidities after randomization should be carefully documented (as should be  
261 the use of these therapies at baseline), because these therapies may confound the interpretation of  
262 both safety and efficacy of the investigational drug or biologic.  
263

264 Improvement in HbA1c has become the standard surrogate outcome measure in many trial  
265 designs for a variety of therapies. In patients with diabetes, the following situations also can be  
266 considered a benefit of therapy: 1) a meaningful reduction of insulin requirements (in either type  
267 1 or type 2 diabetes), or 2) a reduction in the number or doses of oral antidiabetic agents (in type  
268 2 diabetes mellitus), both in the context of stable or improved HbA1c. Even though HbA1c is  
269 appropriate as a surrogate endpoint in many study designs, documented improvement in a serious  
270 morbidity or mortality related to diabetes (i.e., outcome studies) may be more persuasive  
271 evidence of benefit for drugs in which substantial safety issues or questions arise (see sections  
272 V.B., Study Assessments and Endpoints, and V.E., Sample Size and Study Duration, for  
273 additional considerations).  
274

### 2. *Type 1 Diabetes Mellitus*

275 As stated earlier, insulin is the essential glucose-lowering therapy for the treatment of patients  
276 with type 1 diabetes. Therefore, all experimental treatments for type 1 diabetes (and their  
277 matching placebos, as applicable) that are not insulin analogues or other insulin receptor ligands  
278 should be studied as add-on therapies to insulin.  
279  
280

281 Preclinical data or knowledge of a particular mechanism of action may indicate that an  
282 investigational product has the potential to cause or worsen hypoglycemia, either by binding to  
283 insulin receptors or by affecting other aspects of glucose absorption and metabolism. If the  
284 investigational product is anticipated to have the potential to lead to hypoglycemia, either  
285 directly or through potentiation of insulin effect, the study design should include allowance for  
286 insulin dose adjustments to protect trial subjects from hypoglycemia. However,  
287 pharmacodynamic interactions with insulin, as well as the need to adjust insulin doses to prevent  
288 hypoglycemia, may pose significant challenges for study design, interpretation, and inference of  
289 the new drug's efficacy. For example, given the need to titrate insulin to control for glycemia  
290 and to guard against hypoglycemia, the blinding of subject and investigator to treatment  
291 allocation may not be practical or acceptably safe. Unblinded, controlled trials may be  
292 appropriate in some circumstances, particularly for trials incorporating clearly objective  
293 endpoints. On the other hand, unblinding can severely limit the interpretability of subjective  
294 endpoints (i.e., patient-reported outcomes) that might be incorporated as secondary assessments  
295 of efficacy.  
296  
297

298 In phase 1 and phase 2 trials of products intended to prevent or delay the progression of type 1  
299 diabetes, sponsors are encouraged to conduct randomized, placebo-controlled studies, while  
300 investigating early pharmacodynamic markers of effect as well as the safety of the tested  
301 product.  
302

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### 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.

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349  
350 For either phase 2 or phase 3 studies, regardless of HbA1c at entry, subjects whose  
351 hyperglycemia persists or worsens beyond prespecified thresholds should be appropriately  
352 monitored and treated throughout the study. In developing these escape or rescue criteria, it is  
353 useful to consider that even for drugs that show therapeutic effects only after a matter of weeks  
354 (e.g., thiazolidinediones/PPAR agonists), most responders experience a reduction in fasting  
355 blood glucose of greater than 20 mg/dL (1.1 mmol/L) by 6 weeks. For agents that lower  
356 postprandial rather than fasting glucose levels, a clinically meaningful reduction in HbA1c (e.g.,  
357 0.3 percentage units) also usually is evident by 6 weeks. The following are examples of rescue  
358 criteria based on thresholds for FPG or HbA1c:

- 359
- 360 • FPG greater than 270 mg/dL (15 mmol/L) from baseline to Week 6
  - 361 • FPG greater than 240 mg/dL (13.3 mmol/L) from Week 6 to Week 12
  - 362 • FPG greater than 200 mg/dL (11.1 mmol/L) or HbA1c greater than 8.0 percent from  
363 Week 12 to Week 24
- 364

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

369

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

378

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

392

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

396

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

398

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

403

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

417

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

428

### **B. Study Assessments and Endpoints**

429

430

#### *1. General Considerations*

431

432

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

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

440

441 a. Pharmacokinetics

442

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

450

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

463

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

470

471 b. Pharmacodynamic endpoints and biomarkers

472

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

---

<sup>9</sup> 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>.

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

<sup>11</sup> See 21 CFR part 314 for regulations regarding NDAs.

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

485  
486 Glycated endogenous proteins with turnover rates faster than hemoglobin, such as fructosamine,  
487 can be used as preliminary indicators of a product's effects on integrated glycemic exposures in  
488 early phase studies of limited duration. Demonstration of reductions in HbA1c, with a  
489 concomitant meaningful decrease in mean daily insulin requirements in relevant patients, is  
490 desirable but not necessary for the preliminary inference of efficacy from these early studies.  
491 Changes in FPG, plasma glucose level after a standard meal, plasma glucose level after oral  
492 administration of 75 g of glucose, average blood glucose (mean of seven home measurements  
493 obtained before and after each meal and at bedtime), and fructosamine can be used as primary  
494 measures of efficacy in phase 2 studies. They also can be used as secondary, supportive  
495 measures of efficacy in phase 3 studies.

### 496 c. Efficacy endpoints

497  
498  
499 For purposes of drug approval and labeling, final demonstration of efficacy should be based on  
500 reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which  
501 will support an indication of glycemic control. Superiority or noninferiority hypotheses may be  
502 appropriate depending on the trial design. Refer to section V.G., Important Statistical  
503 Considerations, for a discussion of issues related to noninferiority trials and choice of  
504 noninferiority margins as they relate to studies in diabetes. Also see the ICH guidances for  
505 industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and*  
506 *Related Issues in Clinical Trials*.

### 507 d. Effects on markers of insulin resistance and diabetes comorbidities

508  
509  
510 Treatment-associated reduction in endogenous hyperinsulinemia (in type 2 diabetes) or  
511 improvement in insulin sensitivity are arguably salutary health effects, but do not alone provide  
512 sufficient support of a new agent for approval purposes. Effects of antidiabetic agents on blood  
513 pressure and serum lipids are of obvious importance and can be described in labeling with  
514 disclaimers commensurate with the limitations of the trials regarding extrapolation of findings to  
515 conclusions about ultimate drug effects (i.e., on mortality or irreversible morbidity).

### 516 e. Effect of weight loss on diabetes

517  
518  
519 In recent years, the FDA has recommended to sponsors of weight loss products seeking an  
520 indication for the treatment of type 2 diabetes that they should demonstrate that the product's  
521 effect on glycemic control is independent of weight loss. The FDA has reconsidered the  
522 necessity of this recommendation. The FDA's current thinking is that a sponsor can gain  
523 approval for the treatment of type 2 diabetes for a drug or biologic whose principal mechanism

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

526  
527 The development program to support a diabetes indication for these products should be  
528 comparable to the development programs used for antidiabetic products not intended for weight  
529 loss. For example, the product would need to be studied in subjects with a wide range of body  
530 mass indices (from lean to obese), different duration of diabetes (new onset to long-standing),  
531 and under different conditions of use (monotherapy and combination therapy). Sponsors  
532 interested in the development of weight loss products for the treatment of type 2 diabetes should  
533 discuss their plans with the Division of Metabolism and Endocrinology Products.

534

### 535 2. *Insulins*

536

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

549

#### 550 a. *Insulin mixes*

551

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

564

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

566

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

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

### c. New insulin analogues or insulin receptor binding agonists

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

- 581 1. The risk of hypoglycemia under conditions of use ultimately recommended in labeling,  
582 relative to approved insulin products and regimens. In this regard, both test and control  
583 groups should achieve improved and similar glucose control as assessed by HbA1c.  
584
- 585 2. Pharmacokinetic variability should be evaluated, according to injection site, thickness of  
586 fat layer, and other parameters known to affect absorption, distribution, metabolism, and  
587 excretion characteristics. Additionally, pharmacodynamic characteristics should be  
588 carefully studied to direct dosing interval (for long-acting products) and timing of dosing  
589 relative to meals (for short-acting products). Assessment of insulin receptor binding  
590 (affinity and dissociation rates), receptor autophosphorylation, phosphorylation of  
591 signaling elements and promotion of mitogenesis may add important data to the  
592 characterization of new insulin analogues.  
593
- 594 3. As a complex biological protein, insulin has the potential to be immunogenic. Adequate  
595 assays should be developed that measure antibodies to the test product before the  
596 submission of an application. Antibody titers, the timing of their detection and  
597 disappearance (if applicable), and correlation with pharmacological effects should be  
598 ascertained. The potential for any of the antibodies to neutralize the effects of a new  
599 insulin should be assessed, particularly in the presence of high titers of antibodies, and in  
600 the presence of allergic reactions or suspicion of immune-complex deposition, or  
601 apparent loss of clinical effectiveness.  
602

### d. Inhaled insulins

603  
604  
605  
606 Investigations of insulin delivered by inhalation should include preclinical safety, pulmonary  
607 safety, pharmacokinetics, pharmacodynamics, dose proportionality, and hypoglycemic risk. The  
608 extent of preclinical studies needed depend, in part, on the novelty of the formulation (e.g., what  
609 excipients are used) for the inhaled route. Typically, the minimum preclinical program should be  
610 comprised of two 14-day inhalation studies focusing on the histopathology of the respiratory  
611 tract, followed by a 6-month bridging study in the most appropriate species. The  
612 pharmacokinetics (including bioavailability), pharmacodynamics, and hypoglycemic risk of

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<sup>12</sup> It should be noted that proposed labeling may affect the design of trials using a particular insulin with a particular pump.

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

615  
616 We encourage sponsors of inhaled insulin products to enroll at least some patients with  
617 underlying pulmonary disease, such as chronic obstructive pulmonary disease and asthma, to  
618 assess not only effects of inhaled insulin on their pulmonary function, but also the effects of their  
619 disease on insulin kinetics. Cigarette smoking affects inhaled insulin bioavailability, and airway  
620 status may lead to alterations in drug delivery to the absorption site. Therefore, sponsors should  
621 investigate the potential effect of cigarette smoking and inhalational drugs for pulmonary disease  
622 on the efficacy and safety of the inhaled insulin product, including assessments of the effects on  
623 insulin pharmacokinetic and pharmacodynamic endpoints and the rates and timing of  
624 hypoglycemia.

625  
626 Sponsors developing inhaled insulin products should evaluate the pulmonary safety of these  
627 inhaled insulin products (including excipients). Safety assessments should include pulmonary  
628 function as measured by the full battery of pulmonary function tests, including spirometry, lung  
629 volumes, and diffusion capacity. Serial pulmonary function tests should be performed and the  
630 long-term effects of the inhaled insulin product on pulmonary function should be established.  
631 Additional safety assessments include high resolution computed tomography of the chest at  
632 baseline and on treatment. Because of the potential effects of diabetes mellitus on the pulmonary  
633 system, a comparator group is recommended for these safety assessments. In addition,  
634 assessment of anti-insulin antibody responses is essential in the overall safety assessment of the  
635 inhaled insulins, because the inhaled route may lead to a different propensity toward immune  
636 responses. Pre-use storage and in-use handling conditions during these studies should be  
637 designed to mimic actual use of the products. Accuracy of use and dosing should be assessed  
638 and documented.

639  
640 *3. Noninsulin Products*

641  
642 A reduction in insulin dose is not sufficient stand-alone evidence of efficacy for approval or  
643 labeling of a noninsulin product. In addition to showing a meaningful reduction in the insulin  
644 dose, the drug should be shown to independently reduce HbA1c, or at least show that no increase  
645 in HbA1c accompanies the insulin reduction. In this context, the elimination of the need for  
646 insulin entirely in patients with type 1 diabetes or simplification of the insulin regimen while  
647 maintaining or improving glycemia (i.e., optimum control with a nonintensive insulin regimen  
648 resulting in reduced hypoglycemic risks) is considered clinically meaningful.

649  
650 Novel approaches to the treatment of type 2 diabetes, such as the use of gastrointestinal  
651 neuropeptides or products that inhibit degradation of these peptides, have been shown to have  
652 effects beyond the control of insulin secretion and insulin action, such as rate of gastric  
653 emptying, food intake, and glucose counterregulation. Nonetheless, the recommended endpoints  
654 for approval of such products specifically for the treatment of diabetes will be the same as the  
655 traditional approaches used in the development of currently approved insulin secretagogues or  
656 insulin sensitizers (i.e., change from baseline in HbA1c).

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

661  
662 A fixed-dose combination (FDC) of a new agent and an established agent should be studied in a  
663 manner that demonstrates that each of the individual components makes a contribution to the  
664 claimed effects of the FDC, and that the combination is acceptably safe. If the FDC consists of  
665 two currently approved and marketed drugs, and will be labeled for the same indications and  
666 patient populations as the separately approved therapies, and the safety and efficacy of these  
667 drugs have been established in co-administration, a full factorial efficacy trial may not be  
668 necessary to demonstrate the contribution of each FDC component to the claimed effects. In this  
669 setting, pharmacokinetic data defining any drug-drug interactions between the components  
670 generally should be sufficient. There are exceptions to this approach, such as situations where  
671 there are potential safety concerns with the co-administration of the two components. In  
672 addition, we recommend nonclinical toxicity studies for certain FDC products, even when the  
673 components are previously marketed drugs or biologics. For details, see the guidance for  
674 industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

675  
676 4. *Prevention of Type 1 Diabetes Mellitus or Preservation of Beta-Cell Function in*  
677 *Patients Newly Diagnosed with Type 1 Diabetes Mellitus*

678  
679 Studies of products aimed at the prevention of type 1 diabetes in high-risk subjects, or at  
680 preservation of beta-cell function in recent-onset type 1 diabetes with remaining endogenous  
681 insulin reserve, should evaluate metabolic outcomes, such as the following:

- 682
- 683 • Fasting and postprandial glucose and glycemic excursion
  - 684 • Frequency and severity of hypoglycemic events
  - 685 • Fasting and stimulated C-peptide levels
  - 686 • Daily insulin requirements in the subjects with diabetes, expressed in international units  
687 (IU) per kilogram of body weight
- 688

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

697  
698 Phase 2 and phase 3 studies of immunosuppressive products or immunomodulators for the  
699 prevention of type 1 diabetes also should evaluate their effects on general immune responses,  
700 including T-cell proliferation in response to conventional antigens, immunoglobulin subclasses,  
701 and titers of antibodies in response to primary antigens and recall responses. Depending on the  
702 known or suspected mechanism of action, as well as findings from previous clinical and  
703 nonclinical studies, other endpoints should be considered in the overall safety evaluation. These

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

707  
708 Phase 3 studies of investigational products intended for the prevention of type 1 diabetes mellitus  
709 in high-risk individuals typically will designate a delay in the diagnosis of type 1 diabetes as the  
710 criterion for defining efficacy. An appropriate endpoint to support efficacy can be the proportion  
711 of subjects in the treatment groups who develop frank diabetes after a prespecified period of time  
712 (the period being at least 1 year) compared across treatment groups.

713  
714 Preservation of beta-cell function in patients recently diagnosed with type 1 diabetes is being  
715 actively pursued by the pharmaceutical industry and in government and academic collaborations.  
716 We acknowledge the evidence from the DCCT and other studies that have demonstrated clinical  
717 benefits in patients who achieve better glucose control, in terms of delaying the chronic  
718 complications of diabetes. Similarly, we acknowledge that patients who had greater preservation  
719 of endogenous insulin secretory function (as assessed by C-peptide in the serum) at baseline  
720 were more likely to have lower HbA1c with fewer hypoglycemic events over time.

721  
722 Phase 3 development of investigational products intended to preserve endogenous beta-cell  
723 function in patients with newly diagnosed type 1 diabetes can designate a measure of C-peptide  
724 (e.g., AUC following a standardized mixed meal tolerance test) compared to control at 1 year as  
725 the primary efficacy endpoint. Sponsors should analyze the change from baseline to the study  
726 endpoint (typically 1 or 2 years) in both treatment groups, and demonstrate maintenance of C-  
727 peptide or an attenuation in the rate of decline compared to the control group. For this endpoint  
728 to provide convincing evidence of preserved endogenous beta-cell function, the trials should  
729 demonstrate a clinically meaningful reduction in mean daily insulin requirements accompanied  
730 by similar magnitude of glycemic control compared to the control arm. A favorable effect on  
731 these endpoints should be balanced against the risks of the particular intervention being tested.  
732 Subjects should continue to be monitored for an extended period (2 to 4 years or longer) to  
733 investigate both the durability of the effect and whether they experience a lower frequency of  
734 hypoglycemia, diabetic ketoacidosis, and long-term complications of diabetes.

735  
736 As with most prevention claims, we generally will accept fewer risks for treatments intended to  
737 prevent type 1 diabetes compared with treatments that preserve endogenous beta-cell function in  
738 patients already diagnosed with type 1 diabetes.<sup>13</sup> This distinction is made because some  
739 individuals exposed to prevention strategies have no chance for benefit, as they are not  
740 inexorably destined to develop diabetes. Therefore, some patients (who presumably cannot be  
741 pre-identified) would be subject to the risks of the treatment with no hope of benefit.

### 742 743 5. *Prevention of Type 2 Diabetes Mellitus*

744  
745 In phase 3 studies for products intended to prevent the development of type 2 diabetes in high-  
746 risk individuals (such as individuals with impaired glucose tolerance, impaired fasting glucose,  
747 or with a history of gestational diabetes), potential endpoints supporting approval include delay  
748 in type 2 diabetes diagnosis or reduction in the proportion of patients diagnosed with type 2

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<sup>13</sup> See 21 CFR 56.111(a)(1)(i) regarding the unnecessary exposure of subjects to risk.

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

754  
755 For prevention studies of drugs with a pharmacological action of improving glycemic parameters  
756 (e.g., approved treatments used in the prevention setting), improvement in clinical parameters  
757 beyond those that would be expected from glucose lowering alone should be demonstrated, since  
758 the forestalling of a biochemical diagnosis of frank diabetes from the prediabetic state may not  
759 itself be a sufficiently tangible benefit against which one can appropriately judge the risks. Such  
760 supportive evidence can include a demonstration of a durable delay in the onset of type 2  
761 diabetes after the prevention therapy is stopped, or can show that the delay in progression to type  
762 2 diabetes mellitus is accompanied by other indicators of clinical benefit (e.g., delay or lessening  
763 in microvascular or macrovascular complications). That said, the more modest the treatment  
764 effect, the higher the standard for safety and the more restricted (e.g., to subjects at highest risk  
765 for near-term conversion to frank type 2 diabetes) the indicated target population.

### **C. Metabolic Syndrome**

766  
767  
768  
769 The term *metabolic syndrome* represents a cluster of laboratory and clinical findings that serve as  
770 markers for increased risk for cardiovascular disease and type 2 diabetes, and, depending upon  
771 the definition used, is prevalent in as much as 25 percent of the adult American population. A  
772 host of therapies now exist to address individual or multiple components of the syndrome (e.g.,  
773 lipid-altering agents, antihypertensives, insulin sensitizers). A therapeutic product intended to  
774 treat the metabolic syndrome ideally should normalize or improve all components of the  
775 syndrome and ultimately be shown to prevent the development of type 2 diabetes and reduce  
776 cardiovascular morbidity and mortality. As mentioned in the Introduction section, a full  
777 discussion of this syndrome is beyond the scope of this guidance.

### **D. Study Population Considerations**

778  
779  
780  
781 In general, premarket study populations should be representative of the population for which the  
782 product, once approved or licensed, is intended. Two specific considerations with regard to  
783 study populations are listed below.

#### ***1. Pediatric Populations***

784  
785  
786  
787 Under the Pediatric Research Equity Act (PREA), section 505B of the Federal Food, Drug, and  
788 Cosmetic Act (the Act) (21 U.S.C. § 355c), as amended by the Food and Drug Administration  
789 Amendments Act of 2007 (Public Law No. 110-85), sponsors must study a product in all  
790 relevant pediatric populations when submitting an application under section 505 of the Act (21  
791 U.S.C. § 355) or section 351 of the Public Health Service Act (42 U.S.C. § 282) for a new active  
792 ingredient, new indication, new dosage form, new dosing regimen, or new route of  
793 administration. However, the PREA requirements may be waived or deferred in certain

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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.

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### **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.

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

890  
891 Regardless of the choice of control used in phase 3 studies, the duration of the controlled phase  
892 in an efficacy trial is an important issue. In studies of recently approved products that lasted  
893 more than 1 year, sponsors have typically conducted a randomized, controlled study lasting at  
894 least 6 months, followed by an extension phase lasting 6 months or longer. Sponsors should  
895 weigh the advantages and disadvantages when deciding between a controlled and uncontrolled  
896 extension phase, and should ensure that the chosen design will provide interpretable long-term  
897 data.

898  
899 Although uncontrolled extensions still allow for an expanded safety database (both in numbers  
900 exposed and duration of treatment), interpretability of both efficacy and safety data in an  
901 uncontrolled study period is limited by lack of a control group.

902  
903 Since diabetic populations are prone to certain morbidities (such as cardiovascular disease and  
904 renal dysfunction), only longer term comparative safety data would allow for an assessment of  
905 the relative rates of these common, but important morbidities in subjects assigned to the  
906 investigational agent versus the control. Studies lasting longer than 1 year that employ an  
907 appropriate active comparator with adjudication of safety endpoints of interest by an endpoint  
908 committee blinded to treatment are strongly encouraged and may be needed if preclinical or  
909 phase 2 or phase 3 studies reveal a safety signal. Longer term controlled data also allow for  
910 better assessments of the comparative durability of effects on glycemia. Such studies, however,  
911 may have high rates of dropouts; therefore, treatment algorithms for maintenance of adequate  
912 glycemic control should be considered in the study design.

913  
914 Of note, all drugs currently approved for the treatment of diabetes are indicated to improve  
915 glycemic control. The FDA currently bases approval of these drugs and biologics on HbA1c.  
916 We recognize that reducing long-term macrovascular complications in patients with diabetes  
917 should be an important goal of disease management. Although a recommendation to  
918 demonstrate macrovascular risk reduction premarketing may delay availability of many effective  
919 antidiabetic drugs for a progressive disease that often requires multiple drug therapy, sponsors  
920 should conduct large outcomes trials before submission of marketing applications for drugs in  
921 development that show nonclinical or clinical evidence of increasing macrovascular risk.  
922 Therapies that have not demonstrated a deleterious effect on cardiovascular outcome during  
923 extensive premarketing evaluation may need further post-approval assessment for their effects on  
924 long-term macrovascular disease. Interpretation of data resulting from such studies may be  
925 complicated by the need to identify conclusively the effect of a single drug within a multidrug  
926 regimen that usually is part of an adequate treatment for a complex, progressive condition such  
927 as type 2 diabetes and its associated comorbidities.

928  
929 Phase 3 studies with a 6-month, placebo-controlled phase can be extended into a rigorously  
930 controlled, randomized, double-blind active-controlled phase that employs double-dummy  
931 agents.

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932  
933 Before submitting a marketing application, assessment of the immunogenic potential of  
934 therapeutic proteins, including insulins and insulin analogues, and of monoclonal antibodies,  
935 should be performed over a period of at least 6 to 12 months in study subjects reasonably  
936 representative of the intended population. If adverse events characteristic of allergic or  
937 immunologic reactions are identified, we may ask for additional studies, with durations longer  
938 than 12 months. These additional studies may need to be conducted before submission of a  
939 marketing application or as a postmarketing commitment, based on the overall analysis of the  
940 risks and benefits of the product. The appropriate timing of additional studies in these  
941 circumstances can be discussed with the FDA at a pre-BLA meeting, pre-NDA meeting, or other  
942 similar advice meeting.

943  
944 A licensed monoclonal antibody used only in allogeneic transplantation, where patients are  
945 immunosuppressed through multiple modalities, should be newly evaluated for immunogenic  
946 potential in the diabetic or high-risk prediabetic population.

### **F. Premarketing Safety Evaluation**

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

955  
956 Additionally, new antidiabetic agents, used alone or in combination with approved agents,  
957 should be assessed for their tendency to cause or augment hypoglycemia, an event that is part of  
958 diabetes management. Acceptable hypoglycemic risk, although not defined in absolute terms,  
959 usually is risk that is comparable to existing therapies, to which the new drug is directly  
960 compared, when both drugs are used in trials in which subjects are treated to identical glycemic  
961 goals with comparable glycemic outcomes (e.g., ADA guidelines). Furthermore, patients with  
962 diabetes often use multiple medications, not only to control glycemia, but also to address  
963 cardiovascular disease risk factors, such as hypertension and hyperlipidemia, and microvascular  
964 and neuropathic complications of diabetes. Interactions between the new investigational product  
965 and these other medications can result in adverse events that should be considered, documented,  
966 and reported. Finally, worsening of comorbid conditions other than diabetes should be  
967 ascertained, reported, and analyzed in comparison to the rates of similar adverse events in the  
968 control group.

969  
970 Findings of specific safety signals with a product or related product (whether cardiovascular or  
971 otherwise) during any development phase should be investigated further in controlled studies  
972 enriched with the population at risk for the signal. The timing of this investigation (pre-approval  
973 or post-approval) depends on the strength and nature of the signal and whether the treatment  
974 offers a major advance over existing therapies.

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976 For general issues related to risk assessment, pharmacovigilance, and risk minimization plans,  
977 refer to the following guidances:<sup>14</sup>

- 978
- 979 • Guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic*
- 980 *Assessment*
- 981 • Guidance for industry *Development and Use of Risk Minimization Action Plans*
- 982 • Guidance for industry *Premarketing Risk Assessment*
- 983 • ICH guidance for industry *E2C Clinical Safety Data Management: Periodic Safety*
- 984 *Update Reports for Marketed Drugs* and addendum
- 985 • ICH guidance for industry *E2E Pharmacovigilance Planning*
- 986

### **G. Important Statistical Considerations**

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988

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

#### *1. Sample Size*

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994

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

998

999 Sample sizes for noninferiority trials should be based on one-sided significance levels of 2.5  
1000 percent and at least 80 percent power. Because the calculations depend on the noninferiority  
1001 margin, the sponsor should provide a rationale for the choice of margin and should be guided by  
1002 the concept that this margin should not represent a clinically meaningful loss of efficacy relative  
1003 to the active control. Typically, we accept a noninferiority margin of 0.3 or 0.4 HbA1c  
1004 percentage units provided this is no greater than a suitably conservative estimate of the  
1005 magnitude of the treatment effect of the active control in previous placebo-controlled trials. For  
1006 additional guidance on noninferiority studies, refer to ICH E9 and ICH E10.

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

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1009

1010

1011 We encourage sponsors to obtain HbA1c measurements in all subjects, including those who  
1012 withdraw prematurely or receive rescue medication because of poor glycemic control, near the  
1013 calendar date at which they were scheduled to complete the trial. Complete data collection can  
1014 facilitate the desired goal of a true intent-to-treat analysis (i.e., the analysis of all randomized  
1015 subjects) and also serve as a measure of good clinical trial conduct.

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<sup>14</sup> See <http://www.fda.gov/cder/guidance/index.htm>.

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### 1017 3. *Analysis Methods*

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1019 We recommend that the analysis of HbA1c change from baseline adjust for differences between  
1020 groups in HbA1c at baseline (e.g., ANCOVA with baseline HbA1c as a covariate in the model).  
1021 Factors in addition to treatment can be included in the model as appropriate, particularly  
1022 variables with substantial correlation with the outcome and independence from the treatment,  
1023 and variables used to stratify the randomization.

1024

1025 Although every reasonable attempt should be made to obtain complete HbA1c data on all  
1026 subjects, dropouts are often unavoidable in diabetes clinical trials. The resulting missing data  
1027 problems do not have a single general analytical solution. Statistical analysis using last  
1028 observation carried forward (LOCF) is easy to apply and transparent in the context of diabetes  
1029 trials. Assuming an effective investigational therapy, it is often the case that more placebo  
1030 patients will drop out early because of a lack of efficacy, and as such, LOCF will tend to  
1031 underestimate the true effect of the drug relative to placebo providing a conservative estimate of  
1032 the drug's effect. The primary method the sponsor chooses for handling incomplete data should  
1033 be robust to the expected missing data structure and the time-course of HbA1c changes, and  
1034 whose results can be supported by alternative analyses. We also suggest that additional analyses  
1035 be conducted in studies with missing data from patients who receive rescue medication for lack  
1036 of adequate glycemic control. These sensitivity analyses should take account of the effects of  
1037 rescue medication on the outcome.

1038

1039 The full analysis set as described in ICH E9 should be the primary analysis population for both  
1040 superiority and noninferiority analyses. Supporting analyses in one or more subsets of the full  
1041 analysis set also can be conducted and are encouraged in noninferiority analyses.

1042

1043 Analyses of data from studies using withdrawal designs depend on the type of primary endpoint.  
1044 Survival analysis methods should be used if therapeutic failure times are collected. If the  
1045 endpoint is therapeutic success or failure, categorical methods should be used.

1046

1047 If statistical significance is achieved on the primary endpoint, secondary assessments of efficacy  
1048 can be considered. Type 1 error should be controlled across all clinically relevant secondary  
1049 efficacy endpoints that may be intended for product labeling to provide statistical support for  
1050 their inclusion in the label.

1051

1052 The sponsor should report least-square mean treatment differences and associated 95 percent  
1053 confidence intervals from the primary statistical model for all continuous efficacy endpoints.

1054

1055 Rates of hypoglycemia should be compared statistically between groups. If count data are  
1056 analyzed, the sponsor should use robust statistical methods that take account of the dependence  
1057 of events within individual patients.

1058

### 1059 4. *Graphical Methods*

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1061 Graphical methods showing treatment effects over time for study completers should be  
1062 presented. Additional graphical presentations of the data to illustrate the effect of the drug are

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1063 encouraged. For examples, see the guidance for industry *Clinical Studies Section of Labeling for*  
1064 *Human Prescription Drug and Biological Products — Content and Format.*  
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**APPENDIX A:**

**PRECLINICAL CONSIDERATIONS FOR PEROXISOME  
PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS**

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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 PPAR $\alpha$ , PPAR $\gamma$ , PPAR $\alpha$  and  $\gamma$  (dual agonist), or PPAR $\alpha$ ,  $\gamma$ , and  $\delta$  (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,<sup>15</sup> 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.

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<sup>15</sup> See the ICH guidance for industry *S4 Duration of Chronic Toxicology Testing in Animals (Rodent and Nonrodent Toxicity Testing)*.

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- 1110 – Characterization in animals and humans of the potential for plasma volume  
1111 expansion.  
1112
- 1113 • **Hepatic Effects.** The cause of any liver enlargement observed should be determined  
1114 (peroxisome proliferation, mitochondrial proliferation/swelling). Liver tissues should be  
1115 stained to detect the presence of fatty changes. The sections can be stained with Sudan  
1116 IV or Oil Red-O. Liver enzyme levels and biochemical markers of peroxisome  
1117 proliferation (Acyl CoA and CYP 4A) should be analyzed in rodents and nonrodents.  
1118
- 1119 • **Bone Marrow Effects.** Bone marrow smears from femur and sternum should be  
1120 quantified to assess for effects on cellularity.  
1121
- 1122 • **Renal Effects.** Drug-related increases in urothelial tumors have been observed in rodent  
1123 carcinogenicity studies with PPAR agonists. If such tumors are observed, mechanistic  
1124 studies (e.g., urinalysis assessing crystalluria, urine pH, urinary electrolytes) are  
1125 recommended.  
1126
- 1127 • **Muscle Toxicity.** Skeletal and/or cardiac muscle degeneration have been commonly  
1128 observed for agonists with PPAR alpha or PPAR delta activity. Creatine kinase and  
1129 troponin evaluations should be performed in preclinical studies for these subtypes.  
1130 Histopathological evaluations of skeletal muscle should include multiple sites to evaluate  
1131 effects on both type I and type II muscle (e.g., diaphragm, gastrocnemius, soleus,  
1132 intercostals muscles).  
1133
- 1134 • **Other Known Toxicities.** Thymic and lymphoid atrophy, reproductive organ toxicity,  
1135 adipose proliferation, and infiltration are toxicities commonly associated with the  
1136 administration of PPAR agonists in preclinical studies. Preclinical study designs should  
1137 include adequate assessments for these potential toxicities.  
1138
- 1139 • **Electron Microscopy.** Electron microscopy evaluations should be conducted on  
1140 established target organs for PPAR agonists (liver and heart mandatory) and on other  
1141 compound specific target tissues, as identified (e.g., renal proximal tubules, skeletal  
1142 muscle).  
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### **APPENDIX B: HYPOGLYCEMIA**

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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.

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- **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).

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**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.