Guidance for Industry

Developing Products for Weight Management

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Revision 1

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I. INTRODUCTION

This guidance provides recommendations to industry regarding the development of drugs and therapeutic biologics (hereafter *products*) regulated within the Center for Drug Evaluation and Research (CDER) in the Food and Drug Administration (FDA) for the indication of weight management. This guidance applies to products intended to be used for medical weight loss, which can be defined as a long-term reduction in fat mass with a goal of reduced morbidity and mortality through quantifiable improvements in biomarkers such as blood pressure, lipids, and HbA1c. This guidance revises the draft *Guidance for the Clinical Evaluation of Weight-Control Drugs* that issued in September 1996. When finalized, this guidance will replace the September 1996 draft guidance.

The September 1996 draft guidance is being revised to provide advice on conducting studies to evaluate the efficacy and safety of products for weight management in patients with medication-induced weight gain and weight management in obese pediatric patients. Recommendations on the design of studies evaluating the efficacy and safety of combinations of weight-management products are also provided.

This guidance does not explicitly discuss indications for weight loss or maintenance of lost weight (which also can be described as prevention of weight regain); however, weight loss and weight maintenance should be demonstrated over the course of at least 1 year before a product can be considered effective for weight management. Thus, the weight management indication incorporates and signifies weight loss and weight maintenance.

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

This guidance also does not discuss the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.[2]

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

II. BACKGROUND

In January 2004, the FDA issued a notice in the *Federal Register* requesting public comment on the September 1996 draft guidance for the purpose of incorporating the latest scientific and clinical advances in weight management drug development. In September 2004, the FDA convened an advisory committee meeting to discuss the public comments received and to identify specific scientific, clinical, and regulatory issues that should be included in an updated guidance.

As a result, this revised guidance discusses several key areas of interest that are not covered in the September 1996 draft guidance. These areas include recommendations on the development of products for weight management in pediatric patients and in patients with medication-induced weight gain, and recommendations on the development of combinations of weight-management products.

III. OVERWEIGHT AND OBESITY CLINICAL BACKGROUND

A. The Adult Population

Obesity is a chronic, relapsing health risk defined by excess body fat. The pathogenesis of obesity involves the interaction of genetic, environmental, and behavioral factors. Total body fat can be accurately measured using hydrodensitometry and dual-energy x-ray absorptiometry (DEXA). Because body mass index (BMI), expressed as kilograms of weight divided by height in meters squared (kg/m^2), is simple and inexpensive to calculate, and correlates strongly with total body fat in non-elderly adults, it is commonly used as a surrogate for total body fat.

Excess body fat increases the risk of death and major comorbidities such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis of the knee, sleep apnea, and some cancers (Caterson and Hubbard et al. 2004; Calle and Thun et al. 1999). The relationships between BMI and risks for death and major comorbidities vary by age, sex, race, and smoking status, but, in general, are lowest in individuals with BMIs of 18.5 kg/m^2 to 24.9 kg/m^2 and increase in a curvilinear or linear manner with BMIs of 25 kg/m^2 to approximately 40 kg/m^2.

[2] 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.

Based on data relating BMI to mortality risk, the World Health Organization in 1995 and the National Institutes of Health in 1998 adopted the weight classifications by BMI that are shown in Table 1 (Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults 1998).

Table 1. Weight Classification Guidelines

Classification	**BMI**
Underweight	< 18.5 kg/m^2
Normal weight	18.5 kg/m^2 – 24.9 kg/m^2
Overweight	25 kg/m^2 – 29.9 kg/m^2
Obesity (class 1)	30 kg/m^2 – 34.9 kg/m^2
Obesity (class 2)	35 kg/m^2 – 39.9 kg/m^2
Extreme obesity (class 3)	$\geq$ 40 kg/m^2

An increased level of visceral or intra-abdominal adiposity, independent of BMI, increases the risk for metabolic derangements and perhaps cardiovascular disease (Janssen and Katzmarzyk et al. 2004; Rexrode and Carey et al. 1998; Zhu and Wang et al. 2002). Visceral fat content can be accurately measured with computed tomography (CT) or magnetic resonance imaging (MRI). Waist circumference, like BMI, is inexpensive and easy to measure and correlates with CT- and MRI-derived measurements of visceral fat content (Pi-Sunyer 2004). In general, a waist circumference greater than 40 inches (greater than 102 cm) in men and greater than 35 inches (greater than 88 cm) in women is accepted as indicating increased visceral adiposity (The Practical Guide. Identification, Evaluation, and Treatment of Overweight and Obesity in Adults 2000).

In overweight and obese individuals, particularly individuals with comorbidities such as hypertension, dyslipidemia, and type 2 diabetes, long-term weight loss greater than or equal to 5 percent following diet, exercise, and in some cases, drug treatment, is associated with improvement in various metabolic and cardiovascular risk factors (Douketis and Macie et al. 2005).

Although some, but not all, observational studies suggest that modest degrees of intentional weight loss in overweight and obese individuals can reduce the incidence of some cancers, cardiovascular disease, and all-cause mortality, at the time of this writing, there are no data from randomized, controlled trials on the effects of drug-induced weight loss on these clinical outcomes (Parker and Folsom 2003; Eilat-Adar and Eldar et al. 2004; Gregg and Gerzoff et al. 2003).

Lifestyle modification, consisting of changes in patterns of dietary intake, exercise, and other behaviors, is considered the cornerstone of overweight and obesity management. Because all drug and biological therapies impose some risk for adverse events, the use of a weight-management product should be contemplated only after a sufficient trial of lifestyle modification has *failed* and the risks of excess adiposity and the anticipated benefits of weight loss are expected to outweigh the known and unknown risks of treatment with a particular weight-management product.

Patients with BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 if accompanied by weight-related comorbidities historically have been considered appropriate populations for treatment with weight-management medications (Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults 1998). Although these patient-selection criteria are to a degree arbitrary, and an argument may be made for criteria that are more or less restrictive, we believe that individuals with BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 if accompanied by weight-related comorbidities represent patient groups with sufficient baseline risk to justify inclusion in studies of investigational weight-management products.

B. The Pediatric Population

As in adults, BMI correlates with more direct measures of adiposity in children and adolescents (American Academy of Pediatrics 2003; Barlow and Dietz 1998; Dietz and Robinson 2005; Speiser and Rudolf et al. 2005). Also similar to adults, BMI correlates with obesity-related comorbidities such as hypertension, dyslipidemia, and type 2 diabetes mellitus in pediatric patients.

In contrast to adults, the terms overweight and obese are used synonymously in pediatric patients (American Academy of Pediatrics 2003). The American Academy of Pediatrics (AAP) defines a pediatric-aged patient with an age- and sex-matched BMI of greater than or equal to 95th percentile as overweight or obese.

For patients aged 2 to 7 years, the AAP recommends weight loss through lifestyle modification if the BMI is greater than or equal to the 95th percentile for age and sex with the presence of one or more comorbidities. For patients who are 7 years of age or older, weight loss through lifestyle modification is recommended if the BMI is between the 85th and 95th percentile for age and sex with the presence of one or more comorbidities or if the BMI is greater than or equal to the 95th percentile for age and sex regardless of the presence of comorbidities.

Before therapeutic intervention, pediatric patients should receive a medical assessment to identify genetic (e.g., Prader-Willi syndrome) or endocrinologic (e.g., Cushing's syndrome) causes of their obesity. Patients also should be screened for the presence of comorbidities such as hypertension, glucose intolerance, and dyslipidemia.

The use of weight-management products in pediatric patients, as in adults, should be contemplated only after a sufficient trial of lifestyle modification has *failed* and the risks of excess adiposity and the expected benefits of weight loss are believed to outweigh the known and unknown risks of treatment with a particular weight-management product. Such a population might include obese pediatric patients with weight-related comorbidites.

IV. CLINICAL ASSESSMENT OF WEIGHT-MANAGEMENT PRODUCTS IN ADULT PATIENTS

A. Phase 1 and Phase 2 Trials

Before initiating phase 3 clinical trials, the pharmacokinetics and dose-response profiles of a new weight-management product should be well-characterized. Because excess adiposity may influence a product's metabolism and disposition, the pharmacokinetics profile of a weight-management product should be examined in patients with a broad range of BMIs (e.g., 27 kg/m^2 to 35 kg/m^2) (Cheymol 2000). To increase the likelihood of identifying the most appropriate dose for the pivotal clinical trials, early phase clinical studies should include a range of doses and be designed to identify no-effect and maximally tolerated doses. Studies should be designed to differentiate the efficacy of all the active doses versus placebo. The duration of the phase 2 trials should be sufficient to capture the maximal or near-maximal weight loss effects of the active doses. Forethought should be given to whether the product will be ultimately used in a fixed-dose or dose-titration scheme, as this dosing decision will also influence the size and duration of the studies.

Patients included in the early phase efficacy and safety studies generally should have BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 if accompanied by comorbidities. The primary efficacy endpoints should be a comparison of the mean absolute or percent change in body weight between the active-product and placebo-treated groups and the proportion of patients in each treatment group who lose greater than or equal to 5 percent of baseline weight. The effects by dose of the weight-management product on common weight-related comorbidities also should be examined and taken into account when choosing the most appropriate dose for the phase 3 studies.

B. Phase 3 Clinical Trials

1. Trial Design and Patient Populations

In general, phase 3 clinical trials examining the efficacy and safety of weight-management products should be randomized, double-blind, and placebo-controlled. The lifestyle modification programs used in the preapproval trials should be applicable to individual patients prescribed the product post-approval (i.e., programs should strike an appropriate balance between effectiveness and simplicity).

In general, patients should have or be at significant risk for weight-related morbidity and mortality. Such patients include those with BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 in the presence of comorbidities (e.g., type 2 diabetes, hypertension, dyslipidemia, sleep apnea, cardiovascular disease).

Effort should be made to include in the studies a representative sample of patients from the various demographic, ethnic, and racial groups in which the prevalence of obesity is highest. Development programs also should include a representative sample of patients with extreme obesity (BMI greater than 40 kg/m^2).

2. Trial Size and Duration

The number of subjects necessary to demonstrate the efficacy of a weight-management product will be smaller than the number needed to adequately assess safety. A reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 subjects are randomized to active doses of the product and no fewer than 1,500 subjects are randomized to placebo for 1 year of treatment.

For example, the above sample size will provide 80 percent power to rule out with 95 percent confidence an approximately 50 percent increase in the incidence of an adverse event that occurs at a rate of 3 percent in the placebo group (i.e., 4.5 percent versus 3 percent). This sample size also should allow for efficacy and safety analyses to be conducted within important subgroups such as sex, ethnicity, and baseline BMI.

3. Efficacy Endpoints

a. Primary efficacy endpoint

The efficacy of a weight-management product should be assessed by analyses of both mean and categorical changes in body weight.

- Mean: The difference in mean percent loss of baseline body weight in the active-product versus placebo-treated group.

- Categorical: The proportion of subjects who lose at least 5 percent of baseline body weight in the active-product versus placebo-treated group.

b. Secondary efficacy endpoints

Secondary efficacy endpoints should include, but are not limited to, changes in the following metabolic parameters:

- Blood pressure and pulse
- Lipoprotein lipids
- Fasting glucose and insulin
- HbA1c (in type 2 diabetics)
- Waist circumference

In clinical practice, waist circumference is used as an indirect measure of visceral fat content, which when increased is associated with an elevated risk for metabolic abnormalities such as dyslipidemia and diabetes. Because the evaluation of investigational weight-management products routinely includes assessment of changes in patients' metabolic profiles, and in some cases may involve measurement of visceral fat content by CT or MRI, waist circumference should not serve as a surrogate for visceral fat content when measured in a clinical trial investigating the efficacy of a product for weight loss. Rather, it can be a means to confirm that

reductions in waist circumference following treatment with a weight-management product are associated with the expected improvements in metabolic parameters.

It is likely that a large portion of study subjects will be taking concomitant medications to treat weight-related comorbidities such as hypertension, type 2 diabetes, and dyslipidemia. Since weight loss is expected to improve these comorbidities, an important secondary efficacy endpoint should be the proportion of subjects treated with the weight-management product compared with placebo who have a meaningful dose-reduction or complete withdrawal of their concomitant medication. Algorithms that direct dose reduction or withdrawal of concomitant medications based on changes in levels of blood pressure, lipids, or glycemia should be included in the study protocols.

Measures of quality of life from validated instruments also can be appropriate secondary efficacy endpoints.

c. Efficacy benchmarks

In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant

- The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant

Improvements in blood pressure, lipids, glycemia, or other areas commensurate with the degree of weight lost are expected in patients treated with an effective weight-management product. Therefore, changes in common weight-related comorbidites should be factored into the efficacy assessment of investigational weight-management products.

4. Standard of Care and Concomitant Medication

Overweight and obese patients enrolled in clinical studies of investigational weight-management products should receive standard of care, including medication, for comorbidities such as hypertension, dyslipidemia, and glycemic control.

5. Patients with Type 2 Diabetes

Compared with nondiabetic patients, overweight and obese patients with type 2 diabetes often respond less favorably to weight-management products and may face unique safety issues such as risk for sulfonylurea-induced hypoglycemia following weight loss (if the dose of sulfonylurea is not appropriately lowered or the drug discontinued). Therefore, sponsors should consider examining the efficacy and safety of weight-management products in trials dedicated to patients

with type 2 diabetes. The following recommendations should be considered when designing such trials:

- In general, patients should have baseline HbA1c levels between 8 percent and 10 percent.
- Patients should be excluded if they have fasting glucose levels greater than 270 mg/dl.
- Protocols should include escape criteria for poor glycemic control.
- Protocols should include an algorithm for the lowering or elimination of oral hypoglycemia or insulin dose based on fasting glucose levels and/or HbA1c (for patients who lose clinically significant amounts of weight).
- Patient randomization should be stratified by baseline antidiabetic medication (e.g., metformin versus sulfonylurea versus a thiazolidinedione versus insulin) and baseline HbA1c level (e.g., less than or equal to 9 percent versus greater than 9 percent).
- Hypoglycemia safety should be monitored.[3]

C. General Safety Assessment of Weight-Management Products

To ensure that drug or biologic-induced weight loss is caused primarily by a reduction in fat content, not lean-body mass, a representative sample of study subjects should have a baseline and follow-up measurement of body composition by DEXA, or a suitable alternative.

In addition to routine safety monitoring, it may be appropriate for the development programs of some weight-management products to have specialized safety assessments. For example, products that directly interact with the 5HT receptor system, specifically the $5HT_2$ receptor subtypes, probably should include evaluation of risk for cardiac valvulopathy using serial echocardiography. The development plans for centrally acting weight-management products generally should include validated assessments of neuropsychiatric function.

Assessment of the immunogenic potential of therapeutic proteins should be performed over a period of at least 6 to 12 months. If adverse events characteristic of allergic or immunologic reactions are identified, the FDA may ask for additional studies, with durations longer than 12 months. These additional studies may need to be conducted before submission of an application for registration or may be conducted after approval as a postmarketing commitment, based on the overall analysis of the product's risks and benefits. The appropriate timing of such studies can be discussed with the FDA at a pre-biologics license application meeting or other similar advice meeting.

For centrally acting weight-management products, sponsors should anticipate the need to conduct preclinical and clinical studies of abuse liability. Sponsors are encouraged to discuss the design of these studies with members of CDER's Controlled Substance Staff during the early phases of product development.

[3] Defining and Reporting Hypoglycemia in Diabetes: A Report from the American Diabetes Association Workgroup on Hypoglycemia, 2005, *Diabetes Care*, 28(5): 1245-9.

The need for and details of specific safety monitoring may change as new data emerge. Sponsors are encouraged to discuss their plans for specific safety monitoring with the division during the early stages of product development.

D. Weight-Management Products Used in Combination

Two or more products may be combined into a single fixed-dosed combination when each component makes a contribution to the claimed effect or effects (21 CFR 300.50).

Before initiating long-term clinical studies with fixed-dose combinations, sponsors should conduct the appropriate preclinical and pharmacokinetics studies. (See the guidances for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations* and *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations*.)

We recommend that the efficacy and safety of fixed-dose combinations be compared with the individual product components of the combination and placebo in phase 2 trials of sufficient duration to capture the maximal or near-maximal weight-management effects of the products. We have not defined a minimum difference in weight loss between a fixed-dose combination and its individual component products that should be achieved for the combination to be considered more efficacious than either of its components when used alone. However, a fixed-dose combination that is associated with at least twice the weight loss observed with that of each of the individual components will be viewed more favorably than combinations that do not achieve this degree of relative weight loss.

Once a fixed-dose combination has been deemed more effective than its individual components, the combination can then be examined versus placebo in phase 3 trials. This approach may preclude the need to include treatment groups for the individual components of the fixed-dose combination product in late-stage preapproval trials.

The efficacy of a product combination for weight management generally will be assessed using the same factors as those applied to a single product, as defined in section IV.B.3.

E. Weight-Management Products for Patients with Medication-Induced Weight Gain

A number of drugs, notably psychotropic and some anticonvulsant agents, are associated with moderate-to-marked weight gain (Baptista and Zarate et al. 2004; Pierre and Picard 2001). In addition to increasing the risk for adverse health outcomes, medication-induced weight gain may reduce compliance with the drug responsible for the increased body weight.

Before initiating long-term clinical studies in patients with medication-induced weight gain, sponsors should rule out clinically significant drug-drug interactions and perform appropriate preclinical toxicological studies of the subject products. For details, see the guidances for industry *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro, In Vivo Drug Metabolism/Drug Interaction Studies — Study Design, Data Analysis, and*

Recommendations for Dosing and Labeling, and *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

Patients eligible for participation in trials examining the efficacy and safety of products for the treatment of medication-induced weight gain should have a documented increase in body weight of at least 5 percent within 6 months of starting a drug known to cause weight gain. Patients should have BMIs greater than or equal to 27 kg/m^2 with comorbidities or greater than or equal to 30 kg/m^2 with or without comorbidities at the time of screening.

Because most weight-management products act within the central nervous system (CNS) and many of the drugs commonly associated with moderate-to-marked weight gain are used to treat psychiatric or neurological disorders, unique issues of efficacy and safety may arise in studies of products used to treat medication-induced weight gain. For example, it would be important to demonstrate that the efficacy and safety of the medication causing the weight gain (e.g., atypical antipsychotic) was not adversely affected by a weight-management product with a CNS mechanism of action, and vice versa. These and similar issues should be taken into account when designing and determining the sample size of trials for the treatment of medication-induced weight gain.

The efficacy of a product for the treatment of medication-induced weight gain generally will be assessed using the same factors as those for weight management, as defined in section IV.B.3.

Serotonin syndrome, a potentially life-threatening condition characterized by akathisia, tremor, altered mental status, clonus, muscular hypertonicity, and hyperthermia (Boyer and Shannon 2005), has been observed in patients exposed to a single or two or more proserotonergic agents used in combination. Therefore, in general, weight-management products that act as agonists at serotonin receptors, particularly the $5\text{-}HT2_A$ subtype, should not be studied in combination with proserotonergic medications associated with weight gain.

Because of issues related to safety and possibly efficacy that are unique to the particular combinations of drugs studied, approval of a product for weight management in patients with medication-induced weight gain generally will be limited to the weight-inducing drug studied and will not apply to the drug class in which the compound is a member. For example, if a weight-management product is shown to be effective and reasonably safe in the treatment of clozapine-induced weight gain, the approved indication would be limited to clozapine-induced weight gain and would not necessarily apply to the entire class of atypical or second generation antipsychotics.

V. CLINICAL ASSESSMENT OF LONG-TERM WEIGHT-MANAGEMENT PRODUCTS IN PEDIATRIC PATIENTS[4]

Because the benefit of weight-management products should be carefully weighed against potential toxicity, particularly in the pediatric population, we anticipate that phase 3 data in adults generally will be available before a new product is studied in children.

To ensure that the most appropriate dose or doses are studied in phase 3 trials, an assessment of the pharmacokinetics of a weight-management product in pediatric patients may be appropriate before initiation of long-term clinical studies. Pharmacokinetics and dose-ranging studies generally should include patients with age- and sex-matched BMIs greater than or equal to the 95th percentile.

Trials examining the efficacy and safety of a weight-management product in pediatric patients should be randomized, double-blind, placebo-controlled, and 1 year in duration. We suggest that initial pediatric studies be limited to adolescents (i.e., 12 to 16 year olds). Eligible patients should have age- and sex-matched BMIs greater than or equal to the 95th percentile (see http://www.cdc.gov/growthcharts). Patients should have a documented history of failing to lose sufficient weight with lifestyle modification before enrollment into studies of a weight-management product.

We recommend that initial clinical studies include patients with one or more weight-related comorbidities such as type 2 diabetes, dyslipidemia, or hypertension. Once a satisfactory risk-benefit profile has been established in this high-risk group of patients, studies of lower risk patients can be considered. Effort should be made to recruit equal numbers of males and females and representative samples of patients from ethnic groups in which the prevalence of obesity is high.

The lifestyle modification program should continue following randomization to product or placebo and its importance emphasized at appropriate intervals throughout the trials.

Because linear growth should be taken into account when assessing changes in the body weight of children and adolescents, the primary efficacy parameter in weight-management trials of pediatric patients should be a function of the change in BMI (e.g., the mean percent change in BMI and the proportion of patients who lose greater than or equal to 5 percent of baseline BMI). Height measurements should be obtained from a wall-mounted stadiometer.

Since demonstration of adequate safety necessitates a larger sample size than demonstration of efficacy, we anticipate that the sample size of the long-term pediatric weight-management studies will be determined by considerations of the product's mechanism of action and safety profile in adults. Sponsors should discuss and justify their proposed sample size with the division before initiating the study.

[4] For details on preclinical and pharmacokinetic evaluations for pediatric product development, see the ICH guidances for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceutics* and *E11 Clinical Investigation of Medicinal Products in the Pediatric Population.*

In addition to standard safety evaluations specific to growing children (e.g., assessing Tanner stage at baseline and endpoint), studies of centrally acting weight-management products in pediatric patients also should include validated assessments of neuropsychiatric function. Other specialized safety assessments may be appropriate depending on the product's mechanism of action and its safety profile in adults.

The efficacy assessment of a weight-management product in pediatric patients will take into account the product's effectiveness in overweight and obese adults as well as the magnitude of the difference in the mean and categorical (greater than or equal to 5 percent) changes in BMI from baseline to Year 1 in pediatric patients treated with active product versus placebo.

VI. STATISTICAL CONSIDERATIONS

A. Sample Size

The number of subjects in a placebo-controlled trial should be the maximum of sample sizes calculated based on the co-primary endpoints of categorical response defined as greater than or equal to 5 percent reduction in baseline body weight after 1 year, and change from baseline weight. Calculations should be based on two-sided tests of significance at the 5 percent level and at least 80 percent power. Effect sizes for the calculations should represent clinically meaningful differences.

B. Preventing Missing Data from Premature Subject Withdrawal

Historically, there have been high rates of premature subject withdrawal in long-term trials of weight-management products. To allow for a true intent-to-treat (ITT) analysis, we encourage sponsors to obtain body weight measurements in all subjects who prematurely withdraw from late-stage preapproval trials near the calendar date at which they were scheduled to complete the trial (Simons-Morton and Obarzanek et al. 2006). For example, a subject who withdraws from a 12-month study after 6 months of treatment should have a body weight measurement at the time he or she would have completed 12 months of study participation.

C. Analysis Methods

Response rates should be compared between treatment groups using statistical methods appropriate for categorical data. A sensitivity analysis should be conducted that considers subjects who are treated, drop out, and do not have complete post-baseline data as treatment failures.

The analysis of (percentage) weight change from baseline should use ANOVA or ANCOVA with baseline weight as a covariate in the model. The analysis should be applied to the last observation carried forward on treatment in the modified ITT population defined as subjects who received at least one dose of study drug and have at least one post-baseline assessment of body weight. Sensitivity analyses employing other imputation strategies should assess the effect of dropouts on the results. The imputation strategy should always be prespecified and should

consider the expected dropout patterns and the time-course of weight changes in the treatment groups. No imputation strategy will work for all situations, particularly when the dropout rate is high, so a primary study objective should be to keep missing values to a minimum. Repeated measures analyses can be used to analyze longitudinal weight measurements but should estimate the treatment effect at the final time point. Statistical models should incorporate as factors any variables used to stratify the randomization. As important as assessing statistical significance is estimating the size of the treatment effect. If statistical significance is achieved on the co-primary endpoints, type 1 error should be controlled across all clinically relevant secondary efficacy endpoints intended for product labeling.

D. Graphical Methods

Graphical methods showing treatment effects over time for completers should be presented. Cumulative distribution plots can be useful for showing response rates for different definitions of response based on the percentage of subjects with a change value equal to or less than the value on the x-axis selected to define the positive response. Additional graphical presentations of the data to illustrate the effect of the drug are encouraged. For examples, see the guidance for industry *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

VII. LABELING CONSIDERATIONS

Data on the changes in the major weight-related comorbidities are important in assessing the overall risk-benefit profile of a new weight-management product and can be included in the Clinical Studies section of the product's labeling. However, it is important to recognize that even though secondary efficacy endpoints are prespecified and the overall type 1 error rate is controlled for, that does not necessarily guarantee that all secondary endpoints will be included in labeling if the differences between active-product and placebo-treated groups are of nominal statistical significance. The clinical significance and consistency across studies of any observed differences will be important in determining whether the secondary efficacy data merit inclusion in the Clinical Studies section of the labeling.

VIII. STAND-ALONE INDICATIONS FOR THE PREVENTION OR TREATMENT OF WEIGHT-RELATED COMORBIDITIES

As mentioned earlier, weight loss through lifestyle modification is associated with improvements in blood pressure, lipid levels, glucose and insulin metabolism, and other physiometabolic endpoints. Improvements in these comorbidites are expected following drug or biologic-induced weight loss, and from a regulatory perspective, they are considered part of the weight-management indication. Thus, for a weight-management product to obtain a stand-alone indication for the prevention or treatment of type 2 diabetes, dyslipidemia, hypertension, or any other weight-related comorbidity, it should be shown that the product effectively prevents or treats the comorbidity through a mechanism that is independent of weight loss.

IX. METABOLIC SYNDROME

The term *metabolic syndrome* represents a cluster of laboratory and clinical findings that serve as markers for increased risk for cardiovascular disease and type 2 diabetes, and, depending upon the definition used, is prevalent in as much as 25 percent of the adult American population. The FDA does not necessarily consider the metabolic syndrome to represent a distinct disease entity. At present, there is no single etiological factor or central pathogenetic abnormality identified as mediating the constellation of excess visceral adiposity, abnormal lipids, elevated blood pressure, and insulin resistance that comprise the metabolic syndrome. Nonetheless, in addition to lifestyle modification, a host of drug therapies now exist to address individual or multiple components of the syndrome (e.g., lipid altering agents, antihypertensives, insulin sensitizers). Ideally, a therapeutic product intended to treat metabolic syndrome should *normalize* or improve all components of the syndrome, independent of weight loss (see section VIII), and ultimately be shown to prevent the development of type 2 diabetes and reduce cardiovascular morbidity and mortality.

REFERENCES

American Academy of Pediatrics, 2003, Policy Statement, Committee on Nutrition. Prevention of Pediatric Overweight and Obesity, *Pediatrics*, 112:424-430.

Baptista, T, J Zarate, R Joober, C Colasante, S Beaulieu et al., 2004, Drug-Induced Weight Gain, An Impediment to Successful Pharmacotherapy: Focus on Antipsychotics, *Current Drug Targets*, 5:279-299.

Barlow, SE and WH Dietz, 1998, Obesity Evaluation and Treatment: Expert Committee Recommendations, *Pediatrics*, 102(3):e29.

Boyer, EW and M Shannon, 2005, The Serotonin Syndrome, *New England Journal of Medicine*, 352:1112-1120.

Calle, EE, MJ Thun, JM Petrelli, C Rodriquez, and CW Heath, 1999, Body Mass Index and Mortality in a Prospective Cohort of U.S. Adults, *New England Journal of Medicine*, 341:1097-1105.

Caterson, ID, V Hubbard, GA Bray, R Grunstein, BC Hansen et al., 2004, Obesity, A Worldwide Epidemic Related to Heart Disease and Stoke, *Circulation*, 110:e476-e483.

Cheymol, G, 2000, Effects of Obesity on Pharmacokinetics — Implications for Drug Therapy, *Clinical Pharmacokinetics*, 39:215-231.

Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults, The Evidence Report, 1998, NIH Publication No. 98-4083.

Defining and Reporting Hypoglycemia in Diabetes: A Report from the American Diabetes Association Workgroup on Hypoglycemia, 2005, *Diabetes Care*, 28(5): 1245-9.

Dietz, WH and TN Robinson, 2005, Overweight Children and Adolescents, *New England Journal of Medicine*, 352(20):2100-2109.

Douketis, JD, C Macie, L Thabane, and DF Williamson, 2005, Systematic Review of Long-Term Weight Loss Studies in Obese Adults: Clinical Significance and Applicability to Clinical Practice, *International Journal of Obesity*, 29:1153-1167.

Eilat-Adar, S, M Eldar, and U Goldbourt, 2004, Association of Intentional Changes in Body Weight with Coronary Heart Disease Event Rates in Overweight Subjects Who Have an Additional Coronary Risk Factor, *American Journal of Epidemiology*, 161:352-358.

Gregg, EW, RB Gerzoff, TJ Thompson, and DF Williamson, 2003, Intentional Weight Loss and Death in Overweight and Obese U.S. Adults 35 Years of Age and Older, *Annals of Internal Medicine*, 138:383-389.

Janssen, I, PT Katzmarzyk, and R Ross, 2004, Waist Circumference and not Body Mass Index Explains Obesity-Related Health Risk, *American Journal of Clinical Nutrition*, 79:379-384.

Parker, ED and AR Folsom, 2003, Intentional Weight Loss and Incidence of Obesity-Related Cancers: The Iowa Women's Health Study, *International Journal of Obesity*, 27:1447-1452.

Pierre, J and F Picard, 2001, Bodyweight Gain and Anticonvulsants, A Comparative Review, *Drug Safety*, 24:969-978.

Pi-Sunyer, FX, 2004, The Epidemiology of Central Fat Distribution in Relation to Disease, *Nutrition Reviews*, 62:S120-126.

The Practical Guide. Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, 2000, NIH Publication No. 00-4084.

Rexrode, KM, VJ Carey, CH Hennekens, EE Walters, GA Colditz et al., 1998, Abdominal Obesity and Coronary Heart Disease in Women, *Journal of the American Medical Association*, 280:1843-1848.

Simons-Morton, D, E Obarzanek, and J Cutler, 2006, Obesity Research-Limitations of Methods, Measurements, and Medications, *Journal of the American Medical Association*, 295:826-828.

Speiser, P, M Rudolf, H Anhalt, C Camacho-Hubner, F Chiarelli et al., 2005, Childhood Obesity, *The Journal of Clinical Endocrinology & Metabolism*, 90(3):1871-1887.

Zhu, S, Z Wang, S Heshka, M Heo, MS Faith et al., 2002, Waist Circumference and Obesity-Associated Risk Factors Among Whites in the Third National Health and Nutrition Examination Survey: Clinical Action Thresholds, *American Journal of Clinical Nutrition*, 76:743-749.