Obesity and Overweight: Developing Drugs and Biological Products for Weight Reduction

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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Obesity and Overweight: Developing Drugs and Biological Products for Weight Reduction Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to industry regarding the development of drugs and biological products[2] regulated within the Center for Drug Evaluation and Research in the Food and Drug Administration (FDA) intended for reduction and long-term maintenance of body weight in patients with obesity and those with body mass index (BMI) classified as overweight who also have weight-related comorbidities (hereafter, patients *with overweight*).

This guidance focuses on the design of trials to demonstrate sustained weight reduction in patients with obesity or overweight. Weight reduction is defined herein as a long-term reduction in excess adiposity (body fat) with a goal of reduced morbidity and mortality. The expression *long-term* describes the course of body weight observed over a period of at least 1 year on the maintenance dose of the drug.

Although FDA encourages assessment of the effect of drugs on the manifestations of obesity or overweight beyond excess adiposity (e.g., obstructive sleep apnea, osteoarthritis), this guidance focuses on study designs and endpoints to assess the effectiveness of drugs on sustained weight reduction itself in patients with obesity or overweight. Sponsors should consult with the Agency regarding trial design features and endpoints to evaluate other manifestations of obesity or overweight.

In general, FDA's guidance documents 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

[1] This guidance has been prepared by the Division of Diabetes, Lipid Disorders and Obesity in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *drug* or *drugs* includes both human drugs and therapeutic biological products unless otherwise specified.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. CLINICAL BACKGROUND: OVERWEIGHT AND OBESITY

A. The Adult Population

Obesity is a chronic disease characterized by excess adiposity. Excess adiposity is associated with an increased risk of death and major comorbidities such as type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, nonalcoholic steatohepatitis, gallbladder disease, osteoarthritis of the knee, sleep apnea, and some cancers (Guh et al. 2009; Wang et al. 2011; Diehl and Day 2017). The pathogenesis of obesity involves the interaction of genetic, environmental, and behavioral factors. Patients with overweight (i.e., those who have comorbidities indicating metabolic dysfunction) also represent a patient population at increased health risk from excess adiposity.

BMI, expressed as kilograms of weight divided by height in meters squared (kg/m^2), is commonly used to identify patients with obesity or overweight in the clinical setting. BMI is widely used in both clinical and research settings and has a long history of use for regulatory purposes.

- BMI is inexpensive, universally available, easy to calculate, reproducible, and correlates strongly with total body fat in nonelderly adults.

- The relationship between BMI and risk for death varies by age, sex, race, and other factors, such as smoking status, but generally, the annual incidence of all-cause mortality:

  - Is lowest in individuals with BMIs of 22.5 kg/m^2 to 24.9 kg/m^2 and

  - Increases with BMIs from 25 kg/m^2 to greater than 40 kg/m^2 (Prospective Studies Collaboration 2009)

- Change in BMI from baseline is correlated with changes in body fat in patients with obesity or overweight. Mean percentage change in BMI is an effective method to assess change in adiposity in a population with obesity or overweight, adjusted for baseline BMI.

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 (NHLBI Obesity Education Initiative Expert Panel on the Identification, Evaluation, 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[3] obesity (Class 3)	≥ 40 kg/m^2

BMI has several limitations. Although higher BMI is strongly associated with increased body fat, BMI is not a direct measure of body fat, and it does not inform the distribution of excess body fat. In clinical practice, supplementing BMI with other anthropometric measures, such as waist circumference, may be appropriate in certain individuals.

Other methods to evaluate adiposity have important limitations as well. Assessment of skinfold thickness is operator dependent and has relatively poor reproducibility. Bioelectrical impedance may vary depending on the hydration status of the individual. Imaging modalities, such as dual x-ray absorptiometry (DXA) or magnetic resonance imaging, may provide more precise measures of body fat but are expensive and require use of multiple blinded, central readers for implementation in a trial. Trial results based on imaging changes may not be generalizable to clinical care of patients, whereas baseline BMI and percentage change in weight or BMI are available in any office or clinic. Additionally, change in fat mass based on imaging or other modalities is not as clearly tied to clinical outcomes as change in BMI.

In patients with obesity or overweight, particularly patients with comorbidities such as hypertension, dyslipidemia, and type 2 diabetes, long-term weight reduction greater than or equal to 5% of baseline body weight or BMI[4] following diet, exercise, and some, but not all, drug therapies, is associated with improvement in various metabolic and cardiovascular risk factors (Douketis et al. 2005; Jensen et al. 2014.).

Some, but not all, observational studies suggest that modest intentional weight loss in individuals with obesity or overweight can reduce the incidence of some cancers, cardiovascular disease, and all-cause mortality (Parker et al. 2003; Eilat-Adar et al. 2005; Gregg et al. 2003; Ma et al. 2017; Carlsson et al. 2022; Sjöholm et al. 2022). Furthermore, pharmacological weight reduction has been associated with reduced risk of cardiovascular events for at least one agent (Lincoff et. al. 2023).

Although weight loss is associated with the aforementioned clinical benefits, some prospective trials of pharmacological weight-reduction interventions have failed to show benefit on certain clinical outcomes (Nissen et al. 2016; Bohula et al. 2018), and some products have been

[3] The U.S. Centers for Disease Control and Prevention uses the term *severe* rather than *extreme* as a synonym for Class 3 obesity in adults.

[4] For adults of stable height, percentage change from baseline body weight is equal to percentage change from baseline BMI.

associated with potential harm (Connolly et al. 1997; James et al. 2010, Sharretts et al. 2020). For this reason, claims for drug intended for reduction and long-term maintenance of body weight in patients with obesity or overweight will generally be limited to weight reduction unless other benefits related to complications (e.g., improvement in sleep apnea) have also been demonstrated.

B. The Pediatric Population

BMI is used as an inexpensive and simple parameter that correlates with direct methods of measuring body fat, particularly at higher levels of body fat, to estimate adiposity in children and adolescents (Hampl et al. 2023; Barlow and Dietz 1998; Dietz and Robinson 2005; Speiser et al. 2005; Whitlock et al. 2010). Additionally, BMI correlates with obesity-related comorbidities, such as hypertension, dyslipidemia, type 2 diabetes mellitus, and nonalcoholic steatohepatitis in pediatric patients (Krebs et al. 2003; Skinner et al. 2015; Anderson et al. 2015; Cote et al. 2013). A child's BMI category (e.g., healthy weight, overweight) is determined using an age- and sex-specific percentile for BMI rather than the BMI cut-points used for adult categories.

Accepted classifications of pediatric obesity are based on the 2000 U.S. Centers for Disease Control and Prevention growth charts for children and adolescents ages 2 years and older and are defined as the following:

- Overweight: BMI at or above the 85th percentile for age and sex
- Obesity: BMI at or above the 95th percentile for age and sex
- Severe obesity: BMI at or above 120% of the 95th percentile for age and sex (or greater than or equal to 35 kg/m^2) (Kelly et al. 2013; Styne et al. 2017)

If indicated, pediatric patients with obesity or overweight should be evaluated for genetic, endocrine, or other causes.

- Genetic obesity syndromes (e.g., Prader-Willi syndrome, Bardet-Biedl syndrome) typically present with severe, early-onset obesity (before 5 years of age) and characteristic phenotypic features.
- Endocrine disorders (e.g., Cushing's syndrome) may present as mild obesity or overweight accompanied by short stature (or decreased linear growth) or other hormone deficiencies, such as hypogonadism.

III. CLINICAL ASSESSMENT OF WEIGHT-REDUCTION DRUGS IN ADULT PATIENTS

A. Phase 1 and Phase 2 Trials

Before a sponsor initiates phase 3 clinical trials, the pharmacokinetics (PK), pharmacodynamics (PD), and dose-response profiles of a new weight-reduction drug should be adequately characterized.

- The safety and tolerability of a wide range of doses should be studied in early phase trials. Because excess adiposity may influence a drug's metabolism and disposition (Hanley et al. 2010; Smit et al. 2018; Cheymol 2000), phase 1 trials should examine the PK and PD profile of a weight-reduction drug across a broad range of BMIs that adequately covers the population likely to receive the drug.

- Other clinical pharmacology studies, including assessment of drug interactions[5] and the impact of intrinsic and extrinsic factors on the PK and PD of the investigational drug, should be conducted early in drug development to aid in the design of later phase trials.

- Phase 2 trials should include a range of doses and identify the appropriate dosing regimen(s) to take into phase 3 trials. The duration of the phase 2 trials should be sufficient to capture the maximal or near-maximal weight-reduction effects of the active dosing regimen(s).

  - The trial design, size, and duration should account for dosing considerations, such as whether the drug will be ultimately used in a fixed-dose or dose-titration regimen, or whether a period of dose-escalation to achieve the target dose is needed to improve tolerability.

  - Phase 2 trials should also examine the effects by dose of the weight-reduction drug on common weight-related comorbidities (e.g., type 2 diabetes mellitus, hypertension, dyslipidemia), and a sponsor should consider these dose-response data when choosing the most appropriate dosing regimen(s) for phase 3 trials.

- Subjects included in phase 2 efficacy and safety studies generally should be adults who have BMIs greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 if accompanied by at least one comorbidity.

- The primary efficacy endpoint should be a comparison of the mean percentage change in body weight between the group assigned to the investigational drug and the group assigned to the control.

[5] See the ICH guidance for industry *M12 Drug Interaction Studies* (August 2024). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- If a sponsor intends to use one or more clinical outcome assessments (COAs) to support labeling claims, the sponsor should seek FDA input as early as possible and at important milestones throughout the drug development process to ensure the inclusion of fit-for-purpose COAs in phase 3 trials. The sponsor should also discuss with the Agency early in the development program the endpoints, analyses, and anchors to ensure that the COA results are both clinically meaningful and interpretable.

B. Phase 3 Clinical Trials

1. Trial Design and Patient Populations

In general, phase 3 clinical trials examining the efficacy and safety of weight-reduction drugs should be randomized, double-blind, and placebo-controlled, with the investigational drug used as an add-on to standardized recommendations for diet and physical activity in all randomized subjects.

- The lifestyle-modification programs used in the preapproval trials should be applicable to patients who would be prescribed the drug after approval.
  - At least one phase 3 trial should incorporate a standard-of-care diet and physical activity program (i.e., a program that strikes an appropriate balance between effectiveness and simplicity that could be implemented in a primary care setting).
- To ensure that trial subjects have or are at significant risk for weight-related morbidity and mortality, trials should include subjects with the following characteristics:
  - BMI greater than or equal to 30 kg/m^2, including a representative sample of subjects with Class 3 or severe obesity (BMI greater than 40 kg/m^2).
  - BMI greater than or equal to 27 kg/m^2 in the presence of at least one weight-related comorbidity (e.g., type 2 diabetes, hypertension, dyslipidemia, sleep apnea, or cardiovascular disease)
- Because the observed treatment effect of a drug might be substantially different in subjects taking concomitant glucose-lowering medications, it may be reasonable to conduct one or more trials that enroll only subjects with diabetes at baseline (see item 5, Subjects With Type 2 Diabetes, in this section for more details).
- The development program should include subjects with comorbidities, such as cardiovascular disease, heart failure, liver disease, and chronic kidney disease.
- Subjects are expected to reflect the patient populations likely to use the drug in clinical practice, with regard to age, sex, race, and ethnicity in the U.S. population. Sponsors

should implement a diversity plan[6] that accounts for the higher prevalence of obesity and its comorbidities in certain racial and ethnic groups in the United States, such as American Indian or Alaska Native, Asian, Black or African American, Hispanic or Latino, Middle Eastern or North African, Native Hawaiian or Pacific Islander.

2. Trial Size and Duration

To ensure a thorough assessment of a weight-reduction drug, the size of the safety database for a weight-reduction program should exceed the subject exposures outlined in 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* (March 1995). Given the prevalence of obesity and overweight, substantial patient exposure can be expected after a weight-reduction drug is approved. Patients with obesity or overweight have a significant background rate of morbidity and mortality, so evaluation of this population represents a circumstance where the harmonized general standard for the safety evaluation is not applicable.

- The general recommendation for a sample size to assess the safety of a weight-reduction drug is 3,000 subjects randomized to the investigational drug within the to-be-recommended dosage range and no fewer than 1,500 subjects randomized to placebo for at least 1 year of treatment at the maintenance dosage. A sponsor developing multiple dosing regimens should consider a randomization scheme that assigns more subjects to the higher doses and should discuss the overall size of the safety database with the Agency at or before the end of phase 2.

  - The recommended sample size will provide 80% power to detect, with 95% confidence, an approximately 50% increase in the incidence of an adverse event that occurs at a rate of 3% in the placebo group (i.e., 4.5% versus 3%).

  - This sample size also would allow for efficacy and safety analyses to be conducted within important subgroups such as age, sex, race, ethnicity, and baseline BMI, provided that a sufficient number are enrolled in each of these groups.

- As the number of subjects necessary to demonstrate the efficacy of a weight-reduction drug in each individual trial is generally smaller than the number needed to adequately assess safety, sponsors can either increase the sample size of the two adequate and well-controlled trials necessary to support approval, or the safety analysis could be based on integrated data from multiple adequate and well-controlled trials, including the efficacy and safety studies (see section VI for more details).

[6] See the draft guidance for industry *Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies* (June 2024). When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

3. Efficacy Endpoints

a. Primary efficacy endpoint

The efficacy of a weight-reduction drug in adults should be assessed by analyses of mean percentage change from baseline body weight in the investigational drug group versus the control group. Note that in subjects with stable height (i.e., adults who have achieved terminal height) percentage change in body weight equals percentage change in BMI.

b. Secondary efficacy endpoints

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

- Blood pressure
- Lipoprotein lipids
- Fasting glucose
- A1C (in subjects with type 2 diabetes)

Assessments of clinical outcomes from fit-for-purpose COA measures could also be appropriate secondary endpoints to support a labeling claim. For example, if a sponsor seeks to demonstrate clinical benefit on a particular set of functional impacts (e.g., physical functioning), we recommend that the sponsor do the following:

- Specify and define functional impacts that are relevant and important to patients with obesity or overweight and that are likely to demonstrate meaningful and interpretable changes in the planned clinical trial(s).

- Consider whether the target population will have sufficient limitation in their physical functioning and how the extent of limitation in the population at baseline may affect the instruments' ability to observe a clinically meaningful within-patient score change.

- If all randomized subjects do not have sufficient limitation in physical functions, we recommend prespecifying a subgroup to be analyzed and providing details of the proposed analyses. The proposed analysis plan should be submitted to FDA for review and agreement before conducting the trial.

In clinical practice, waist circumference is sometimes used as an indirect measure of visceral fat, as it is easy and inexpensive to measure; but for regulatory purposes, it is not considered a surrogate for visceral fat content or metabolic abnormalities because the procedure is not standardized, the measurement is impacted by the extent of non-visceral fat, and the accuracy is reduced in patients with BMI greater than 35 kg/m^2. Nevertheless, change in waist circumference may be evaluated as a secondary endpoint. Acceptability for labeling would depend on the quality of the data.

Because changes in major weight-related comorbidities are informative to prescribers, it may be appropriate to present secondary endpoints from adequate and well-controlled trials in the CLINICAL STUDIES section of labeling upon review of the data. Results suitable for labeling generally would include clinically meaningful and statistically significant treatment effects demonstrated on prespecified endpoints controlled for type 1 error and consistent across trials. Statistical robustness alone is generally necessary, but not sufficient, to support inclusion of an endpoint in labeling.

Responder analyses on continuous variables (i.e., the proportion of subjects achieving prespecified thresholds of weight reduction compared with the control arm; for example, greater than or equal to 5%, 10%, or 15% of baseline body weight or BMI) should be interpreted with caution. Specifically, responder analyses may inappropriately exaggerate treatment effects (Abugov et al. 2023). For example, consider a hypothetical case in which treatment benefit exceeds risk if the mean treatment effect is 5% or greater reduction in weight, and in which the means of normally distributed percentage reductions in weight for treatment and control are 6% and 4%, respectively, each with a standard deviation of 1%. Analysis on the continuous outcomes would indicate an inadequate treatment effect equal to 2% weight reduction, while analysis based on a responder threshold of 5% would suggest a large treatment effect, with the difference in response rate between treatment and control equal to 68%. For this reason, responder analyses for the evaluation of weight reduction are generally not recommended. A sponsor intending to pursue a responder analysis as an endpoint should consult with the Agency.

c. Efficacy benchmarks

In general, a drug is considered effective for weight reduction and maintenance in patients with obesity or overweight with comorbidities if, after 1 year of treatment at the maintenance dosage, the difference in mean percentage weight reduction between the investigational drug and control-treated groups is at least 5% and the difference is statistically significant.

4. Standard of Care and Concomitant Medication

Subjects with obesity or overweight enrolled in clinical trials of investigational weight-reduction drugs should receive standard-of-care treatment, including medication, for comorbidities such as hypertension, dyslipidemia, and glycemic control. Data should be collected on initiation and/or discontinuation or dose reduction of medications for these comorbidities to support evidence of the drug effect on blood pressure or glycemic control.

5. Subjects With Type 2 Diabetes

Compared with their effects in patients without diabetes, weight-reduction drugs are typically less efficacious at reducing weight in patients with concomitant type 2 diabetes. Furthermore, patients with type 2 diabetes may face unique safety issues such as a risk for hypoglycemia, because of either improved glycemia following weight reduction or a direct glucose-lowering effect of the weight-reduction drug. Because patients with type 2 diabetes represent an important subgroup of patients with obesity or overweight, it is expected that sponsors evaluate sufficient subjects with type 2 diabetes to assess the efficacy and safety in this subgroup, either in

dedicated trials of subjects with type 2 diabetes (with concomitant obesity or overweight) or in adequately powered subgroups of larger weight-reduction trials that also include subjects without diabetes.

- Subjects with diabetes should be on a stable regimen of medications intended for glycemic control before enrollment in a weight-reduction trial.

- Trials should generally exclude subjects with poor glycemic control at baseline (e.g., A1C greater than 10% or fasting glucose levels greater than 270 mg/dL).

- Subject randomization should be stratified by the effect of common baseline glucose-lowering medications on weight (i.e., weight gain promoting, weight loss promoting, weight neutral) and baseline A1C (e.g., less than or equal to 8% versus greater than 8%).

- Protocols should include rescue criteria for subjects who experience worsening glycemic control during the trial. Increased dose or initiation of new glucose-lowering medication should be documented.

- Because weight reduction may result in improved insulin sensitivity or glycemic control, sponsors should consider including an algorithm for the lowering or elimination of glucose-lowering medications or reduction of insulin dose based on glucose levels or A1C in clinical protocols.

- Hypoglycemia safety should be monitored and reported consistent with published guidelines (International Hypoglycaemia Study Group 2017; Abraham et al. 2018).

6. 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. Approval of a metabolic syndrome indication would most likely require demonstrating a reduction in the risk of cardiovascular morbidity or mortality in persons with metabolic syndrome—or some other clinically meaningful benefit that outweighs the potential risks of treatment—associated with improvement in most or all components of the syndrome.

Issues related to seeking a metabolic syndrome indication include the following:

- Depending on the definition used, the thresholds defining the individual parameters that constitute metabolic syndrome, including increased visceral adiposity, lipid parameters, blood pressure, and insulin resistance, may not define disease states.

- Available pharmacological therapies targeting the individual components may already be indicated in the subset of patients diagnosed with a recognized disease or condition (e.g., triglyceride lowering in patients with severe hypertriglyceridemia, blood pressure

reduction in patients with hypertension, glycemic control in patients with diabetes mellitus, or low-density lipoprotein cholesterol (LDL-C) lowering in patients with cardiovascular disease or increased cardiovascular risk).

- Demonstration of improvement in one or more of the individual parameters in individuals meeting the definition of metabolic syndrome but without a disease diagnosis (i.e., severe hypertriglyceridemia, hypertension, type 2 diabetes, or cardiovascular disease) is not clearly linked to improvement in clinical outcomes and thus could not be considered substantial evidence of effectiveness to support a metabolic syndrome indication.

7. Delay or Prevention of Type 2 Diabetes

Obesity is a risk factor for the onset of type 2 diabetes. Although there is evidence that weight loss in individuals with obesity or overweight can reduce the incidence of type 2 diabetes diagnosis, delayed biochemical diagnosis of type 2 diabetes has not been shown to improve microvascular outcomes (Diabetes Prevention Program Research Group 2015). For a drug intended for weight reduction and maintenance, an additional indication for the delay of onset of type 2 diabetes would need to be supported by the establishment of clinical benefit(s) of the delay; trials demonstrating delayed biochemical diagnosis of type 2 diabetes alone would most likely not be sufficient. Benefits on quality of life, disease management burden, or psychosocial functioning could be considered. It is unclear what would constitute a minimum trial duration for a delay or prevention of type 2 diabetes claim, but the magnitude of the benefit of any delay in the onset must be clinically meaningful. Because some drugs intended for weight reduction may have glycemic effects, how a trial would demonstrate that diabetes diagnosis is delayed or prevented, rather than concealed by early antihyperglycemic treatment initiation, would need to be clarified.

C. General Safety Assessment of Weight-Reduction Drugs

Safety assessment of drugs intended for weight reduction should include evaluation of cardiometabolic parameters as part of routine safety monitoring (including but not limited to assessment of blood pressure, heart rate, plasma lipids, glycemic control parameters, and electrocardiography).

In addition to routine safety monitoring, additional specialized safety assessments may be appropriate for some weight-reduction development programs. For example:

- Programs should include a comprehensive cardiovascular assessment, which should generally include features such as ambulatory blood pressure monitoring.[7] A cardiovascular outcomes trial may be necessary if a signal for CV risk is identified during development. Whether such a trial would be needed premarket or could be conducted postmarket would depend on the nature of the signal(s); we recommend early consultation with FDA if early phase trials demonstrate such a signal.

[7] See the draft guidance for industry *Assessment of Pressor Effects of Drugs* (February 2022). When final, this guidance will represent the FDA's current thinking on this topic.

- Programs for drugs that directly interact with the serotonin (5-HT) receptor system, specifically the 5-HT_2 receptor subtypes, should include evaluation of risk for cardiac valvulopathy using serial echocardiography.

- The development plans for centrally acting weight-reduction drugs generally should include fit-for-purpose assessments of neuropsychiatric function, such as the Patient Health Questionnaire-9 (PHQ-9) and Columbia Suicide Severity Rating Scale (C-SSRS). Additionally, sponsors should anticipate the need to conduct nonclinical and clinical studies to assess abuse liability[8] and discuss the design of these studies with FDA during the early phases of drug development.

- Assessment of the immunogenic potential of therapeutic proteins (or related biological entities, such as peptides) should be consistent with published FDA guidance.[9]

Loss of lean mass is observed after weight reduction in patients with obesity or overweight regardless of intervention type (lifestyle, bariatric surgery, or pharmacotherapy). Patients with obesity or overweight have greater lean mass than lean individuals, including greater muscle mass, higher bone density, increased organ weight (i.e., liver, kidneys, and pancreas), and greater absolute total body water (despite lower percentage body water). In pharmacological trials, reduction of fat mass has typically accounted for 60% to 90% of weight reduction, and the accompanying reduction in lean mass has not been considered adverse. To ensure that drug-induced or biologic-induced weight reduction is caused primarily by a reduction in fat content, not lean-body mass, a representative sample of trial subjects should have a baseline and follow-up measurement of body composition by DXA or a suitable alternative. Sponsors seeking an efficacy claim related to changes in body composition would need to consult with FDA early in development to align on the clinical condition being treated. Trial design, including appropriate choice of population and selection of endpoints that measure how a patient feels, functions, or survives, to potentially support such a claim is beyond the scope of this guidance.

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 drug development and at the end of phase 2.

D. Weight-Reduction Drugs Used in Combination

Two or more drugs may be combined into a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug:[10]

[8] See the guidance for industry *Assessment of Abuse Potential of Drugs* (January 2017).

[9] See the guidance for industry *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019).

[10] See 21 CFR 300.50(a).

- Before initiating long-term clinical studies with a fixed-combination drug product (FCDP),[11] a sponsor should conduct the appropriate nonclinical and PK studies.[12]

- Sponsors should compare the efficacy and safety of an FCDP with the individual components of the combination in trials of sufficient duration to capture the maximal or near-maximal weight-reduction effects.

E. Weight-Reduction Drugs for Patients With Medication-Induced Weight Gain

This section addresses development of drugs intended for weight reduction in patients with obesity or overweight caused by or exacerbated by medication-induced weight gain. It is not intended to address development of drugs for the prevention of weight gain in patients with a normal BMI, which is outside the scope of this guidance.

Certain drugs, notably some psychotropic and anticonvulsant agents, are associated with moderate-to-marked weight gain. In addition to increasing the risk for adverse health outcomes, medication-induced weight gain may reduce adherence with the drug responsible for the increased body weight.

- Before initiating long-term clinical studies in patients with medication-induced weight gain, a sponsor should evaluate potential clinically significant drug-drug interactions and perform appropriate nonclinical toxicological studies.[13]

- Participants in trials examining the efficacy and safety of drugs for the treatment of medication-induced weight gain should have a documented increase in body weight of at least 5% temporally associated with starting a drug known to cause weight gain.

- Generally, patients should have BMIs greater than or equal to 27 kg/m^2 with one or more weight-related comorbidities or greater than or equal to 30 kg/m^2 with or without comorbidities at the time of screening.

- The efficacy of a drug for the treatment of medication-induced weight gain generally should be assessed using the same factors as those for weight reduction, as defined in section III.B.3 of this guidance.

[11] For the purposes of this guidance, an FCDP is one in which two or more active ingredients are combined at a fixed dosage in a single dosage form.

[12] For details, see the guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations* (March 2006) and the draft guidance for industry *Bioavailability* and *Bioequivalence Studies Submitted in NDAs or INDs — General Considerations* (March 2014). When final, this guidance will represent the FDA's current thinking on this topic.

[13] For details, see ICH M12 and the guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

- The design of the clinical program may need to consider unique efficacy or safety issues with drugs used to treat medication-induced weight gain and should consider the specific indication sought. For example, approval of a drug for weight reduction in patients with medication-induced weight gain generally would most likely be limited to the weight-inducing drug(s) studied and not the entire drug class of which the compound is a member or other drug classes. In addition, the development program for a weight-reduction drug with a central nervous system mechanism of action should evaluate whether the drug changes the efficacy or safety of a central nervous system–acting medication causing the weight gain.

IV. CLINICAL ASSESSMENT OF WEIGHT-REDUCTION DRUGS IN PEDIATRIC PATIENTS

Under the Pediatric Research Equity Act, pediatric assessments are required in certain drugs and biological products developed for diseases and/or conditions that occur in both the adult and pediatric populations unless an exception, waiver or deferral is applicable. Studies must use appropriate formulations for each age group.[14] Plans for pediatric studies should be submitted early in the drug development process, no later than 60 calendar days after the end-of-phase 2 meeting or such other time as agreed upon between FDA and the sponsor.[15] Generally, efficacy and safety data in adults should be available before a new drug is studied in children to support the prospect of direct benefit and the potential for a favorable benefit-risk profile in this population.

- In some cases, PK characterization in pediatric patients may be appropriate before initiation of long-term pediatric clinical trials. PK and dose-ranging studies generally should include subjects with age-matched and sex-matched BMIs greater than or equal to the 95th percentile (see http://www.cdc.gov/growthcharts).

Phase 3 trials examining the efficacy and safety of a weight-reduction drug in pediatric subjects should be randomized, double-blind, placebo-controlled, and at least 1 year in duration at the target dosage.

- Pediatric trials should include subjects aged 6 years and older. Separate trials or cohorts are generally recommended for adolescents (aged 12 years and older) and younger pediatric subjects (aged 6 to 11 years).

- Eligible subjects should have age-matched and sex-matched BMIs greater than or equal to the 95th percentile (or 85th percentile in the presence of one or more weight-related

[14] See the draft guidance for industry *Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act* (May 2023). When final, this guidance will represent the FDA's current thinking on this topic.

[15] See the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

comorbidities—that is, type 2 diabetes, hypertension, or dyslipidemia—in adolescents) and a documented history of failure to lose sufficient weight with lifestyle modification.

- Trials should target equal proportions of males and females and representative samples of subjects from racial or ethnic groups in which the prevalence of obesity and its comorbidities is high in the U.S. population.

- Trials should include a substantial proportion of subjects (30% or greater recommended) who meet BMI criteria for severe obesity.

- The lifestyle-modification program should continue following randomization and its importance emphasized at appropriate intervals throughout the trials.

- Because linear growth should be considered when assessing changes in the body weight of children and adolescents, the primary efficacy parameter in weight-reduction trials of pediatric subjects should be a function of the change in BMI (e.g., the mean percentage change in BMI). Height measurements should be obtained at all study visits using a wall-mounted stadiometer and following appropriate procedures[16] specified in the protocol.

- As in adults, demonstration of adequate safety may necessitate a larger sample size than demonstration of efficacy. Sponsors should justify their proposed sample size and obtain FDA agreement before initiating the trial(s).

- Baseline and follow-up measurement of body composition by DXA or suitable alternative should be obtained in pediatric subjects.

In addition to standard safety evaluations specific to growing children (e.g., assessing Tanner stage and bone age at baseline and endpoint), trials of centrally acting weight-reduction drugs in pediatric subjects also should include fit-for-purpose assessments of depression, suicidality, and neuropsychiatric function. Other specialized safety assessments may be appropriate depending on the drug's mechanism of action and its safety profile in adults.

[16] See the draft guidance for industry *Measuring Growth and Evaluating Pubertal Development in Pediatric Clinical Trials* (November 2022). When final, this guidance will represent the FDA's current thinking on this topic.

V. STATISTICAL CONSIDERATIONS

A. Estimands

Study protocols and statistical analysis plans should clearly prespecify how intercurrent events[17] and missing data[18] will be handled during the trial and how they will be accounted for in the statistical analyses. Sponsors should consult with FDA regarding these issues during trial design. Although we are open to considering alternative estimands, we generally recommend inclusion of analyses using the treatment policy estimand, in which all subjects, regardless of intercurrent events, continue to be measured at each prespecified clinical visit unless consent to collect such data is explicitly withdrawn, and in which all such measurements are included in the statistical analyses. For other strategies to address specific intercurrent events, sponsors should justify that the estimand addresses a meaningful clinical question of interest and can be estimated with plausible assumptions.

B. Minimizing Missing Data From Premature Study Withdrawal or Loss to Follow-Up

To help minimize the uncertainty associated with imputation of missing data, we recommend the following:

- The protocol and informed consent form should clearly differentiate between treatment discontinuation (i.e., discontinuation of intervention) and study withdrawal (i.e., withdrawal of consent to continued participation in study procedures, including data collection).

- To help inform the imputation process, medical reasons for treatment discontinuation or study withdrawal should be recorded on the case report forms and data sets (e.g., "nausea" rather than "patient decision" or "investigator decision").

- The only grounds for study withdrawal (discontinuing the collection of outcome information) should be withdrawal of subject consent to continued collection of data.

- To help ensure collection of data after early treatment discontinuation, the patient consent form and investigator training should include material emphasizing the scientific importance of data recorded after treatment discontinuation.

[17] Intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest, for example, discontinuation of assigned treatment, use of prohibited medications, use of alternative or additional medications, and corrective surgery. See the ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

[18] Missing data include withdrawal of informed consent for collection of additional data, missed clinical visits, and loss to follow-up.

- The study protocols should establish systematic plans to avoid or minimize loss to follow-up of subjects who do not actively maintain contact with the investigator (e.g., timing and number of telephone calls from investigator staff to the subject and subject's relatives, calls to the subject both at work and at home, offers of transportation to the clinic).

- The protocol should include options to ascertain key outcome information in subjects who discontinue study treatment and are unable or unwilling to continue all study visits, including returns only for the visit at which primary and key secondary endpoints are evaluated.

C. Estimators

Despite the best precautions, some data will inevitably be missing. How the statistical analyses will account for missing data should be prespecified in the statistical analysis plan. Missing data should be imputed in a fashion consistent with what the values, with their corresponding uncertainty, would likely have been had they been collected.

We recommend the multiple imputation of missing data based on data retrieved from subjects who discontinued treatment (i.e., retrieved dropout), calculated according to study treatment and study month of an intercurrent event. For continuous endpoints, multiple imputations can be aggregated using Rubin's method. For categorical endpoints, particular imputation models should be discussed with FDA during study planning.

D. Sensitivity Analyses

The use of retrieved data to impute missing data adds uncertainty because the outcomes of subjects who support continued collection of data after intercurrent events may differ from outcomes of subjects who withdraw from study. To assess the sensitivity of results to such uncertainty, tipping point analyses should be conducted that vary assumptions about the missing data. The tipping point analyses should be two-dimensional (i.e., should allow assumptions about the missing outcomes on the two treatment arms to vary independently) and should include scenarios where dropouts on treatment have worse outcomes than dropouts on placebo. The goal is to evaluate the plausibility of the assumed expected values for missing outcomes in each treatment arm under which the conclusions change (i.e., under which there is no longer evidence of a treatment effect). In the tipping point analyses, all observed data should be included as nonmissing, regardless of adherence to treatment or use of prohibited medications. For continuous data, we recommend centering the tipping point analysis around the analysis that most appropriately addresses missing data.

Sensitivity analyses are distinct from supplementary analyses, which target a different estimand or different estimator of the same estimand. Supplementary analyses may be useful to provide additional insights into the evidence of treatment effect but do not directly test the missing data assumptions of the primary analysis.

E. Sample Size

The number of subjects in trials designed to provide substantial evidence of effectiveness should provide adequate power (e.g., 90%) to evaluate the primary endpoint.

F. Analysis Methods

The analysis of percentage weight change from baseline should use analysis of variance or analysis of covariance with baseline weight as a covariate in the model. The statistical model should incorporate as factors prognostic covariates as well as any variables used to stratify the randomization. If statistical significance is achieved on the primary endpoint, the type 1 error rate should be controlled across all clinically relevant secondary efficacy endpoints intended for drug labeling.

Because the number of safety events in any one trial may be limited, safety data are commonly integrated across studies. Integrated analyses of safety data should generally be stratified by trial. Stratification is important to prevent confounding (e.g., Simpson's paradox) that can occur when pooling trials with different randomization ratios and populations with different risks of adverse events. In addition, sponsors should consider the impact of the following differences across studies:

- Different treatment durations.
- Different trial populations: Trial populations may have different risks of certain adverse events that occur spontaneously as background events or different susceptibility to adverse reactions to the drug (e.g., older adults or participants with particular comorbidities).
- Different methods of adverse event ascertainment (e.g., questionnaire versus general inquiry, different frequencies of querying, or substantial differences in reporting patterns).
- Incompatible trial designs: It is not generally appropriate to integrate safety data collected from controlled and uncontrolled trials to assess the impact of treatment on common adverse events because between-group comparisons of event incidence will no longer be possible.

To facilitate the assessment of integrated trial results, we recommend inclusion of forest plots, with estimates of treatment effects from the individual trials as well as from the integrated analysis.

G. Graphical Methods

Sponsors should provide graphs showing treatment effects over time for completers, with additional graphs to illustrate the effect of the drug, such as cumulative distribution functions, histograms, or waterfall plots.

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