An estimated 70% of adult men and 60% of adult women in the United States are overweight or obese. Excess body fat increases the likelihood of developing hypertension, dyslipidemia, and type 2 diabetes mellitus and is an independent risk factor for cardiovascular disease. Obesity is linked to an increased risk for certain cancers, osteoarthritis, and sleep apnea. Obese people are stigmatized. Medical costs attributable to obesity are enormous. The healthcare community and patients would thus welcome the development and approval of new obesity drugs with favorable benefit-risk profiles.

To facilitate drug development, the US Food and Drug Administration’s (FDA’s) Center for Drug Evaluation and Research issues guidance documents for the pharmaceutical industry. These documents provide the agency’s current thinking on therapeutic indications, target populations, clinical trial designs, and data analyses. This article examines the origins and evolution of the FDA’s guidance document for the development of drugs to treat obesity.

**Background**

In 1947, the FDA approved the first prescription obesity drug, desoxyephedrine or methamphetamine. Approval of amphetamine congeners (eg, phentermine), fenfluramine, and other appetite suppressants followed over the next 2½ decades. Then, in 1973, with the country struggling with a long-running epidemic of amphetamine abuse, the FDA, concerned about the abuse potential of the amphetamine congeners and their transient efficacy, limited the indication of all obesity drugs to short-term use (ie, a few weeks). This restriction did little to counter opinions that vanity was the only reason to lose weight and that obesity drugs had no role in long-term weight loss.

This mindset began to change in subsequent years. “[While] most public attention and economic activity related to obesity has been devoted to cosmetic and esthetic concerns about body weight, it has become increasingly obvious that obesity is a serious public health concern, with adverse effects on health and longevity,” declared members of a 1985 National Institutes of Health (NIH) Consensus Conference on obesity. Long-term studies (eg, >6 months) of approved and investigational obesity drugs were also initiated during this time period.

The discovery in the early 1990s of leptin, an adipocyte-derived hormone integral to the regulation of body weight, coincided with the transfer of regulatory oversight of obesity drugs from the FDA’s Division of Neuropharmacologic Drugs to the Division of Metabolism and Endocrinology Products (the Division).14

**1995 FDA Advisory Committee Meeting**

In 1995, the Division convened a public meeting with its advisory committee and a number of obesity experts to facilitate the development of a guidance document for the development of obesity drugs.

The overriding message from the first day of presentations by experts in the field was that obesity is a chronic disease. And as with any chronic disease, pharmacotherapy is effective only when taken long term. There was no reason to believe, it was pointed out by an academic bariatrician, that a patient with hypertension would benefit long term from a short course of an antihypertensive. Why, then, did some people persist in believing that long-term pharmacotherapy had no place in the treatment of obesity? First, he remarked, “obesity is a stigmatized condition” (G. Bray, Endocrinologic and Metabolic Drugs Advisory Committee Meeting). If obese individuals would simply push themselves from the dining room table, the refrain went, they would have no need for an obesity drug. Second, he noted that obesity drugs suffered under the “negative amphetamine halo.” The approved weight-loss drugs had structural similarities to amphetamine. Thus, many believed that they were addictive and should be avoided. Third, he indicated that in past studies, by and large, pharmacologically induced weight loss was not maintained long term.17
Yet, this bariatrician displayed optimism as he presented data to the committee demonstrating that dexfenfluramine-associated weight loss was sustained for 1 year. Furthermore, combining fenfluramine, a serotonergic compound, with phentermine, an adrenergic compound (fen-phen), he observed, was a very effective way to lose weight and sustain it long term. Some obese individuals treated with this combination, he informed the committee, were able to reach and maintain ideal body weight for as long as 4 years.

“Did any of these studies really address the issue of morbidity and mortality?” asked an advisory committee member (J. Cara, Endocrinologic and Metabolic Drugs Advisory Committee Meeting). “The numbers are too small for mortality,” responded the bariatrician. “I mean, what is the mortality of a 30-year-old population? You need tens of thousands. You really can’t address that question … so the answer is no.” Regarding morbidity, he stressed that the fen-phen studies demonstrated “improved high density lipoprotein cholesterol levels and decreased triglyceride [levels].” Furthermore, “… you can get a reduction in blood pressure with modest reductions in body weight,” he continued. “How would you design a trial to be able to provide data about long-term morbidity and mortality if all you looked at was simply weight loss?” inquired another committee member (E. Siris, Endocrinologic and Metabolic Drugs Advisory Committee Meeting). That, according to the bariatrician, was an issue best handled by the National Institutes of Health, not drug companies. The first studies to demonstrate that lowering cholesterol or blood pressure with drugs reduced cardiovascular morbidity and mortality, he indicated, were government-sponsored trials. Drug development would be stifled, he believed, if companies were required to evaluate morbidity or mortality end points before drug approval.

On the second day of the meeting, a senior FDA official reminded the committee that the obesity drug guidance was not intended to be an obstacle to drug development. Rather, it was viewed as a means to advance the field of obesity pharmacotherapy by ensuring that new drugs were approved on the basis of “sound scientific data showing benefits to health and well-being” (G. Troendle, Endocrinologic and Metabolic Drugs Advisory Committee Meeting). “If the old policies are continued,” she cautioned, “and drugs are approved on the basis of a few kilograms of weight loss for 3- to 6-month intervals following which there is a clear tendency for excess weight to return, medical experts will continue to believe that in the long-run patients would be better off if left untreated.”

Nearing the meeting’s end, the Division asked the advisory committee a number of questions: Is weight loss alone an appropriate end point on which to base approval of a new drug? What degree of weight loss should be considered clinically significant? And what duration of preapproval study is appropriate to assess the efficacy and safety of a new drug?

The majority of the committee believed that weight loss alone would be sufficient for approval, provided that it was clinically significant, which was variously referred to as a 5%, a 5% to 10%, or a 10% to 15% reduction in body weight. Most members supported 1-year trials to assess efficacy, with some recommending a second year for efficacy and safety.

**The 1996 Draft Obesity Drug Guidance**

After the 1995 advisory committee meeting, a draft guidance for obesity drugs was published in 1996. The goal of this guidance was to facilitate the development of drugs to improve health and self-esteem by reducing body fat.

The target population included individuals with a body mass index (BMI) \(\geq 30\ \text{kg/m}^2\) or \(\geq 27\ \text{kg/m}^2\) if accompanied by weight-related comorbidities such as hypertension, dyslipidemia, and type 2 diabetes mellitus. These BMI thresholds reflected a recommendation that individuals be treated when their body weight was at least 20% above “desirable weight” based on Metropolitan Life Insurance data from 1983. A BMI of \(\sim 27\ \text{kg/m}^2\) for men and women corresponded to being 20% above desirable weight and was associated with increased risks for hypertension, hypercholesterolemia, and diabetes mellitus, as well as premature death.

The guidance recommended that the pivotal studies be randomized, double blind, and placebo controlled for 1 year, with open-label drug exposure during a second year. Only subjects whose weight loss plateaued and remained above ideal body weight after at least 6 weeks of lifestyle modification were to be randomized to active drug or placebo. Approximately 1500 subjects were to complete 1 year of double-blind, placebo-controlled treatment, with 200 to 500 completing a second year of open-label drug exposure. These sample sizes mirrored those historically used for the development of lipid-altering drugs and were aimed at assessing safety rather than efficacy because far fewer subjects would generally be necessary to demonstrate statistically significant weight loss. Because diet-induced reductions in body weight of 5% to 10% reduced blood pressure, indexes of glycemia, and levels of triglycerides and increased levels of high-density lipoprotein cholesterol, the guidance used 5% as an efficacy benchmark. In addition to assessing efficacy by comparing the mean changes in body weight between treatment groups, it was also considered informative to compare the frequency of 5% weight-loss responders between treatment groups.

Hence, demonstration of weight-loss efficacy was possible if the drug effect is significantly greater than the placebo effect and the mean drug-associated weight loss exceeds the mean placebo weight loss by at least 5% or the proportion of subjects who lose at least 5% of their initial body weight is significantly greater in subjects on drug than placebo.

Efficacy was to be assessed after 1 year of treatment. Companies were encouraged to measure biomarkers of cardiovascular and metabolic risk because they may have a place in determining the balance of benefit versus risk for the drug.

**Approval of Drugs for the Long-Term Treatment of Obesity**

Although the development programs for dexfenfluramine (Redux), sibutramine (Meridia), and orlistat (Xenical) were initiated before publication of the 1996 draft obesity guidance, they were all aimed at gaining regulatory approval for the treatment of obesity without restriction on the duration of...
use. The mean placebo-subtracted weight loss associated with these drugs after 1 year of treatment was <5%, but a greater proportion of drug-treated compared with placebo-treated subjects lost at least 5% of baseline body weight.26–28 In general, biomarkers of cardiovascular risk moved in the appropriate direction with dexfenfluramine and orlistat.29,30 However, the stimulation of the sympathetic nervous system by sibutramine led to small to modest increases in blood pressure and pulse relative to placebo.31

Some scientists were convinced, on the basis of primate data, that dexfenfluramine was a neurotoxin.32 Others pointed to epidemiological data indicating that dexfenfluramine increased the risk for primary pulmonary hypertension, a rare but fatal disease.33 Because this risk did not manifest until at least 3 months of exposure to the drug, it was argued that the benefit-risk profile could be enhanced by limiting the use of dexfenfluramine to overweight and obese individuals who lost at least 4 pounds during the initial month of treatment because they were more likely to lose at least 10% of their initial body weight by the end of 1 year of treatment.34 The chief safety issue with orlistat was the possibility of developing a fat-soluble vitamin deficiency.35,36 Vitamin supplementation, it was assumed, would negate this potential harm. The sympathomimetic effects of sibutramine were concerning but deemed manageable through monitoring of blood pressure and pulse.

All things considered, the FDA believed that the benefits of these drugs outweighed their risks, and each was approved for the long-term treatment of obesity: dexfenfluramine in 1996, sibutramine in 1997, and orlistat in 1999.

Postapproval data linking dexfenfluramine and fenfluramine (approved in 1973 for short-term use) to cardiac valve damage—requiring valve replacement in some cases—rendered the benefit-risk profiles of these drugs unfavorable.37,38 Both were removed from the market in 1997.

The 2004 FDA Advisory Committee Meeting
In 1998, the National Institutes of Health issued Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.39 In these guidelines, normal weight was defined as a BMI of 18.5 to 24.9 kg/m²; overweight, as a BMI of 25 to 29.9 kg²/m²; obesity, as a BMI ≥30 kg/m²; and extreme obesity, as a BMI ≥40 kg/m². The classifications were based largely on cross-sectional data relating BMI to mortality in which the risk for death in some, but not all, analyses begins to increase at a BMI of ~25 kg/m².40–42 Given the new weight classifications and other developments in the field of obesity since issuance of the 1996 obesity guidance, the Division again convened its external advisory committee and a group of obesity experts in 2004 to discuss updating the guidance document.

Because the recommended target population for drug therapy in the 1996 obesity drug guidance included individuals with BMIs of ≥27 kg/m² and overweight was defined in the 1998 National Institutes of Health guidelines as a BMI of 25 to 29.9 kg/m², a researcher from the Centers for Disease Control and Prevention was asked by the Division to provide the advisory committee with an overview of the epidemiology of overweight, with a focus on data related to individuals with BMIs in the range of 25 to <27 kg/m².

As recent data from the National Health and Nutrition Examination Surveys indicated, the Centers for Disease Control and Prevention researcher pointed out to the committee that ~30 million American adults had a BMI in the range of 25 to <27 kg/m².43 About 12 million, half of whom were ≥60 years of age, had hypertension, hypercholesterolemia, or diabetes mellitus. She highlighted that, in general, the prevalence of diabetes mellitus, hypertension, and hypercholesterolemia increased as BMI increased but without clear inflection points.

There was little information on the health benefits of weight loss in this BMI range of 25 to <27 kg/m², the Centers for Disease Control and Prevention researcher observed, because these individuals had not, for the most part, been included in weight-loss studies. Nonetheless, she remarked, “short-term weight loss has beneficial effects on risk factors such as blood pressure and cholesterol” (K. Flegal, Endocrinologic and Metabolic Drugs Advisory Committee Meeting), and most studies suggest that the relationship between weight loss and risk factor improvement is monotonic.44 “You would infer from this,” she continued, “that weight loss is very likely to improve blood pressure and other risk factors, certainly in the range of BMI of 25 to 27 [kg/m²], as well as perhaps at any weight level.”44 This researcher cautioned, however, that “there are [some] observational studies that suggest some association of weight loss with increased rather than decreased mortality.”44

As an FDA drug use specialist next informed the committee, white women accounted for ~80% of obesity drug prescriptions in the United States, with ~60% of the prescriptions being written for individuals between 18 and 44 years of age and 33% for people 45 to 64 years of age.43 Although the majority of obesity drugs were paid for by cash, the committee learned, third-party payment had increased from ~20% to 30% during the years 1999 to 2003.43

The morning session of the meeting concluded with a presentation by a bariatrician and then president of the American Obesity Association. “I have looked into the eyes of [obese] people and seen the pain and heard the pain as they talk, and I have failed them and I think we have all failed them” (R. Atkinson, Endocrinologic and Metabolic Drugs Advisory Committee Meeting), he opined to the committee.45 Discussing barriers to the use of drugs to treat obesity, he stated that “obesity is the last bastion of socially acceptable bigotry.”45 Physician ignorance was another barrier. Economics played a part. Drugs approved for the long-term treatment of obesity are expensive and “insurance companies and employers are worried about breaking the bank.”45 Additional barriers to obesity drugs were “limited choices and poor efficacy.”45

During the afternoon session, the committee responded to a number of questions posed by the Division, including 3 fundamental ones: Should the target population for drug treatment be expanded to include individuals with BMIs of 25 to <27 kg/m² with an obesity-related comorbidity? Should obesity drug efficacy continue to be judged by the 5% weight-loss benchmark? And should preapproval trials of
Table 1. Key Features of the Food and Drug Administration’s 2007 Draft Obesity Drug Guidance

<table>
<thead>
<tr>
<th>Target population</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI ≥27 kg/m² plus a weight-related comorbidity or a BMI ≥30 kg/m²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Size and duration of the phase 3 clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4500 Overweight and obese subjects studied for at least 1 y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean placebo-subtracted weight loss ≥5% or proportion of drug-treated subjects who lose ≥5% of baseline body weight is ≥35% and approximately double the proportion who lose ≥5% in the placebo group</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary end points of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure and pulse</td>
</tr>
<tr>
<td>Lipoprotein lipids</td>
</tr>
<tr>
<td>Fasting glucose and insulin</td>
</tr>
<tr>
<td>Hemoglobin A1c (in diabetics)</td>
</tr>
<tr>
<td>Waist circumference</td>
</tr>
<tr>
<td>Quality of life</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary analysis population</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Intention to treat”</td>
</tr>
<tr>
<td>BMI indicates body mass index.</td>
</tr>
</tbody>
</table>

Investigational obesity drugs include a second year of open-label drug exposure.

Some panelists recommended lowering the target population to include individuals with BMIs of 25 to <27 kg/m² with at least 1 obesity-related comorbidity; however, the majority favored keeping the BMI cutoff at ≥27 kg/m² when accompanied by a comorbidity. As 1 panelist commented, “…because we don’t have outcomes data related to mortality or morbidity [with drug-induced weight loss], I personally would not lower the BMI cut point ….” (M. Wierman, Endocrinologic and Metabolic Drugs Advisory Committee Meeting).

There was uniform agreement by the committee that weight-loss efficacy should continue to be defined by the 5% benchmark. Some panelists favored a second year of open-label drug exposure, although more believed that 1-year trials would provide sufficient data to assess the preapproval efficacy and safety of a new obesity drug.

The 2007 Draft Obesity Drug Guidance

After this latest advisory committee meeting, an updated draft guidance was issued in 2007 for the purpose of facilitating development of obesity drugs for medical weight loss, 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 hemoglobin A1c (Table 1).

The target population for inclusion in studies of investigational obesity drugs remains individuals with a BMI ≥30 kg/m² or ≥27 kg/m² when accompanied by weight-related comorbidities. The 2007 draft guidance recommends that subjects with extreme obesity (ie, BMI >40 kg/m²) be included in development programs. To define efficacy and to provide a reasonable estimate of safety, the guidance recommends that ≥3000 subjects be randomized to active doses of the investigational drug and no fewer than 1500 subjects be randomized to placebo for 1 year. This sample size provides 80% power to rule out with 95% confidence an ∼50% increase in the incidence of an adverse event that occurs at a rate of 3% in the placebo group (ie, 4.5% versus 3%).

To simulate the real-world setting, a lifestyle modification program that strikes an appropriate balance between effectiveness and simplicity was recommended as standard of care for all study subjects.

Efficacy continues to be assessed with the 5% mean and categorical criteria: The difference in mean weight loss between active-treated and placebo-treated groups is at least 5% and the difference is statistically significant, and the proportion of subjects who lose ≥5% of baseline body weight in the active-treated group is at least 35%, approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

The standard that the proportion of active-treated group who lose ≥5% of baseline body weight be at least 35% and approximately double the proportion in the placebo group was based on clinical trial data from previously approved obesity drugs. In long-term studies of sibutramine and orlistat, the proportion of subjects treated with active drug plus lifestyle modification who lost at least 5% of baseline body weight was generally double the proportion of subjects treated with placebo plus lifestyle modification. Moreover, because the absolute proportion of subjects losing at least 5% of baseline body weight is directly related to the intensity of the lifestyle modification program, data from a clinical trial of orlistat conducted in the primary care setting that used a realistic real-world lifestyle modification program provided the basis for the requirement that at least 35% of subjects treated with active drug lose at least 5% of baseline body weight.

In general, an obesity drug will be considered effective if after 1 year of treatment either of the above efficacy criteria was satisfied. Moreover, improvements in blood pressure, lipids, glycemia, and other weight-related comorbidities commensurate with the degree of weight loss are expected and will be factored into the benefit-risk assessment of the drug.

The dropout rates in long-term obesity drug trials have historically been high (eg, ∼40%–50%). Although the guidance does not stipulate a maximally tolerated dropout rate, in addition to encouraging companies to do all they can to increase subject retention, the guidance recommends that body weight measurements in all subjects who prematurely withdraw from long-term clinical trials be obtained near the calendar date at which they were scheduled to complete the trial. This will allow the primary efficacy analyses to be conducted with a modified intention-to-treat population, defined as subjects who received at least 1 dose of study drug and have at least 1 postbaseline assessment of body weight. To assess the effect of dropouts on the weight-loss results, companies are encouraged to conduct sensitivity analyses using imputation strategies.

New to the 2007 draft guidance are sections on the study of overweight and obese individuals with type 2 diabetes, combination drug therapy, the treatment of medication-induced weight gain, and the development of obesity drugs for the pediatric population.
Study in Overweight and Obese Type 2 Diabetics

Compared with nondiabetic subjects, overweight and obese subjects with type 2 diabetes mellitus often lose less weight on obesity drugs and may face unique safety issues such as risk for sulfonylurea-induced hypoglycemia after weight loss (if the dose of sulfonylurea is not appropriately lowered or the drug discontinued). Therefore, the 2007 draft guidance recommends that the efficacy and safety of obesity drugs be examined in a trial dedicated to overweight and obese subjects with type 2 diabetes mellitus. Successful completion of a single trial may lead to inclusion of glycemia-related data in the clinical studies section of the labeling of the drug but is not considered sufficient to support approval of a standalone indication for the treatment of type 2 diabetes mellitus.

Companies interested in obtaining a standalone indication for the treatment of type 2 diabetes mellitus for their obesity drug are required to study their drug comprehensively as an antidiabetic agent and are referred to the FDA guidance documents Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention and Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.

Of note, the 2007 draft obesity drug guidance states that for an obesity drug to obtain a standalone indication for the treatment of type 2 diabetes mellitus, it should be shown that the drug effectively treats type 2 diabetes mellitus through a mechanism that is independent of weight loss. However, the agency has reconsidered this requirement since issuance of the draft guidance. Thus, a drug with a principal mechanism of action of weight loss may gain approval and a standalone indication for the treatment of type 2 diabetes mellitus by showing clinically and statistically significant improvement in glycemia within the context of a full development program aligned with the 2 antidiabetic drug guidance documents.

Parenthetically, a weight-loss–inducing antidiabetic drug could be approved for the treatment of obesity if the weight loss satisfied the mean or categorical obesity drug efficacy criterion and the development program was, in general, aligned with the key features of the obesity drug guidance, including study in overweight and obese nondiabetic subjects.

Fixed-Dose Combination Products

Two or more drugs may be combined into a single fixed-dose combination 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. Special cases of this general rule include the addition of a component to enhance the safety or effectiveness of the principal component or to minimize the potential for abuse of the principal active component.

The draft guidance recommends that the efficacy and safety of fixed-dose combination obesity drugs be compared with the individual components and placebo in phase 2 trials of sufficient duration to capture the maximal or near-maximal weight-loss effects of the drugs. Although the guidance does not define a minimum difference in weight loss between a fixed-dose combination and its individual components, a combination drug that is associated with at least twice the weight loss observed with each of the individual components will be viewed more favorably than a combination that does not achieve this degree of relative weight loss. If a fixed-dose combination drug is shown to be more effective than its individual components in a phase 2 study, the phase 3 trials may be limited to examining the efficacy and safety of the combination compared with placebo over the course of 1 year. The efficacy of the combination will be assessed with the standard 5% mean and categorical weight-loss criteria.

Treatment of Medication-Induced Weight Gain

A number of drugs, notably psychotropics, are associated with moderate to marked weight gain and new-onset type 2 diabetes mellitus. The 2007 draft guidance recommends that subjects eligible for participation in trials examining the efficacy and safety of obesity drugs for the treatment of medication-induced weight gain have a documented increase in body weight of at least 5% within 6 months of starting a drug known to cause weight gain. Furthermore, subjects should have BMIs ≥30 kg/m² or ≥27 kg/m² with comorbidities at the time of study screening. Because many, if not most, obesity drugs act within the central nervous system, as do many drugs that cause weight gain, the guidance stresses the need to demonstrate that the efficacy and safety of the medication causing weight gain are not adversely affected by a centrally acting obesity drug. For example, it would be important to document that the efficacy of an antipsychotic used to treat schizophrenia was not diminished when coadministered with a centrally acting obesity drug. Efficacy of a drug used to treat medication-induced weight gain will be assessed with the standard 5% mean and categorical weight-loss criteria.

Obesity Drug Development in the Pediatric Population

In terms of obesity drug therapy for children and adolescents, the 2007 draft guidance recommends that the efficacy and safety of an investigational obesity drug first be examined in adults before studies are initiated in pediatric subjects. Additionally, to ensure that the most appropriate dose or doses are studied, an assessment of the pharmacokinetics of an obesity drug in pediatric subjects may be necessary before embarking on long-term studies. Trials examining the efficacy and safety of obesity drugs in pediatric subjects should be randomized, double blind, and placebo controlled and should be 1 year in duration.

Initial studies should be limited to adolescents (ie, 12–16 year olds) with age- and sex-matched BMIs >95th percentile and ≥1 weight-related comorbidities. Once a satisfactory benefit-risk profile has been established in this high-risk group, studies of lower-risk adolescents or children will be considered. Linear growth needs to be taken into account in assessments of changes in body weight of pediatric subjects. Hence, the primary efficacy parameter of obesity drugs in pediatric subjects should be a function of the change in BMI. The 2007 draft guidance does not provide a sample size for the phase 3 trials of pediatric subjects. Rather, the size of the pediatric development program will be determined on the
basis of the mechanism of action of the drug and its safety profile in adults.

The efficacy assessment of an obesity drug in pediatric subjects will take into account the effectiveness of the product in adults and the magnitude of the difference in the mean and categorical changes in BMI in active- versus placebo-treated subjects.

With respect to the overall safety assessment of investigational obesity drugs, in addition to standard biochemical and clinical monitoring of patients, on the basis of research implicating activation of the 5HT2c receptor as the mechanism responsible for dexfenfluramine- and fenfluramine-associated valvular heart disease, the 2007 draft guidance recommends that serotonergic compounds that interact directly with the 5HT2 receptor system be evaluated with serial echocardiography to rule out cardiac valve injury.55,56 Moreover, the draft guidance notes that as new scientific data emerge, the need for specific safety assessments for investigational obesity drugs may change accordingly. As detailed below, recent experience with rimonabant and sibutramine is illustrative in this regard.

**Rimonabant**

The endocannabinoid system is involved in a vast array of physiological functions, including energy homeostasis. Activation of cannabinoid type 1 receptors in the central nervous system influences appetite and feeding behavior, whereas activation in the periphery affects substrate metabolism in fat, skeletal, and liver cells.57 Rimonabant was the first-in-class cannabinoid type 1 receptor antagonist developed for the treatment of obesity.

Data submitted to the FDA in a new drug application in 2005 indicated that, over the course of 1 year, rimonabant 20 mg once daily was associated with an $\sim 5\%$ mean reduction in body weight compared with placebo in overweight and obese nondiabetics.58 Approximately 50% of rimonabant-treated subjects lost at least 5% of initial body weight compared with $\sim 20\%$ of placebo-treated subjects. Changes in biomarkers of cardiovascular and metabolic risk were favorable with rimonabant treatment. Thus, rimonabant was an effective obesity drug when gauged by the standards of the draft obesity drug guidance.

However, the doubling of reports of anxiety and depression, a signal for suicidal ideation as identified by a retrospective analysis of adverse event data, and an ill-defined constellation of neurological signs and symptoms in rimonabant-treated subjects led an FDA advisory committee to unanimously conclude that, on the basis of the available data, the potential benefits of rimonabant did not outweigh the potential risks.59 The rimonabant application was voluntarily withdrawn from the FDA by the sponsor shortly after the advisory committee meeting. On the basis of this experience, the draft obesity guidance recommends that the development programs for centrally acting obesity drugs prospectively assess neuropsychiatric function, including suicidality, with validated instruments.

Meanwhile, the European Medicines Agency had approved rimonabant for the treatment of obesity in 2006. And the favorable changes in biomarkers of cardiometabolic risk associated with rimonabant led the sponsor of the drug to initiate the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial in 2005. This study of $\sim 9000$ subjects randomized to rimonabant and $\sim 9000$ to placebo was powered to demonstrate a 15% reduction in the relative risk of major cardiovascular events in rimonabant-treated subjects. Demonstration that long-term treatment with rimonabant reduced the incidence of cardiovascular death, myocardial infarction, or stroke would have greatly enhanced the benefit-risk profile of the drug.

But, in January 2009, the European Medicines Agency suspended the marketing authorization for rimonabant.60 This action followed an updated assessment of available data indicating that the risk for serious psychiatric disorders, including suicide, appeared to be higher than observed in the preapproval clinical trials. Together with evidence that many real-world patients were taking rimonabant for short periods of time and therefore were unable to reap the benefits of sustained weight loss, European regulators concluded that the benefits of rimonabant no longer outweighed its risks. At the time the marketing and worldwide study of rimonabant came to an end, participants in the CRESCENDO trial had been treated for an average of 13.8 months (planned duration was at least 33 months). The interim hazard ratio for major cardiovascular events was 0.97 (95% confidence interval, 0.84–1.12; $P=0.68$).61 Psychiatric disorders were reported by 32% of the subjects in the rimonabant group compared with 21% of the subjects in the placebo group. Four individuals randomized to rimonabant committed suicide compared with 1 randomized to placebo.

**Sibutramine and the Sibutramine Cardiovascular Outcomes Trial**

From 2002 to 2009, the Sibutramine Cardiovascular Outcomes (SCOUT) trial was conducted in Europe, Australia, and Latin America. SCOUT was a randomized, double-blind, placebo-controlled study designed to test the hypothesis that long-term treatment with sibutramine reduces the risk for major cardiovascular events.62 Approximately 10 000 overweight and obese subjects between 51 and 88 years of age with or at risk for cardiovascular disease received lifestyle modification plus once-daily placebo or lifestyle modification plus 10 or 15 mg once-daily sibutramine. Three cardiovascular risk subgroups were defined at baseline: (1) subjects with type 2 diabetes mellitus with no history of cardiovascular disease, (2) those with a history of cardiovascular disease without type 2 diabetes mellitus, and (3) subjects with a history of cardiovascular disease with type 2 diabetes mellitus.

After an average of 3.4 years of treatment, the mean reduction in body weight was 3.8% in the sibutramine group and 1.8% in the placebo group. Throughout the trial, mean systolic and diastolic blood pressures and heart rate were slightly and statistically significantly higher in the sibutramine compared with the placebo group. The incidence of major cardiovascular events, defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or resuscitated cardiac arrest, was 11.4% in the sibutramine group compared with 10% in the placebo group (hazard ratio, 1.16;
Table 2. Incidence of Major Adverse Cardiac Events in Subgroups of Cardiovascular Risk From the SCOUT Trial

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Sibutramine</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
<th>Interaction P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>1151</td>
<td>1141</td>
<td></td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>CVD only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>722</td>
<td>745</td>
<td></td>
<td>1.3</td>
<td>0.91–1.80</td>
</tr>
<tr>
<td>CVD + DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>3016</td>
<td>2998</td>
<td></td>
<td>1.2</td>
<td>1.0–1.40</td>
</tr>
</tbody>
</table>

SCOUT indicates Sibutramine Cardiovascular Outcomes trial; MACE, major adverse cardiac events; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; and CV, cardiovascular disease.

*Log-rank test interaction P value.

95% confidence interval, 1.03–1.31; P=0.02). This risk corresponds to ∼4 excess major cardiovascular events per 1000 patient-years. Interestingly, post hoc exploratory analyses suggested that sibutramine-associated increases in blood pressure did not predict increased risk for major cardiovascular events.

Although the results of SCOUT indicated that sibutramine increased rather than decreased the risk for cardiovascular events, Abbott Laboratories, the sponsor of the drug, questioned the relevance of the data to the real-world setting. The labeling for sibutramine recommended against use in individuals with a history of cardiovascular disease because of its sympathomimetic properties, whereas roughly 75% of subjects enrolled in SCOUT had a history of coronary artery, cerebrovascular, and/or peripheral artery disease. This enrichment, however, was necessary to ensure a sufficient number of clinical events to examine the effect of sibutramine on the atherothrombotic process. Nonetheless, it was argued that because ∼60% of individuals prescribed sibutramine in the United States were <50 years of age, many without a history of cardiovascular disease, the results of SCOUT were less than informative. Support for this was found in the cardiovascular risk subgroup analysis from SCOUT. The hazard ratio for major cardiovascular events in the subgroup of subjects without a history of cardiovascular disease was 1.0 (95% confidence interval, 0.72–1.40; Table 2). Yet, there was no statistical evidence of treatment heterogeneity among the 3 cardiovascular risk subgroups (log-rank interaction, P=0.56). Furthermore, the results in the subgroup without documented cardiovascular disease were consistent with as much as a 40% increase in the relative risk for major cardiovascular events. Additionally, prescription-use data indicated that people >50 years of age, some with congestive heart failure, ischemic heart disease, or cardiac arrhythmias, were being prescribed sibutramine.

Absent convincing evidence that sibutramine offered noncardiovascular benefits to offset the cardiovascular risk observed in the SCOUT trial, the FDA concluded that, at the population level, the benefit-risk profile of the drug was unfavorable. Moreover, the FDA determined that risk-mitigation strategies aimed at enhancing the benefit-risk profile of sibutramine at the individual-patient level, by, for example, ruling out subclinical cardiovascular disease before sibutramine was started or using on-drug increases in blood pressure as a predictor of cardiovascular risk, were impractical and not supported by clinical trial data, respectively.

On October 8, 2010, sibutramine was voluntary withdrawn from the US market.

Given the experience with sibutramine, the Division plans to hold an advisory committee meeting in 2012 to discuss what role cardiovascular risk assessment should play in the overall benefit-risk evaluation of obesity drugs, in particular those with pressor effects.

New Obesity Drugs

In 2010, the Division held public advisory committee meetings to discuss 3 new obesity drug applications: (1) a fixed-dose combination of phentermine and topiramate, (2) lorcaserin, and (3) a fixed-dose combination of naltrexone and bupropion. At the time of this writing, these 3 applications remain under FDA review. Because a federal regulation precludes the FDA from publicly discussing information about unapproved applications except under certain situations such as a public advisory committee meeting, interested readers are referred to the proceedings from the 2010 advisory committee meetings for details on the efficacy and safety profiles of phentermine plus topiramate, lorcaserin, and naltrexone plus bupropion.

Conclusions

As several academic bariatricians recently wrote, “many factors have mitigated against active drug development, including the poor safety and efficacy of previously approved antiobesity drugs.” Nevertheless, despite this unfortunate history, obesity drug research remains very active. Moreover, the adverse physical, emotional, and economic effects of obesity ensure that the goals of developing and approving obesity drugs with favorable benefit-risk profiles will endure.

Disclosures

None.

References


16. Bray G. Presented at: Endocrinologic and Metabolic Drugs Advisory Committee Meeting; January 19–20, 1995; Silver Spring, MD.


20. Cara J. Presented at: Endocrinologic and Metabolic Drugs Advisory Committee Meeting; January 19–20, 1995; Silver Spring, MD.

21. Siris E. Presented at: Endocrinologic and Metabolic Drugs Advisory Committee Meeting; January 19–20, 1995; Silver Spring, MD.

22. Troendle G. Presented at: Endocrinologic and Metabolic Drugs Advisory Committee Meeting; January 19–20, 1995; Silver Spring, MD.


33. Flegal K. Presented at: Endocrinologic and Metabolic Drugs Advisory Committee Meeting; September 8, 2004; Silver Spring, MD.

34. Atkinson R. Presented at: Endocrinologic and Metabolic Drugs Advisory Committee Meeting; September 8, 2004; Silver Spring, MD.

35. Wierman M. Presented at: Endocrinologic and Metabolic Drugs Advisory Committee Meeting; September 8, 2004; Silver Spring, MD.


63. US Food and Drug Administration. Transcript for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting; Silver Spring, MD: US Food and Drug Administration; September 15, 2010.

64. US Food and Drug Administration. Transcript for the Endocrinologic and Metabolic Drugs Advisory Committee Meeting; Silver Spring, MD: US Food and Drug Administration; September 15, 2010.


71. Availability for public disclosure of data and information in an application or abbreviated application. Code of Federal Regulations. Title 21, Pt 314.430 (d)(1).


KEY WORDS: cholesterol, diabetes mellitus, type 2, hypertension, lipids, obesity