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Council 2007

April 9, 2007

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Food and Drug Administration
5600 Fishers Lane
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President-Elect
Gary Foster, PhD
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RE: Docket No. 2007D-0040

Draft Guidance for Industry on Developing Products for Weight Management

Vice-President
David Allison, PhD
University of Alabama
Birmingham, AL

Dear Sir:

Immediate Past President
Thomas Wadden, PhD
University of Pennsylvania
Philadelphia, PA

Thank you for the opportunity to comment on the Draft Guidance for Industry on Developing Products for Weight Management published on February 15, 2007 at Fed. Reg. 72;31:7441-7442. The Obesity Society (formerly called the North American Association for the Study of Obesity, NAASO) is North America's premier scientific and medical society composed of some 1,800 researchers and clinicians. The Society publishes the leading peer-reviewed journal in the field, *Obesity*, and conducts the largest and most comprehensive annual scientific meeting on obesity in North America.

Secretary/Treasurer
Caroline Apovian, MD
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Boston, MA

We applaud the Food and Drug Administration for publishing the draft guidance and support most of its provisions. Our specific comments are intended to support and enhance the overall direction of the document.

Councilors
Penny Gorden-Larsen, PhD
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Since the announcement of this draft document, The Obesity Society has consulted with its members who conduct pharmacological and non-pharmacological research. The following comments are, to the best of our ability, a reflection of widely-shared observations on the draft document.

Regional IASO Vice-President
Jennifer Lovejoy, PhD

Executive Vice President
Morgan Downey, J.D.

At the outset, we note two changes from the current (1996 Draft Guidance). The first is the elimination of the run-in period for clinical trials and a second year study to collect safety data. We agree that such provisions should be eliminated.

2007 D-0040

C3

1. Introduction

“Section I, 1.22-25: “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.”

Comment: The document addresses three issues: (a) weight management (b) medical weight loss and (c) obesity. “Weight management” is a broad category including prevention of weight gain in both overweight and obese patients and in the non-overweight category as well as weight gain in populations experiencing involuntary weight loss, such as patients with HIV/AIDs, some cancers and other diseases. Therefore, it is too broad for the content of the guidance. “Medical Weight Loss” is also a broad category encompassing both obesity and non-obesity conditions and may encompass different interventions than drugs. Since this document addresses obesity (as defined by Body Mass Index cut points) we suggest that the document be re-named, “Draft Guidance for Industry on Developing Products for the Treatment of Obesity”

2. Weight Maintenance

Section I, 1.35: “This guidance does not explicitly discuss indications for weight loss or maintenance of loss weight (which also can be described as prevention of weight regain); however, weight loss and weight management 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.”

Comment: We find this language confusing. One product may produce significant weight loss continually with no maintenance. Another product might successfully maintain present body weight but not produce significant weight loss. It appears to be asking a great deal of one product to effect both meaningful weight loss and long term weight maintenance. We recommend that these be made separate indications.

3. Requirement for Lifestyle Modification

Section III, A, 1.117: “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.” (Emphasis in original).

Comment: We agree that lifestyle modification is important in obesity management. However, we do not agree that the patient must have failed on a “sufficient trial” of lifestyle modification. We note that public opinion polling has

consistently observed that large numbers of American adults are trying to lose weight at any one time. Most Americans try several lifestyle changes before presenting for drug intervention or surgery. Were such language reflected in labeling conditions, state medical board requirements or third-party payor requirements, many patients would have treatment delayed to the detriment of their health and self-confidence by 'failing' once again. We observe that other, similar conditions like high blood pressure and high cholesterol, which may also be positively affected by lifestyle modifications, do not have similar restrictive language from the Food and Drug Administration. In practice, for these conditions lifestyle changes and drug treatments are often instituted simultaneously not sequentially.

The section is also unclear on what constitutes a "sufficient trial" of lifestyle modification. Is the intent a specific weight loss treatment in an organized program, documented by a healthcare provider or is it taking the patient's word that they have tried self-help regimens without success?

It is also unclear how the anticipated benefits of weight loss are to be compared to the "unknown" risks of treatment of a particular weight loss product. The implication of this language is that all possible future obesity treatment products will have some unknown risk. As noted, all drug therapies may impose some risk. Drugs for obesity treatments should not be treated differently from other diseases nor should patients or physicians be made to fear unknown effects without evidence.

4. BMI Categories

Section III, A, 1.125: "Patients with BMIs greater than or equal to 30 kg/m² or greater than or equal to 27 kg/m² 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/m² or greater than or equal to 27 kg/m² if accompanied by weight-related comorbidities represent patient groups with sufficient baseline risk to justify inclusion in studies of investigational weight-management products."

Comment: We note that the applicability of BMI cutoff points for different racial and ethnic groups is a topic of active research. Latitude should be given to investigators looking for safety and efficacy in such important subgroups at lower BMI levels. We also agree with including more subjects with morbid or severe obesity, i.e. BMI > 40 in clinical trials, in numbers sufficient to determine whether the investigational medication has significant effect on weight and/or comorbidities within this group.

5. Pediatric Population

Section III, B, 1.160: “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 comorbidities. (*Italics in original*).

Comment: We are not aware of any evidence that outcomes are better in adolescents who engage in lifestyle modification before starting a drug regimen compared to those initiating both lifestyle modification and drug intervention at the same time.

6. Phase 3 Clinical Trials

Section IV, B, 3, 1.230: “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 of 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.

Comment: Body weight is a marker for excess adipose tissue. DEXA, plethysmography and bioelectrical impedance are better measures of excess adiposity than body weight. While not all subjects need to be measured by these techniques, a subgroup should be so measured to correlate loss of body weight with loss of adipose tissue.

7. Combination Therapies

Section IV, D, 1. 360: “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 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 each of the individual components will be viewed more favorably than combinations that do not achieve this degree of relative weight loss.” (Emphasis added).

Comment: A doubling of the weight loss effect in combination therapy is too high a threshold for combination therapies. Some additive value should be demonstrated or a reduction in adverse events.

8. Medication-Induced Weight Gain

Section IV, E, 1.394: "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% within 6 months of starting a drug known to cause weight gain."

Comment: Because there are specific medications known to be associated with weight gain and/or obesity-associated comorbidities, we recommend that trials of weight management medications for patients with medication-induced weight gain or obesity-associated comorbidities be conducted with patients from the time they are placed on such medications and further recommend that the primary outcome measures be differences between experimental and control groups in weight gain and development of comorbidities risk factors.

9. Stand Alone Indications

"Section VIII. L.553: "Stand-Alone Indications for the Prevention or Treatment of Weight Related Comorbidities. As mentioned earlier, weight loss through life-style modification is associated with improvements in blood pressure, lipid levels, glucose and insulin metabolism, and other physiometabolic endpoints. Improvements in these comorbidities 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." (Emphasis Added).

Comment: "Independent" effect should be eliminated. It is inexplicable that obesity products would have to demonstrate improvement in blood pressure, lipid levels, glucose and insulin metabolism for approval but could not receive an indication for these conditions for lack of an "independent" mechanism. Such a requirement only serves to keep patients and their doctors unaware of the powerful effects of weight loss on improving these coronary heart disease risk factors.

Thank you again for the opportunity to comment on this draft. We would be pleased to provide any additional information the agency may request.

Sincerely,



Eric Ravussin, Ph.D.
President