

March 28, 2007

Division of Dockets Management (HFA-305)  
US Food and Drug Administration  
5630 Fishers Lane Rm 1061  
Rockville, MD 20852

Re: Docket # 2007D-0040; GUIDANCE FOR INDUSTRY: Developing Products for Weight Management: DRAFT Guidance February 2007

Dear Dr. Colman and Associates:

This response represents the input from several physicians at the Pennington Biomedical Research Center, a Division of Louisiana State University in Baton Rouge, Louisiana. It was written by myself, George A. Bray, M.D. and edited and supplemented by the other signatories. As the principal author, I have had a long-standing interest in this Guidance process, having participated in the pre-conference for the 1995 DRAFT and having responded to an earlier version of this proposal. My colleagues at the Pennington Center have also had many years of experience with obesity, exercise physiology, and clinical trials, on which we have all been called upon for our comments.

Collectively, we want to thank the FDA for this thoughtful document. It has several important additions, including:

1. A discussion of the pediatric population.
2. A discussion of medications to prevent weight gain associated with some psychoactive drugs.
3. A discussion of the metabolic syndrome.

In responding to the document, we want to begin by making three general points. We will respond line-by-line to other parts of the document.

1. Since obesity is a problem among the elderly, and since this segment of our population is increasing more rapidly than some other segments of the American population, we would encourage the FDA to ADD a section B, titled: "The Elderly Population" to follow the Adult Population after line 134. Such issues as losing height (which will amplify BMI), sarcopenia in the elderly, and the difficulty of the elderly accruing muscle after it has been lost, suggest that somewhat different criteria should be used in testing drugs for the elderly than those for younger adults. The position statement from NAASO, the Obesity Society, and the American Society for Nutrition might be useful as a reference (Villareal DT, et al. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. *Obes Res* 2005;13:1849-1863)

2. In order to define an indication for weight-loss products, you use BMI >30 kg/m<sup>2</sup> or BMI >27 kg/m<sup>2</sup> with co-morbidities. Perhaps the time has come to rethink the rationale for this. If I remember correctly, the BMI of 27 kg/m<sup>2</sup> originated at the time that a BMI of just about 27 (27.4 and 27.8 kg/m<sup>2</sup>) was used as the upper limit for normal, based on earlier NCHS criteria. The relatively low risk associated with BMI 25-29 kg/m<sup>2</sup> would suggest that including people with a BMI >30 kg/m<sup>2</sup> would provide enough individuals, since 30% of the US adult population meets this criterion. This would avoid the issues of having to identify "co-morbidities" when including people with a BMI of 27-29.9 kg/m<sup>2</sup>. Thus, we suggest that the FDA adopt a SINGLE, lower BMI level of 30 kg/m<sup>2</sup> for clinical trials of weight-loss medication.

However, if the goal is to provide access to weight-loss medications to individuals who are overweight and who would benefit from weight loss, by virtue of being at higher risk (i.e., having co-morbidities), then a BMI >25 might be more appropriate. There is ample evidence that certain ethnic groups (Asians, for example) experience greater risk for morbidity at lower BMI than we see in the typical US population.

3. Third, we endorse your concept that, for a weight-loss product to be given an indication for one of the "co-morbidities" or for the Metabolic Syndrome, that weight-loss drug must work through a mechanism that is independent of weight loss.

#### Specific Comments:

Line 23: You note that this guidance applies to long-term reduction in body fat mass with a goal of reduced morbidity and mortality. Since visceral fat and subcutaneous fat can be manipulated selectively (liposuction, omentectomy, thiazolidinediones, growth hormone, cortisol), we can conceive of developing drugs that would selectively reduce visceral adipose tissue with resulting major benefits. This would not fit into your guidance, and we would suggest adding the words:

"or selective fat deposits" after "long-term reduction in fat mass."

Line 81: You might want to consider adding the reference by Poirier P et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2006;113:898-918.

Line 84: The line implies that risk stops at BMI 40 kg/m<sup>2</sup>. It might be more appropriate to indicate that risk rises progressively as BMI increases above 25 kg/m<sup>2</sup>.

Line 86: The WHO Consultation was held in June 1997 and the preliminary report issued in 1998. It was based on the International Obesity Task Force report that was issued in early 1997. This was checked with Professor Philip James, M.D. head of the IOTF.

Line 99: The waist circumference values of >40 inches for men and >35 inches for women need to be interpreted in an ethnically specific manner. The International Diabetes Federation and the Asian Obesity Task Force have recommended much lower values for men and women. The 40- and 35-inch criteria reflect an Americocentric view, which is probably too generous.

Line 108: In addition to the paper by Douketis, you might want to reference the exceptional meta-analysis by Avenell et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health Technol Assess* 2004; 8: iii-iv, 1-182.

Line 121: The word "failed" needs to be defined. Do you mean cessation of weight loss? Weight loss of <5%? Weight loss with subsequent regain? The principal author of this response comes from the time when low-sodium diets were used to treat hypertension. As soon as good drugs (thiazides) first appeared in 1958, the "lifestyle" strategy took a back seat. We suspect that the same thing will happen with obesity when more safe and effective drugs become available.

Line 125: Again, we would endorse a simpler approach by requiring a BMI >30 kg/m<sup>2</sup>. The paper by Flegal and colleagues (Flegal K et al. Excess deaths associated with underweight, overweight, and obesity. *JAMA* 2005;293: 1861-1867) argued that, from the National Center for Health Statistics data, a BMI in the "overweight" range (BMI 25-29 kg/m<sup>2</sup>) had a lower risk than a BMI of 18.5-24.9 kg/m<sup>2</sup>.

Line 156: We suggest inserting "potential" before "genetic."

Line 161: Here again, the word "failed," and the fact that this must happen **before** anything else can be done, need reconsideration.

Line 176: We suggest increasing the BMI to >40 kg/m<sup>2</sup> here.

Line 219-220: Does this mean that 4500 patients would need to be randomized? That is how the sentences seem to read now.

Line 256: We completely agree that waist circumference should not be the only measure of visceral fat, since liposuction will reduce waist circumference without changing VAT. Moreover, we can imagine a setting in which visceral fat could remain stable while subcutaneous fat increased, yet risk factors were reduced, as happened during treatment with pioglitazone (Smith SR et al. Effect of pioglitazone on body composition and energy expenditure: A randomized controlled trial. *Metabolism* 2005;54:24-32).

Line 301: In the Look AHEAD study of weight loss in diabetic patients, the lifestyle program produced a weight loss of nearly 8.5%, which is better than in the Diabetes Prevention Program. Thus, the idea that diabetics cannot lose weight effectively may not be true.

Line 308: Since the goal of the American Diabetes Association clinical guidelines encourages a HbA1c value <7% as a general treatment goal, with a value as close to normal (<6%) as possible without significant hypoglycemia (American Diabetes Association Position Statement, *Diabetes Care* 2007;30[S1]: S4-S41), diabetes management has become more aggressive toward blood glucose levels in these patients, with HbA1c values >8% less common and less representative of the general obese type 2 diabetes patient. Thus, because the use of an HbA1c inclusion criterion cutoff of 8% or greater would leave a substantial proportion of these patients not represented in a clinical trial population, and make patient enrollment into the study difficult, we would have the lower limit for HbA1c be 7.0 rather than 8.0

Line 314: Sulfonylurea medications have been associated with hypoglycemia upon initiation of dietary interventions, and may require dose reduction in patients experiencing hypoglycemia, while other oral diabetes medications do not. The magnitude of the drop in HbA1c in diabetes studies appears to be directly proportional to the baseline level of HbA1c, irrespective of drug class (Bloomgarden ZT et al. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. *Diabetes Care* 2006;29:2137-2139). Thus, considering the number of anti-diabetic drugs now available, I believe that stratification should be for sulfonylurea medications and for glycohemoglobin values above and below 8%. Further stratification runs the risk of creating groups too small for meaningful analysis.

Line 420: A recent article suggests that weight gain associated with anti-psychotics is related to the histamine-1 receptor and may be a class effect (Kim SF et al. Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. *Proc Natl Acad Sci U S A.* 2007;104:3456-3459). Thus, you might want to consider making the demonstration of a weight-loss response to one member of a "class" of drugs that produce weight gain as appropriate for use against other members of the same class that produce weight gain. Thus the third generation of anti-psychotics with weight gain (clozapine, olanzepine, and risperidone) might be grouped together, as might the serotonergic anti-depressants.

Line 451: The co-morbidities are of much lower prevalence in adolescents than in adults. Using this criterion will make it difficult to enroll adequate numbers in these trials.

Lines 498 and later Lines 531. We like the idea of weighing all patients at the end of a trial. However, when patients "withdraw" and/or "withdraw consent," we are not allowed to pursue them. We certainly endorse a study design whereby subjects who stop medications are not withdrawn but are scheduled to return for a final weight at study end. That is not the current usual practice. The practicalities are that the percentage (or number) of drop-outs will be significant in weight-loss trials, since enrolled volunteers who are not losing weight do not wish to return for weighing, and those who experience adverse events are unlikely to wish to pursue the study. And in one sense, the drop-out is informative. It is telling us something about the efficacy and tolerability (weight loss and

drug side effects) of the agent being tested. Fewer patients may drop out from arms of clinical trials with effective drugs, as compared to placebo, unless the side effects of the drug pose a problem. We would thus encourage clinical trials to evaluate BOTH completers (those who reached the last measurement taking medication) AND those who stop taking medication (as much as possible).

A useful statistic for clinicians is the percentage of the enrolled population achieving 5% weight loss and comparing drug versus placebo. That figure tells the clinician what the odds are that the patient for whom s/he is prescribing will have clinically meaningful weight loss.

Mean weight loss of completers tells physicians what we can tell patients about how much weight they will lose, on average, if they continue to take the medication for a defined period.

The drop-outs tell us about the "tolerability" issues and give clinicians information to transmit to our patients about how easy or difficult it will be to take the medication.

Although statisticians want ITT, we believe that these other analyses are more informative for the clinical practice of medicine.

We appreciate the opportunity to respond to the DRAFT Guidance from the US Food and Drug Administration, and we will be happy to answer questions that you may have. We have included our individual e-mail addresses for that purpose.

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