Comments on: Draft Guidance for Industry Developing Products for Weight Management

Pertaining to Docket No: 2007D-0040.

Submitted by:

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Date: February, 2007

Submitted to:

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

We are please to see the FDA attend to this important issue and produce the Draft Guidance (hereafter *DG*). The high prevalence of obesity, its substantial adverse impact on health and quality and quantity of life, and the substantial consumer demand for weight loss therapies all speak to the need to evaluate novel therapeutics in the most rigorous and effective manner possible. In fact, inspired in part by the September 2004 FDA advisory committee meeting that discussed this topic, we and other colleagues recently applied for and obtained an NIH grant to host a 2-day conference on *Design, Analysis, and Interpretation of Randomized Clinical Trials for Obesity*. The meeting was held in December of 2006 and the complete videotaped proceedings are available for free viewing at http://main.uab.edu/Shrp/Default.aspx?pid=97738#schedule. We encourage the FDA staff working on this guidance document to view these videos as they contain much pertinent information from leading experts.

We offer specific comments below.

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1. ***Body Fat as a Primary Endpoint.*** The DG states "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*** [emphasis added] with a goal of reduced morbidity and mortality through quantifiable improvements in biomarkers such as blood pressure, lipids, and HbA1c." We applaud this statement. Obesity can be defined as an excess of body fat where excess denotes an amount sufficient to impair heal or longevity. Unfortunately, largely for practical reasons, in much obesity research body fat is not measured and weight or BMI are used as surrogates. While this is justified and necessary in some cases (e.g., some large epidemiologic studies), in the 21st century virtually every major university and medical center has access to equipment, such as dual energy x-ray absorptiometers (DXAs) that allow precise determination of body fat. Given this and the fact that there is reason to believe that it is loss of fat mass and not loss of weight per se that confers health benefits among obese persons[1], we believe it should be the expectation, rather than the exception that studies use body fat measurements rather than body weight measurements as the primary endpoint. We were therefore disappointed by the DG's later statement that "The primary efficacy endpoints should be a comparison of the mean absolute or percent change in body weight between the active-product and placebo-treated groups and the proportion of patients in each treatment group who lose greater than or equal to 5 percent of baseline weight." This seems to contradict the earlier statement we quoted. We urge FDA to replace weight with fat mass in statements about desired primary endpoints. This is an opportunity for FDA to lead the field.

2. ***Is Specifying a Mechanism of Health Benefit Necessary?*** Returning to the DG's statement "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*** [emphasis added]," we question whether the phrase we have highlighted in necessary and useful. A drug that caused weight or fat loss and reduced morbidity and mortality but did so through mechanisms other than those listed above and even through unknown and therefore unquantified mechanisms would not necessarily be less valuable. Yet the statement might imply that it were and hamper development or approval of such drugs. We therefore recommend eliminating this phrase.

3. ***Criterion for Weight Maintenance.*** We find the text "however, weight loss and weight maintenance should be demonstrated over the course of at least 1 year before a product can be considered effective for weight management. Thus, the weight management indication incorporates and signifies weight loss and weight maintenance" to be vague and potentially confusing. For example, it might be taken to imply that a treatment group must lose a given amount of weight prior to the end of the first year and then either achieve weight stability in the group mean

[1] Allison, D. B., Zannolli, R., Faith, M. S., Heo, M., Pietrobelli, A., VanItallie, T. B., Pi-Sunyer, F. X., & Heymsfield, S. B. (1999). Weight loss increases and fat loss decreases all-cause mortality rate: results from two independent cohort studies. International Journal of Obesity, 23, 603-611.

or experience no more than a certain amount of weight regain by the end of 1 year to be considered efficacious. This would seem to eliminate from consideration treatments that produce continued weight loss throughout the 1 year period because no maintenance has been demonstrated. Some rewriting of this text for clarity might be useful.

4. ***Statistical Analysis***. The DG states "The analysis should be applied to the last observation carried forward on treatment in the modified ITT population defined as subjects who received at least one dose of study drug and have at least one post-baseline assessment of body weight. Sensitivity analyses employing other imputation strategies should assess the effect of dropouts on the results." While we strongly agree with the use of ITT approaches, we believe that the use of last observation carried forward (LOCF) is markedly out of step with modern statistical thinking. This perhaps reflects the fact that the 2004 FDA advisory meeting addressing this topic did not include a statistician with clinical trial expertise. A review of the video tapes referred to above will show that several leading statisticians all eschewed LOCF and suggested alternatives. These alternatives are now well established[2] and available in major statistical packages. We have a paper nearing completion that compares the performance of these various approaches in multiple real obesity trials and will be glad to share a copy with FDA upon request. LOCF does not have a sound statistical foundation and can be biased in either direction (i.e., it is not necessarily conservative). Our own work suggests that multiple imputation may be the best method for conducting ITT analyses in obesity trials and that standard mixed models also work quite well in reasonably sized studies.

5. ***The Logic of Requiring Prior Attempts at Lifestyle Therapy.*** The DG states "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." We do not see how the premise (even if accepted) that "all drug and biological therapies impose some risk for adverse events" leads to the conclusion that "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." This conclusion seems to presuppose several other premises that may not be valid. Such premises include (but may not be limited to): (a) All patients in need of and desirous of weight loss are willing to try a lifestyle intervention first; (b) All lifestyle interventions have lesser risks for known and unknown adverse events than do pharmaceuticals; and (c) For a person in need of and desirous of treatment, there is a sufficiently large probability that they could lose a sufficient

[2] Gadbury, G. L., Coffey, C. S., & Allison, D. B. (2003). Modern Statistical Methods For Obesity Trial Data: Beyond LOCF. Obesity Reviews, 4, 175-184.

amount of weight with a lifestyle intervention that a pharmaceutical would no longer be valuable.

With respect to premise (a), we think it is not likely to be true. There will be some individuals that simply refuse to first try a lifestyle intervention without pharmaceutical support. Though one might advise them otherwise, if they persist in their opinion, it seems inappropriate to deny them treatment.

With respect to premise (b), while this may be true, it seems more an article of faith than a matter of demonstrated fact.

With respect to premise (c), lifestyle treatments for obesity on average produce ***no more than*** a 12% loss of baseline weight[3]. Therefore, assuming height remains constant, anyone with a baseline BMI greater than, at most, 30/(1-.12) or 34.1 would still be predicted to have a BMI greater than 30 even after lifestyle treatment. We emphasize that this is in fact conservative as a recent systematic review concluded that lifestyle modification therapies lead to less than 5 kg of weight loss after 2-4 years[4] which corresponds to a loss of less than about 5% for the average size person in an obesity trial. Thus, for these people, it would seem unwise to put off the very likely need for additional treatment.

Finally, the DG is the guidance for industry for developing products for weight management, and it is not clear that there is a benefit to also trying to make it a policy statement on a hierarchy of appropriate interventions suggested to an average obese individual living in the community wishing to lose weight.

For these reasons, we question whether "use of a weight-management product should be contemplated only after a sufficient trial of lifestyle modification has failed."

6. ***Inclusion of Very Obese Subjects.*** The DG states "Because excess adiposity may influence a product's metabolism and disposition, the pharmacokinetics profile of a weight-management product should be examined in patients with a broad range of BMIs (e.g., 27 kg/m^2 to 35 kg/m^2)." Because so substantial a proportion of the US adult population now have BMIs greater than 35 and even 40, we suggest replacing "(e.g., 27 kg/m^2 to 35 kg/m^2)" with "(e.g., $\geq$ 27 kg/m^2 and representative of the distribution of BMIs among persons in the United States with BMIs > 27 kg/m^2)."

7. ***Sample Size for Safety Evaluation.*** Section 2 of the DG addresses the sample size needed for safety evaluation, stating "A reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 subjects are randomized to active doses of the product and no fewer than 1,500 subjects are randomized to placebo for 1 year of treatment. For example, the above sample size will provide 80 percent power to rule out with 95 percent confidence an approximately 50 percent increase in the incidence of an adverse event that occurs at a rate of 3 percent in the placebo

[3] Miller WC, Koceja DM, Hamilton EJ. A meta-analysis of the past 25 years of weight loss research using diet, exercise or diet plus exercise intervention. Int J Obes Relat Metab Disord. 1997 Oct;21(10):941-7.
[4] Duoketis JD, Macie C, Thabane L, Williamson DF. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. Int J Obes. 2005;29:1153-67.

group (i.e., 4.5 percent versus 3 percent)." While we are not necessarily advocating a different sample size, we wish to mention some recent results from a survey we conducted of patients entering obesity treatment trials[5]. These patients were asked what risk of death or another severe adverse event they would be willing to accept for various magnitudes of weight loss. The median self-defined tolerable risks were only slightly above zero in most cases and well below 1.5% absolute increase in risk listed above. Thus, more than 50% pf patents entering into obesity treatment trials would seem to want studies that had greater power to detect smaller risks than will be offered by the sample sizes suggested in the DG.

8. ***Testing for Weight-Loss Independent Effects.*** The DG states "Improvements in blood pressure, lipids, glycemia, or other areas commensurate with the degree of weight lost are expected in patients treated with an effective weight-management product. Therefore, changes in common weight-related comorbidities should be factored into the efficacy assessment of investigational weight-management products." We were not certain we understood the import of these sentences. It seems to imply that investigators should evaluate whether drugs have beneficial effects on risk factors above and beyond the effects of weight loss, as stated later in the DG "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." We agree that this is a valuable and interesting question worthy of investigation. A key question is how should one analyze data or design studies to address such questions. To our knowledge, this has not yet been addressed in the published literature. This was the subject of Dr. Allison's talk at the aforementioned December meeting for which the videos are available.

9. ***Seeking positive synergy in combination therapy***. The DG states "a fixed-dose combination that is associated with at least twice the weight loss observed with that of each of the individual components will be viewed more favorably than combinations that do not achieve this degree of relative weight loss." If *drug A* produces a weight loss of δ_A and *drug B* produces a weight loss of δ_B, this suggestion would imply that the combination of *drugs A and B*, should produce a weight loss of $2*\max(\delta_A,\delta_B)$. In contrast, even if the drugs were purely additive, the combination would only produce an effects of $(\delta_A+\delta_B)$. Thus, this suggestion asks for positive synergy which seems like an excessively high demand. A combination product that fails to demonstrate a positive synergy might still offer greater efficacy than either drug alone and might also be superior to individual components in other aspects such as improved tolerability; we suggest that this could be a consideration for approval.

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[5] Allison, D, Faith, M., Sargent, S., Berkowitz, R., Cutter, G., McVie, T., Gadde, KM., Foster, G. Sample Size and Risk Assessment in Obesity Trials: Patient Perspective vs. Current Practice. (2006). Abstract 667-P Obesity Vol. (14), Supp. A212

10. ***Criterion for treating drug-induced weight gain***. The DG states "Patients eligible for participation in trials examining the efficacy and safety of products for the treatment of medication-induced weight gain should have a documented increase in body weight of at least 5 percent within 6 months of starting a drug known to cause weight gain." We agree that drug-induced weight gain is a major problem.[6] In fact, for individuals taking certain atypical antipsychotic agents, it is such a large problem that we wonder if it is wise to wait for subjects to show weight gain. We advocate studies of prophylactic use of antiobesity agents from the outset of treatment with agents that cause major weight gain.

11. ***Use of Run-in Periods***. The DG does not mention use of run-in periods. We believe that the decision to neither advocate for or against them is wise because, at present, there are no published data suggesting that the use of run-in periods does or does not have any particular desirable or undesirable effect. We believe it is worth mentioning this explicitly in the DG.

Minor Points.

12. The DG states "Obesity is a chronic, relapsing health risk defined by excess body fat." A risk is generally defined as a probability. Obesity is a physical condition and therefore cannot be called a risk. Rather it is a condition that can increase the risk of undesirable events.

13. We suggest changing "Total body fat can be accurately measured using hydrodensitometry and dual-energy x-ray absorptiometry (DEXA)" to "Total body fat can be accurately measured using hydrodensitometry, dual-energy x-ray absorptiometry (DEXA) and other methods."

14. We suggest changing "Excess body fat increases the risk of death and major comorbidities such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis of the knee, sleep apnea, and some cancers…" to "Excess body fat increases the rate of death and risk of major comorbidities such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, osteoarthritis of the knee, sleep apnea, and some cancers..." Alas, the risk of death is 1.0 for all of us.

15. Similarly, we suggest changing the word 'risk' to 'rate' whenever referring to mortality as the outcome (unless you are specifying a precise finite period of time, e.g. "the risk of dying in 10 years" or "the risk of death before age 50").

16. We suggest changing "…in general, are lowest in individuals with BMIs of 18.5 kg/m^2 to 24.9 kg/m^2 and increase in a curvilinear or linear manner with BMIs of 25 kg/m^2 to approximately 40 kg/m^2." to "…in general, are lowest in individuals

[6] Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry. 1999 Nov;156(11):1686-96.

with BMIs of 18.5 kg/m^2 to 24.9 kg/m^2 and increase in a monotonic manner with BMIs > 25 kg/m^2."

17. In Table 1, how would a person with a BMI of, for example, 24.95 be classified? Should the categories not be amended to not leave intervals (however small) out by use of the '<' symbol at the appropriate points?

18. The DG offers a standard definition of childhood overweight or obesity as being above the 95 percentile of an age and sex-matched BMI distribution. It is important to note that the particular distribution referred to is one that is 'fixed' to that of a past US population, rather than the current population distribution. Use of the latter would tautologically always result in 5% of the childhood population always being obese.

19. We suggest changing "Secondary efficacy endpoints should include, but are not limited to, changes in the following metabolic parameters:" to "Secondary efficacy endpoints should include, but are not limited to, changes in the following metabolic variables:". Similarly, in other places where the word 'parameter' is used to mean variable, it should be replaced by the word 'variable.'

20. The DG states "Because the evaluation of investigational weight-management products routinely includes assessment of changes in patients' metabolic profiles, and in some cases may involve measurement of visceral fat content by CT or MRI, waist circumference should not serve as a surrogate for visceral fat content when measured in a clinical trial investigating the efficacy of a product for weight loss. Rather, it can be a means to confirm that reductions in waist circumference following treatment with a weight-management product are associated with the expected improvements in metabolic parameters." We are unclear why it is important "to confirm that reductions in waist circumference following treatment with a weight-management product are associated with the expected improvements in metabolic parameters" nor exactly how to determine the expected improvements in metabolic variables.

21. We suggest changing "The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant" to "The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent ***of baseline body weight*** [assuming that this is what is meant] and the difference is statistically significant."