

Re: Docket Number 2003D-0570:  
Comments on Clinical Evaluation of Weight Control Drugs Guidance issued 9-24-96

Thank you for the opportunity to provide my ideas about the procedures for the Clinical Evaluation of Weight Control Drugs as outlined in your Guidance document of 9-24-96. Prior to the issuance of this Guidance, Dr. Leo Lutwak had convened an expert panel to give input to the FDA about this problem. One signatory to this letter (GAB) was one of those initial participants. More than a decade has passed since this conference, and we are pleased to provide you with our current ideas.

**General Comment:** We view the procedures for evaluating a drug in the treatment of obesity as an opportunity to demonstrate the efficacy of the drug and its high level of safety; considering the population in which it will be used, we also view this process as a basis for developing information about the use of a drug by physicians in the practice of medicine and the care of their patients.

**Paragraph by Paragraph Comments:**

1. Introduction: Well done.
2. General Rationale:
  - a. In the middle of this paragraph it says: "Since it is possible that a new "set point" will be developed at a reduced body mass, drug administration might be required for only a limited time"; for the purpose of drafting a new Guidance, this statement should be removed. We know of no evidence that obesity can be cured. Years ago, the rationale for the jejuno-colic by-pass was that when patients lost weight the operation would be reversed they would be able to maintain the lower weight. As Payne et al [1] found, to their chagrin, all of the patients regained weight after reversal. Since, in our view, obesity is a "chronic relapsing neurochemical disease" [2], it is only a matter of time after any treatment is discontinued before weight will return to "baseline". However, this doesn't mean that treatment needs to be "continuous". At least two studies using discontinuous therapy with anti-obesity drugs [3]; [4] demonstrate that anti-obesity drugs produce as much weight loss at 9 or 12 months as continuous therapy. Indeed, trials with intermittent therapy might be worth evaluating.
  - b. Weight loss has two components. One is medical and one is cosmetic. When health is at risk, the potential risks of a drug can be greater than when the goal is cosmetic. Since the majority of patients seek weight control for "cosmetic" reasons, safety concerns become more important than if people were only using them were for high risk of diabetes, gall bladder, cardiovascular or other diseases. Since the motivations for taking these medications will be the desire to "look good," and the desire to improve the quality of life is an important

medical end-point, recognition that anti-obesity drugs will have BOTH cosmetic and medical uses is important in designing trials and in developing information for the physician and consumer.

c. Length of clinical trials. Although anti-obesity drugs may have long-term use, for most consumers the continuous use is likely to be only a few weeks to a few months. This is true for two reasons. First, clinical trials for weight loss demonstrate that weight loss ceases after 4 to 8 months of treatment – a plateau develops. This occurs with behavioral, dietary, medical and surgical interventions. It is the nature of a homeostatic, compensatory system. However, when weight loss does reach a plateau that plateau is often less than 10% of initial body weight and many patients discontinue the medication because they conclude that the medication “isn’t working”. Moreover, discontinuation is more likely if the medication is expensive. We know from experience with over-the-counter herbal ephedra preparations that consumers will pay up to \$30/month for fairly long term use. However, we also know from the experience with sibutramine and orlistat that they will not pay \$100/month for an equivalent amount of weight loss. Thus the interaction of cost and the compensatory plateau make it unlikely that many consumers will use anti-obesity drugs for an extended time – at least not with any current drug. However, they will typically use them for short periods when weight loss is needed for cosmetic reasons such as a wedding, a divorce, a reunion or to achieve a personal weight goal.

3. Early Clinical Trials. The statement is very clear and useful.

4. Dose-ranging Finding. The criteria for designing the initial dose-ranging studies are clearly stated. Because only 75% of the maximal weight loss is achieved by 3 months, trials of 6 months might be more appropriate. We would also prefer the trial to begin without a “run-in” period, unless the run-in is to establish tolerability to the medication procedure without other active (lifestyle or diet) therapy.

5. We will take this section paragraph by paragraph.

5.1 Population: The current Guidance was written before the NHLBI and WHO provided uniform recommendations for classification of obesity. We would encourage the FDA to include in their trials individuals with a BMI > 25 kg/m<sup>2</sup> since all of our epidemiological data, particularly that for diabetes, shows that the risks of disease begin at that level. The selection of 27 kg/m<sup>2</sup> with co-morbidities harks back to the days when the NCHS was using the 27.3 and 27.8 kg/m<sup>2</sup> BMI unit cut-points to define overweight. Now that these cut-points are no longer used, the FDA might want to seriously reconsider its selection of 27 kg/m<sup>2</sup> and move to 25 kg/m<sup>2</sup>. Measuring body fat can be useful, but the BMI and waist circumference have proven to be very useful criteria for assessing risk [5]; [6]; [7]. Measurement of waist/hip ratio and sagittal diameter have nothing over the simple measurement of waist circumference, and I would recommend that the waist circumference be used along with the BMI.

## 5.2 Procedures:

**Subject Selection:** We strongly object to the use of the run-in for clinical trials of anti-obesity drugs. It is confusing to the physician, to the patient, and not instructive for the effect of the drug. When a patient receives medication from a physician for the treatment of obesity, what both the doctor and patient want to know is how much weight loss their patient is likely to achieve, and what side effects might occur. The idea of “placebo-subtracted” weight loss is unhelpful to either physician or patient. Similarly, few physicians have the office set-up to conduct an active lifestyle change program or to give diet counseling. An effective anti-obesity medication will usually be used with minimal behavioral or lifestyle therapy. Thus, for both patient and physician, knowing how much weight loss is achieved from initiation of the drug is the question of interest, NOT how much weight loss might occur after an active lifestyle or dietary intervention. Thus, we think the run-in should be eliminated or shortened to a non-therapeutic period of 1 week.

We like the discussion of the weight maintenance strategies at the end of paragraph 5.2. These have proven to be very useful and important.

**End-point evaluation.** Since men and women are included and they have different percentages of body fat and often different initial body weights, we would prefer to have the primary end-point the Percent Change in Body Weight. Since height doesn't change, the change in BMI provides no more information than the change in body weight, and is a more cumbersome unit for weight loss. We would NOT just use change in BMI. Change in body fat in kg and % separated by genders would also be useful, as would changes in visceral adipose tissue in a subsample.

**Weight loss demonstrations.** We would prefer a criterion of >5% from baseline and significantly greater than placebo. At present, no drug consistently meets the criterion of 5% below placebo. To require a drug to be >5% below placebo encourages trials with a “weak” placebo effect to make it easier to see the 5% criterion. This in turn penalizes long-term trials, since patients on placebo losing only small amounts of weight are likely to drop out. Although we would like drugs to produce >10% below baseline as monotherapy, almost none have done so, and if this were the criterion, we might have no drugs at all. Moreover, for many people a weight loss of 5-10% is sufficient for the “cosmetic” effects that are often wanted. It will also produce significant health benefits [8]; [9].

The use of improvements in “risk” factors is good. We would drop sagittal diameter and use waist circumference. Studies in diabetic populations and hypertensive populations are valuable.

Since in many patients with recent onset diabetes, weight loss can lead to remission, it might be claimed that drugs producing weight loss are “anti-diabetic” drugs. We would not favor this position. If the drug doesn't have an independent

effect of glucose metabolism or the action of insulin, we would not favor approving it for diabetes. Weight loss in diabetics and pre-diabetics, on the other hand, is clearly beneficial, because it will lower the cost of treatment for diabetes and may lead to remission. Thus, weight loss drugs might be labeled as weight loss adjuncts for the treatment of diabetes.

Improvement in the quality of life is one of the major reasons that most people seek help with their weight. Having some measure of how much improvement there is would be valuable.

Except in the very obese, the issue of excess fluid does not exist. When we measured intracellular and extracellular water in a group of obese patients, the only ones with abnormal distributions were those who were “very” obese, i.e., more than 400 pounds. However, we think documentation of the extent of change in lean body mass and calcium loss (DXA bone changes) could be considered in a subset of patients.

5.3 Duration of Trials. We would propose that a 12-month double-blind, randomized, placebo-controlled trial should demonstrate 5% or greater reduction from baseline weight for the drug-treated group at 12 months that is also significantly lower than placebo. Viewing the 4-year XENDOS trial [10] the drug-treated group and placebo-treated group both began to regain weight following the plateau at 12 months, but the drug-treated group remained more than 2% below the placebo-treated group even after 4 years. Unless there is evidence of escape from the therapeutic effect of the drug as occurred with fluoxetine [11], we think that a 12-month trial is sufficient to show efficacy and safety.

The issue of follow-up and handling of drop-outs is an important one. Our experience with follow-up after discontinuation from a clinical trial is dismal. If patients quit they usually don't want to be followed up by phone or otherwise. With our current IRB constraints the problem is even more difficult. For the package insert, we would propose that only the completers analysis be used. What the physician and patient both want to know is how much weight loss they might achieve if the drug is used for 12 months. Including patients who drop out lowers the apparent effect of the drug, and fails to give either patient or physician a clear idea of what to expect. We would thus propose using the completers analysis for informing physicians and patients.

Obesity, a chronic medical disease like hypertension or diabetes, has multiple and redundant control mechanisms. It is likely that, as with diabetes and hypertension, multiple medications working by different mechanisms will need to be employed for effective management. Since combinations of drugs have been approved for hypertension and diabetes, this raises the issue of combination therapy in the treatment of obesity, and the criteria for approving such combinations of drugs to treat obesity. The advantages of combination therapy are that lower doses of active medication might be used with fewer side effects,

or that the magnitude of weight loss might be significantly greater. To document these changes, clinical trials comparing active agents would be required after the approval of the parent compound. Strategies for reducing dosages and for increasing the magnitude of the response may require placebo-controlled trials lasting 6 to 12 months. Longer periods might not be needed, since each group would already have been approved with longer trials.

Thank you for the opportunity to respond to your Request for Comments on a Draft Guidance on the Clinical Evaluation of Weight-Control Drugs.

Sincerely yours,

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