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Director
Scientific and Regulatory Affairs



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April 23, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Request for Comments on a Draft Guidance on the Clinical Evaluation of Weight-Control Drugs [Docket No. 2003D-0570, 69 *Federal Register*, 3589, January 26, 2004]

Dear Madam/Sir:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA members invested an estimated \$33.2 billion in 2003 in discovering and developing medicines. PhRMA companies are leading the way in the search for new cures.

PhRMA welcomes the opportunity to provide the attached comments on a Draft Guidance on the Clinical Evaluation of Weight-Control Drugs and would appreciate your careful consideration of these comments as you work to revise this document.

Please contact me if there are any questions regarding these comments.

Sincerely,

A handwritten signature in cursive script that reads 'Michael Garvin'.

Michael Garvin, Pharm.D.

Pharmaceutical Research and Manufacturers of America

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2003D-0570

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Comment on Guidance for the Clinical Evaluation of Weight-Control Drugs (9-24-96)

General Comments:

In the past seven and one half years since the publication of the Guidance for the Clinical Evaluation of Weight-Control Drugs, it has become increasingly clear that obesity is a serious and growing medical problem in the US and throughout the world. Obesity as a disease is causally linked to insulin resistance, Type 2 Diabetes Mellitus (DM), hypertension (HTN), cardiovascular disease, cancer, arthritis, respiratory and sleep disorders. The initial treatment of obesity is based on caloric restriction and the maintenance or increase in physical activity to induce weight (fat) loss. Unfortunately this is not effective in the vast majority of people. Pharmacological therapy plays a crucial role when diet and exercise fail. Treatment of the underlying obesity can improve the comorbidities, as seen with Type 2 DM, dyslipidemia, and hypertension.

The updated Guidance for the Clinical Evaluation of Weight-Control Drugs should more closely reflect the causal link between obesity and the diseases mentioned above (insulin resistance, Type 2 Diabetes Mellitus (DM), hypertension (HTN), cardiovascular disease, cancer, arthritis, respiratory and sleep disorders). The reference to obese subjects as 'relatively healthy' sends the wrong message and the language throughout the Guidance should reflect the significance of obesity as a disease.

The updated Guidance should parallel the Guidance for other chronic conditions (Type 2 DM, dyslipidemia, and hypertension). There should be appropriate demonstration of safety and efficacy that warrants the appropriate use of these agents.

As indicated in FDA's recently issued paper on Innovation Stagnation (US Department of Health and Human Services, March 2004), the FDA is uniquely positioned to help identify the challenges of developing safe and effective therapeutic agents. The obesity guidance revision process will be greatly enhanced by broad consultation with experts in the field, and we therefore encourage the FDA to take full benefit of the larger scientific and medical community on developing solutions in the field of obesity research.

Specific Comments

1. Introduction:

- a. The Introduction should identify the significant health risk of excess weight (adipose tissue) and move away from implications of obesity as a lifestyle problem or merely a problem with 'self-esteem'.
- b. The use of the terminology "weight-control" should be replaced with the "prevention and treatment of obesity".
- c. It would be important to clarify the statement "only those aspects of the trials that are specific to weight-control drugs". It would be important to identify appropriate assessments for safety and efficacy (both weight loss requirements and associated measurements of obesity related disorders) for the evaluation of drugs for the prevention and treatment of obesity.
- d. Reference to "healthy obese" or "otherwise healthy" should be eliminated and replaced with "obesity uncomplicated by associated co-morbid disease".

2. General Rationale:

- a. This crucial section should be expanded to amplify the important role of obesity in multiple costly diseases including Type 2 DM, HTN, cardiovascular disease, cancer, arthritis, respiratory and sleep disorders.
- b. It would be important to identify the recognized benefit of treating obesity with respect to Type 2 DM, HTN, cardiovascular disease, cancer, arthritis, respiratory and sleep disorders.
- c. The discussion of the natural history of weight changes (loss followed by regain) is important and should be amplified. It is clear that short-term therapy does not lead to lasting benefit. The need to address excess weight as a chronic disorder requiring chronic intervention is important in order to realize the full benefit of weight loss.
- d. As suggested in the Guidance, unique mechanisms of action of agents in the future may allow a successful maintenance of weight lost. This concept is an important one to include in consideration of "long term safety and efficacy".
- e. This Guidance should be consistent with other guidelines for chronic use therapies in the metabolic area (DM, HTN, dyslipidemia) regarding the assessment of safety and efficacy.
- f. The current guidance document states that "weight is frequently (usually) regained promptly after it has been lost if the weight loss was induced by weight-control drugs and the drugs have been discontinued". This statement should be removed since it is common to have a rebound effect when either pharmacological intervention or non-pharmacological intervention is terminated (Clinical Guidelines of the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The Evidence Report, NIH September 1998). Weight maintenance interventions should be considered a chronic intervention with potentially life-long therapies in the same context as treatment of other metabolic and CV risk factors & diseases (dyslipidemia, hypertension).

3. Early Clinical Trials

- a. Consider defining this as Phase 1.
- b. We recommend adding the early study of pediatric, adolescents and young adults, as these groups are significantly affected.

4. Dose Range Finding

- a. Consider defining this as Phase 2.
- b. We recommend deleting the first sentence since it implies that excess weight is not a serious concern (“relatively healthy” subjects). The reference to the “drug dose recommended not be excessive” is addressed in the second sentence.
- c. The choice of doses will depend on the proposed mechanism of action. The guidance should therefore not set a lower limit on the number of doses required for study. It would be ideal to allow this flexibility while perhaps providing the usual number of doses (i.e. “at least 3 doses...”).
- d. The guidance should also address the possibility of different dose regimens, such as continuous or intermittent treatment for weight loss, weight maintenance and use in combination with other obesity treatments.
- e. The subjects in these Phase 2 / Dose range studies should be similar to those that will be studied in the Phase 3 / Trials to Establish Efficacy.
- f. The current Guidance identifies individuals who are overweight (BMI>27) with comorbidities or who are obese (BMI>30) as relevant subjects for study. This unnecessarily limits the addressable population. The description of relevant subjects for inclusion should be changed to incorporate the definition of excess weight from the WHO and NHLBI recommendations in conjunction with the current guidelines.

Recommendations:

- a. BMI-25 to 30 (over weight) with an associated comorbidity (insulin resistance, Type 2 DM, HTN, cardiovascular disease, cancer, arthritis, respiratory and sleep disorders)

or

- b. BMI \geq 30 with or without an associated comorbidity

5. Trials to Establish Efficacy

Consider defining this as Phase 3.

5.1 Population

- a. The current guidance states, “Subjects in long term trials should be moderately to markedly obese with BMI at least 30 for otherwise healthy individuals, and BMI at least 27 for those with comorbidities”. These restrictions are inconsistent with the understanding that risk of excess weight begins at a BMI below 27. As in section 4 (Dose Range Finding), the WHO and NHLBI recommendations consider subjects with a BMI between 25 and 30 as being overweight. Expanding the

addressable population would enable effective study of weight-control drugs in the relevant population.

- b. The Guidance should recognize and define the Metabolic Syndrome (The National Cholesterol Education Program Adult Treatment Panel III report defined metabolic syndrome as the presence of any 3 of the following 5 risk factors: abdominal obesity, elevated triglycerides, decreased HDL, increased blood pressure, or impaired fasting glucose). The Guidance should consider the inclusion of subjects who meet the criteria for the Metabolic Syndrome.
- c. It is important to identify subjects with excess adiposity. Although BMI is an excellent marker, it will be important to look beyond BMI. It would be useful to identify the utility of waist circumference, W/H ratio, skin fold assessment, BIA, and DEXA as potential measurements to enhance specificity for excess adiposity.

5.2 Procedures

The intention of this section is critical for the evaluation of efficacy and safety of weight control drugs. It is imperative to efficiently and effectively assess the activity of a drug candidate to impact body weight in an unbiased way.

- a. The description of the subject selection with a pre-drug treatment weight loss phase is described within this section. This is perhaps only relevant for otherwise qualified subjects who have never attempted weight loss. In this case it is not clear if the subject could lose weight without the use of a drug. But, a vast majority of subjects have had multiple attempts to reduce their weight and have not been successful. The subject selection process as described is not feasible, and should be modified to allow subjects who have attempted and failed to lose weight historically to enroll without the further hurdle of weight loss criteria during a lead-in.
- b. The utility of a hypocaloric lead-in phase within a study is perhaps more relevant for short-term studies (up to 6 months). Since data for long term (1 year) trials are required for efficacy, and changes of weight after 1 year are not affected by the lead-in weight loss phase, it should be feasible to remove this requirement.
- c. In addition to the biomarkers currently listed in the guidance document we suggest that the following additional CV biomarkers for assessment be considered where applicable for agents with potential to demonstrate benefit: left ventricular mass, inflammatory markers (e.g. C-reactive protein) and clotting factors (e.g. PAI-1 and fibrinogen).
- d. The efficacy endpoint evaluation should reflect the relevance of modest weight loss and the maintenance of that loss to achieve improvements in obesity associated disorders.

Indication for weight loss (needs to meet at least one of the three):

- Total weight loss from baseline $\geq 5\%$ at 12 months and statistically significant difference between the treatment and placebo arms
- Placebo-adjusted weight loss $\geq 5\%$ at 12 months

- Significantly greater proportion of individuals losing $\geq 5\%$ and $\geq 10\%$ of their initial body weight at 12 months

Indication for weight maintenance

The draft guidance suggests that maintenance of weight loss may be the principal benefit of anti-obesity therapy. Further clarification on the design of studies to demonstrate weight maintenance should be detailed in the future guidance. Three treatment paradigms could be proposed to assess weight maintenance: (1) weight maintenance after drug-induced weight loss, (2) weight maintenance after diet-induced weight loss (e.g. 6 weeks of a very low calorie diet) or (3) prevention of weight gain associated with use of certain medications (e.g., sulfonylurea, anti-psychotics, anti-epileptics, corticosteroids, etc.) or therapies (e.g., smoking cessation). In the first two paradigms, it should be possible to demonstrate the efficacy of drug-treatment to reduce body weight regain (or further decrease body weight) in studies of one year duration or less. Sponsors should assess the between-group difference in proportion of patients who maintain a clinically meaningful degree of weight loss (e.g., 5% of baseline body weight). For the third paradigm, it should be possible to demonstrate efficacy by establishing a statistical difference in weight gain between the drug- and placebo-treated groups in studies lasting one year or less.

5.3 Duration of Trials

- a. **Efficacy:** A one year trial for efficacy is consistent with guidelines for other drugs used to treat metabolic disorders. Further, studies have shown maximal effect of weight loss drugs are evident within 6-12 months.
- b. **Safety:** As it is adequate for a 1 year exposure for drugs used to treat Type 2 DM, HTN, and dyslipidemia, it is not clear why agents used to treat obesity should be required to be studied for 2 years. Given the desire to ensure safety in a drug that would be used chronically and make this consistent with the other Guidances, the duration of study should be 1 year for approval with a need to develop longer term (2 year) safety data if approved.

Additional Considerations

Accelerated approval/Fast track requirements:

Obesity is now recognized in the US as a serious and life-threatening disease. The Guidance should consider weight loss drugs as eligible for accelerated approval and Fast Track designation.

Abuse Liability Assessment:

Many anti-obesity agents are centrally-acting anorectics which may require assessment of abuse liability potential (21CFR 314.50(d)(5)(vii)). A distinction should be made in the future guidance between misuse (e.g. weight loss in non-obese subjects) and abuse (e.g., unintended use of product). The absence of clear guidance for the assessment of abuse liability may hamper progress in the development of novel therapeutic agents. The FDA could clarify this by issuing the pending guidance on Assessment of Abuse Potential of Drugs or provide specific direction to Sponsors on the preclinical/clinical studies required to assess abuse liability.

Metabolic Syndrome

Given the potential benefit for improvement in the Metabolic Syndrome with the treatment of obesity, and the clear link to increased cardiovascular morbidity and mortality, the Guidance should delineate a path toward an indication for the Metabolic Syndrome.