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2007 '04 APR 27 11:17



Global Research & Development

April 26, 2004

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

Re: Draft Guidance on the Clinical Evaluation of Weight-Control Drugs
[Docket No. 2003D-0570, 68 *Federal Register*, 3588-3589, January 26, 2004]

Dear Sir or Madam,

Please make reference to the *Federal Register* notice of January 26, 2004 requesting review and comment of the early Draft Guidance on the Clinical Evaluation of Weight-Control Drugs [2003D-0570]. Thank you for the opportunity to comment. Attached are the Pfizer prepared comments on the Draft Guidance.

Given the interest in this topic, Pfizer suggests the Agency consider sponsoring a public workshop prior to releasing the next version of the guidance. We also invite direct dialogue with the Agency if you would consider the opportunity valuable.

Feel free to contact me if there is a need to clarify or expand on any of the points made in our comments.

Sincerely,

A handwritten signature in black ink that reads "William R. Murphy". The signature is written in a cursive, flowing style.

William R. Murphy, Ph.D.
Director, Pfizer Global Research and Development
Worldwide Regulatory Affairs

2003D-0570

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Pfizer Comments
Draft Guidance for the Clinical Evaluation of Weight-Control Drugs

General Comment:

Pfizer welcomes the opportunity to comment on the Food and Drug Administration's (FDA) Draft Guidance on the Clinical Evaluation of Weight-Control Drugs (1996). We applaud this effort to raise awareness and to solicit early comments from industry of key issues for the development of weight control drugs. We look forward to the issuance of the "formal" Draft Guidance as we share the FDA's commitment to the field of obesity and are looking forward to working with the Agency on addressing this major public health problem. As stated in the cover letter, Pfizer would welcome direct dialogue with the Agency or participation in a public workshop to facilitate final review and discussion of the guidance document before it is issued.

Our specific comments have been grouped under the following headings:

Include in the General Rationale:

- obesity is a chronic disease, which may require pharmacotherapy, in addition to diet, exercise and lifestyle modification
- 5% weight loss is associated with substantial health benefit
- reduction in body fat (weight) is associated with improvement in cardiovascular disease risk factors, sleep apnea, infertility, ...

Labeling Claims Achievable for Agents Reducing Body Fat (weight):

- Indication for weight loss
- Indication for prevention of weight regain (of recent weight loss)
- Indication for treatment of type 2 diabetes (and other obesity-related co-morbidities)
- Indication for prevention of type 2 diabetes (and other obesity-related co-morbidities)

Population:

For weight loss & prevention of weight regain indications:

- BMI > 30 for individuals without obesity related co-morbidities
- BMI > 25 for individuals with obesity-related co-morbidities (dyslipidemia, hypertension, type 2 diabetes, sleep apnea, infertility, osteoarthritis) or increased risk for development of these co-morbidities (e.g., positive family history)

Indication for treatment of type 2 diabetes:

- BMI>25 and diagnosis of type 2 diabetes per ADA criteria

Indication for prevention of type 2 diabetes:

- BMI>25 and diagnosis of "pre-diabetes" or diabetes per ADA criteria

Additional considerations:

- There should be another set of enrollment criteria based on total or central adiposity for all indications.
- Subjects who meet either the NCEP or WHO criteria for the metabolic syndrome should be eligible for inclusion regardless of their BMI. If these subjects are included, additional consideration should be given to independent labeling claims for this population.

Efficacy Criteria Definitions:

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 prevention of weight regain (of recent weight loss):

- Proportion of individuals who have maintained $\geq 80\%$ of the initial body weight loss 12 months post-randomization is significantly greater in the treatment vs. the placebo arm.

Indication for treatment of type 2 diabetes (needs to meet one of the two):

- Reduction in HbA1c $\geq 0.6\%$ from randomization and statistically significant difference between the treatment and placebo arms at 12 months
- Placebo-adjusted difference in HbA1c $\geq 0.6\%$ at 12 months

Indication for prevention of type 2 diabetes:

- Significantly greater proportion of individuals with "pre-diabetes" progress into overt type 2 diabetes in the placebo vs. treatment arm

Run-in Period Prior to Randomization (reference Procedures):

Suggest eliminating this period from the design of the trials, rationale:

- Similar period is not used during trials for other chronic diseases (diabetes, hypertension, dyslipidemia)
- It is not standard clinical practice – patients who are candidates for pharmacotherapy for obesity have typically already tried diet + exercise multiple times
- The run-in period leads to selection bias, i.e., a subset of population otherwise eligible for treatment is arbitrarily excluded from the studies, thus reducing generalizability of the result
 - It can be used to select a population MORE likely to lose weight with intervention (if non-responders in the run-in are excluded), which would exaggerate total weight loss response above what might be seen in a more typical population.
 - If on the other hand subjects who respond during the run in are excluded, that eliminates from the trials subjects who would most likely experience a robust weight loss with all associated health benefits. Experience with other weight loss drugs (sibutramine) has demonstrated that the best predictor of long-term successful weight loss is the response during the first 4 weeks of therapy (4 pounds in 4 weeks).