

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: 7 August 2004

FROM: David Orloff, MD
Eric G. Colman, MD
Division of Metabolic and Endocrine Drug Products (DMEDP)
Office of Drug Evaluation 2 (ODE 2)
Center for Drug Evaluation & Research (CDER)
Food & Drug Administration (FDA)

TO: Members and Consultants,
Endocrinologic & Metabolic Drugs Advisory Committee

SUBJECT: 8 September 2004, Advisory Committee meeting on the draft guidance:
Clinical Evaluation of Weight-Control Drugs

On 8 September 2004, key personnel from the Division of Metabolic and Endocrine Drug Products will meet with its Advisory Committee members and consultants to discuss the FDA draft guidance document entitled, *Clinical Evaluation of Weigh-Control Drugs* (hereafter, Obesity Drug Guidance) (**enclosed**). The meeting agenda includes five oral presentations during the morning session, with open discussion in the afternoon (**enclosed**).

Broadly speaking, drugs that are FDA approved for the treatment of obesity fall into two categories: those approved for short-term use (i.e., a few weeks) and those approved for long-term use (Table enclosed). All of the drugs indicated for short-term use were approved prior to 1974. In general, the pre-approval trials for these drugs included fewer than 100 patients and were no more than 12 weeks in duration.

In the spring of 1996 the Agency approved dexfenfluramine for the long-term treatment of obesity. Pre-approval trials for this drug included hundreds of subjects exposed to drug for as long as 52 weeks. As you know, dexfenfluramine (and fenfluramine) were withdrawn from the market due to reports linking their use to left-sided cardiac valvulopathy.

In the fall of 1996, following input from its advisory committee, the Division of Metabolic and Endocrine Drug Products issued the Obesity Drug Guidance. Among other things, the guidance recommended the following:

- The study population include those with a body mass index (BMI) of 27 kg/m^2 to $< 30 \text{ kg/m}^2$ when accompanied by comorbid conditions (i.e., hypertension, type 2 diabetes mellitus) and those with a BMI of $\geq 30 \text{ kg/m}^2$, with or without comorbidities;
- Efficacy be based on weight loss following at least one year of double-blind, placebo-controlled treatment;
- Safety be based on one year of double-blind treatment and a second year of open-label therapy;

- That approximately 1500 subjects complete 12 months of therapy, with 200-500 of those completing a second year of study.

The FDA approved sibutramine in 1997 and orlistat in 1999, both for the long-term treatment of obesity. Like dexfenfluramine, the pre-approval trials for these two compounds involved hundreds of patients exposed to drug for a minimum of one year.

Recent estimates indicate that phentermine, approved in 1959 for the short-term treatment of obesity, is still the most widely-used weight-loss drug, followed by orlistat and sibutramine (paper by Stafford and Radley, **enclosed**).

While it has been more than five years since the Agency approved an obesity drug, a large number of weight-loss agents, with a variety of mechanisms of action, are currently being studied under Investigational New Drug applications. Given the increasing magnitude of the obesity problem, the Division anticipates that development of drugs in this therapeutic class will greatly expand in the coming years. The Obesity Drug Guidance will therefore continue to be an important source of direction for pharmaceutical sponsors of weight-loss drugs.

To ensure that the Obesity Drug Guidance reflects up-to-date scientific information and advice, the FDA requested public comment on the document in the 26 January 2004, issue of the Federal Register. Seventeen responses, mostly from the pharmaceutical industry, were received by the closing date of 26 April 2004 (**enclosed**). Comments and suggested revisions related to all aspects of the guidance were submitted, but several areas received considerable attention. These included:

- Broadening the inclusion criteria for trial participation to include subjects who are overweight (extending the lower bounds of the entry criterion to a BMI ≥ 25 kg/m²);
- Eliminating the need for a second year of open-label study;
- Reducing the number of subjects required to evaluate a drug's safety profile from 1500 studied for one year to approximately 300-600 patients exposed for 6 months and 100 patients for one year. These latter numbers reflect the International Committee on Harmonization's general recommendations for assessing clinical safety of a new drug (**enclosed**).

We anticipate that these topics, among others, will be discussed in great detail at the September 8th meeting and ask that you keep them in mind as you read the enclosed briefing material.

We sincerely appreciate your willingness to participate in the advisory committee process and look forward to a productive meeting in September.