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April 15, 2004

Division of Dockets Management (HFA-305)
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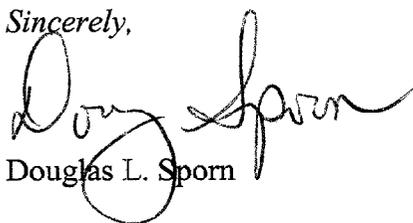
Re: Docket No. 2003D-0570, CDER 2003186. Request for Comments on the Draft Guidance on the Clinical Evaluation of Weight-Control Drugs.

Abbott Laboratories (Abbott) is very pleased to have the opportunity to comment on the Draft Guidance on the Clinical Evaluation of Weight-Control Drugs, published in the Federal Register on January 26, 2004.

While supporting, in general, the Pharmaceutical Research and Manufacturers of America's (PhRMA) position on this draft guidance, Abbott would like to thank the Agency for their consideration of the following attached comments.

Should you have any questions, please contact Ivone Takenaka, Ph.D. at (847)-935-9011 or by FAX at (847) 938-3346.

Sincerely,



Douglas L. Sporn

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**Comments on the Draft Guidance for the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

Docket No. 2003D-0570

The following comments are provided on behalf of Abbott Laboratories (Abbott).

Sections 1 and 2. INTRODUCTION and GENERAL RATIONALE

Abbott recommends the Introduction and General Rationale sections be revised by considering the following observations.

Obesity is a worldwide public health problem, afflicting more than 300 million people.⁽¹⁾ In the United States, approximately 300,000 deaths per year may be attributed to obesity.⁽²⁾ The World Health Organization (WHO) considers obesity a global epidemic.⁽³⁾ There has been a dramatic increase in the prevalence of obesity over the past decades.⁽⁴⁾ The 1999-2000 National Institutes of Health Examination Survey (NHANES) indicates 64.5% of US adults are overweight and 30.5% obese.⁽⁵⁾ Of concern 15.5% of adolescents aged 12-19 now exceed the 95th percentile for age-and sex-specific measures of Body Mass Index (BMI).⁽⁶⁾ A recent Surgeon General's report identified obesity as a national priority for treatment.⁽⁷⁾ The Secretary for Health and Human Services Tommy Thompson calls overweight and obesity "among the most pressing new health challenges we face today"⁽⁸⁾ and the Commissioner of Food and Drugs, Mark McClellan has acknowledged that "we have an obesity epidemic in this country, with about two-third[s] of Americans overweight, and a third obese and [at] heightened risk for many health problems."⁽⁹⁾

In adults, overweight and obesity are defined as a BMI of 25.0 to 29.9 kg/m² and ≥ 30 kg/m², respectively.⁽¹⁰⁾ Studies show that mortality begins to increase with a BMI > 25 kg/m².⁽¹¹⁾ The increase in mortality rates is primarily associated with obesity-related cardiac and vascular complications. Significantly increased risk of death from cardiovascular disease was noted in women with a BMI greater than 25.0 and in men with a BMI greater than 26.5.⁽¹²⁾ According to the Nurses' Health Study involving 115,195 women followed over a period of 16 years, the risk of death was 60-70 percent higher among subjects with a BMI between 29 and 32 compared to subjects with a BMI between 25 and 27.⁽¹³⁾ The risk of morbidity related to a number of health conditions such as hypertension, dyslipidemia, and glucose control rises with increasing BMI.⁽¹⁴⁾ In addition, obesity is a well-recognized risk factor for type 2 diabetes mellitus,⁽¹⁵⁾ gallbladder disease,⁽¹⁶⁾ osteoarthritis,⁽¹⁷⁾ sleep apnea and other respiratory problems,⁽¹⁸⁾ and certain types of cancers (e.g., endometrial, breast, prostate, and colon).⁽¹⁹⁾

The effect of obesity on cardiovascular morbidity and mortality has been associated with hypertension, diabetes and hyperlipidemia. Increased blood pressure is a well-known cardiovascular risk factor. About two-thirds of all patients with hypertension are either

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overweight or obese.⁽²⁰⁾ In the Framingham study,⁽²¹⁾ for every 10% rise in relative weight, systolic blood pressure rose by 6.5 mmHg, fasting cholesterol by 12 mg/dL (0.3 mmol/L) and fasting blood glucose by 2 mg/dl (0.11 mmol/L). Increased blood pressure has been linked to increased risk for stroke, coronary heart disease, and all-cause mortality after a mean of 10 years of follow-up (range 6-25 years).⁽²²⁾

One of the benefits expected from weight loss is the reduction in blood pressure that may offset pre-existent hypertension or improve blood pressure control. Moderate weight loss using a variety of dietary approaches has been correlated to blood pressure reduction of approximately 1 mm Hg systolic (SBP) and 2 mm Hg diastolic (DBP) for each 1% reduction in body weight.⁽²³⁾ Pooled results from dietary intervention trials showed that a mean weight difference of 9.2 kg compared to the control group was associated with 3 mmHg lower DBP and 6 mm Hg lower SBP.⁽²⁴⁾ Data accrued during the past 20 years from population studies⁽²⁵⁾ confirm that both SBP and DBP have continuous and graded relationships to cardiovascular outcomes in men and women, independent of other known risk factors.

The location of body fat is also a predictor of the relative health hazards of obesity. Epidemiological studies have shown that the regional distribution of body fat is a significant and independent risk factor for cardiovascular disease. Accumulation of adipose tissue in the abdominal region (visceral adiposity), which is estimated by the waist circumference, correlates with increased risk of cardiovascular disease and premature death.^{(26), (27), (28), (29)} Subjects with visceral obesity represent a subgroup of obese individuals with the highest risk for cardiovascular disease and who are also at greatest risk for metabolic complications compared to patients with lower body obesity. Visceral adiposity, in particular, is related to dyslipidemia, insulin resistance (detected by measuring high insulin levels) and is predictive of an increased risk for type 2 diabetes mellitus.

The prevalence of type 2 diabetes mellitus has tripled in the past 30 years in parallel with the upsurge in obesity. A subanalysis of the Nurses' Health Study found that a weight gain of 7- to 10-kg after 18-years of age was associated with a twofold increase in risk of diabetes and an adult BMI of ≥ 31 was associated with a 40-fold increased risk.⁽³⁰⁾ The Finnish Diabetes Program⁽³¹⁾ and the Diabetes Prevention Program⁽³²⁾ showed that overweight patients who lost approximately 5% of their body weight reduced their risk for developing type 2 diabetes by 58%. Intentional weight reduction of any amount in women 40- to 60-years of age that had never smoked reduced all-cause mortality by 20% and diabetes-associated mortality by 30 to 40%.⁽³³⁾ Clinically significant improvements in lipid abnormalities,⁽³⁴⁾ glycemic control⁽³⁵⁾ and hypertension,⁽³⁶⁾ have also been associated with modest weight reduction.

Epidemiological evidence suggests that low HDL levels and increased triglyceride levels are independent risk factors for cardiovascular disease.^{(37), (38), (39)} Results from two landmark trials, VA-HIT⁽⁴⁰⁾ and the Helsinki Heart Study,⁽⁴¹⁾ showed that raising HDL

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and lowering TG levels (with gemfibrozil, in men only), even without lowering LDL levels, reduced death from coronary heart disease and nonfatal myocardial infarction and stroke, in subjects whose primary lipid abnormality was low HDL. Specifically, a 6-8% increase in HDL levels was associated with a 23-24% reduction in the composite of these events.

Taken together, overweight and obesity should be considered as serious medical conditions that require therapeutic options to be made available to patients as part of a comprehensive weight loss program that may include drug therapy. The known long-term risks of overweight and obesity necessitate action by the FDA to provide an appropriate medical perspective for this condition. It has been well established in the literature that modest weight loss, in the range of 5-10% of initial body weight, is sufficient to improve obesity-related conditions.⁽⁴²⁾

3. EARLY CLINICAL TRIALS (suggestion: rename as Phase I)

4. DOSE RANGE FINDING (suggestion: rename as Phase II)

- ❖ The first sentence of this section “*Because a drug for weight loss may be prescribed extensively for relatively healthy subjects, it is particularly important that the drug dose recommended not be excessive*” does not seem relevant. Dose-ranging studies for compounds are designed to identify an effective dose for Phase III trials ultimately to provide an appropriate dose in support of an acceptable benefit/risk assessment. It does not seem relevant to point this fact out specifically for treatment of overweight and obesity.
- ❖ Inclusion criteria should be revised to reflect the WHO and the National Heart, Lung and Blood Institute (NHLBI) recommendations: Overweight and obesity in adults are defined as a BMI of 25.0 to 29.9 kg/m² and ≥ 30 kg/m², respectively.⁽⁴³⁾ The rationale behind these definitions is based on epidemiological data that show increases in mortality with BMIs above 25 kg/m². The increase in mortality tends to be modest until a BMI of 30 kg/m² is reached. For persons with a BMI of ≥ 30 kg/m², mortality rates from all causes, and especially from cardiovascular disease, are generally increased by 50 to 100 percent above that of persons with BMIs in the range of 20 to 25 kg/m². In epidemiological studies, BMI is the favored measure of excess weight to estimate relative risk of disease. Moreover, calculating BMI is simple, rapid, and inexpensive, and can be applied easily to adults.⁽⁴⁴⁾
- ❖ Abbott recommends that requirements relevant to number of patients and duration of study be removed. These requirements may vary depending on the nature of the compound in development and the mechanism of action. Therefore, the specific requirements for these factors should be defined

through discussions between the sponsor and FDA during the development of the drug.

5. TRIALS TO ESTABLISH EFFICACY (suggested: rename as Phase III)

5.1. Population

- ❖ Inclusion criteria should be revised to reflect the WHO and NHLBI recommendations: Overweight and obesity in adults are defined as a BMI of 25.0 to 29.9 kg/m² and ≥ 30 kg/m², respectively.⁽⁴⁵⁾
- ❖ The final paragraph of this section, “*Methods used to recruit subjects for obesity trials should be noted. Race, socioeconomic status, and education should also be included in demographic data*” should be modified. Abbott recommends that socioeconomic status and education be removed and only race be included as part of the demographic information. Only racial differences have been noted in the prevalence of obesity and related complications.

5.2. Procedures

- ❖ Candidates for weight management trials should be subjects who have not been successful with diet and exercise, as noted in the NHBLI guidance. The NHBLI guidance recommends that all subjects meeting the BMI criteria, as defined in the treatment algorithm, should attempt to lose weight.⁽⁴⁶⁾ The three major components of weight loss therapy are dietary therapy, increase physical activity and behavior therapy. Lifestyle therapy should be tried for at least 6 months before considering pharmacotherapy.⁽⁴⁷⁾ A short run-in phase may be considered to familiarize the patients with the behavioral modification program.
- ❖ Abbott concurs that the principle benefit of a drug over placebo might be either weight loss or weight maintenance.

Endpoint Evaluation

- ❖ Regarding criteria one and two for weight-loss demonstrations, Abbott agrees with these criteria as a 5 % reduction in weight has been associated with improvement of obesity-related conditions in adults.⁽⁴⁸⁾ The Finnish Diabetes Program⁽⁴⁹⁾ and the Diabetes Prevention Program⁽⁵⁰⁾ showed that overweight patients who lost approximately 5% of their body weight reduced their risk for developing type 2 diabetes by 58%.

- ❖ Abbott contends that treatment duration for the clinical trial should not be defined in this section as was recommended by the American Obesity Association in their letter to the Division of Dockets Management dated March 8, 2004. The issue of duration of trials is discussed in another section of the Guidance document. Any description of duration of trial should be stated in a general nature such as “at the endpoint”.
- ❖ Regarding paragraphs “*Changes in risk factors or in waist to hip circumference or sagittal diameter may be appropriate endpoints depending on the population studied. Development of diabetes or other complication of obesity may be a suitable endpoint in certain cases,*” and “*It may be advantageous to determine effects of drug-induced weight loss on quality of life and related factors. Favorable changes in risk factors and quality of life may be mentioned in the package insert and might lead to an indication for risk-factor alteration. Treatment of hypertension or type 2 diabetes may be a suitable indication.*” As previously provided, weight reduction impacts obesity related conditions, quality of life and/or risk factors and, as such, should be considered as potential outcomes or indications for treatment.

Incorporating “delay to onset” along with “development of” for risk-factors would be an appropriate addition to the above as an option of study design. The weight-loss endpoint, however, as described in the guidance document should continue to be the focus for registration as defined by the weight-loss criteria set forth in the draft guidance document. Other options provided by the above would be considered optional to the sponsor.

- ❖ Last sentence of section 5.2, “*...or in the small dense LDL that might be present in patients with abdominal obesity*” should be amended to reflect the fact that LDL cholesterol is not directly related to visceral adiposity.

5.3 Duration of Trials

- ❖ Abbott recommends that the exposure requirement defined by the draft Guidance be removed, as these requirements will largely depend on the compound being developed and experiences with marketed drugs in a similar class.
- ❖ The duration of the efficacy study may depend on the intended use of the drug, i.e., short-term weight loss and / or long-term weight maintenance.
- ❖ This criterion should be defined through discussions between FDA and the sponsor during development, e.g., pre-IND meeting.

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