

Phone 317 276 2000

April 21, 2004

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

Re: Docket Number 2003D-0570
Request for Comments on: 1996 Draft Guidance for Industry on the Clinical
Evaluation of Weight-Control Drugs.

Eli Lilly and Company (Lilly), as a global research based pharmaceutical company, is committed to the development of innovative medications for the treatment of obesity.

The obesity epidemic is a pervasive health problem in the United States. Obesity in the United States has increased steadily since the 1980s. From 1988 through 1992, fewer than 56 percent of American adults were overweight and fewer than 23 percent were obese; however, today over 64 percent are overweight and over 30 percent are obese (Flegal et al., 2002; Working Group on Obesity, 2004). This epidemic is not confined to adults. Data published by the Centers for Disease Control and Prevention (CDC) in 2003 demonstrates that 15 percent of children and adolescence ages 6 through 19 are overweight, which is double the percentage of two decades ago (cited in Working Group on Obesity, 2004). As Americans become heavier, their health suffers. Overweight and obesity increase the risks of other diseases such as type 2 diabetes, coronary heart disease, and certain cancers. According to some estimates, at least 400,000 deaths annually may be attributed to obesity (Mokdad, et al., 2004).

Lilly congratulates the FDA on its initiative described in the 11-February-04 Report of the Working Group on Obesity to aggressively address this pervasive, important health problem. In particular, Lilly is encouraged by the FDA's plan to revise the 1996 draft guidance cited above and appreciates the opportunity to comment. Lilly participated in the April 2003 and March 2004 meetings, hosted by the American Obesity Association (AOA), that provided opportunity for the AOA-industry representatives to discuss with FDA suggested changes to the draft guidance. Prior to the March 2004 meeting, AOA submitted to FDA a revision of the 1996 draft guidance that addressed issues for which there was general agreement among the AOA-industry participants on the need for change. Lilly supports AOA's revision and offers additional comments below as they relate to each of the six major sections of the AOA revision.

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GUIDANCE FOR THE CLINICAL EVALUATION OF DRUGS FOR THE TREATMENT OF OVERWEIGHT AND OBESITY

1. INTRODUCTION

Obesity is a Disease: Obesity is a chronic metabolic disease characterized by excess adiposity and associated with significant morbidity and mortality due to the complications of the cardiovascular, metabolic and other organ systems. Treatment of obesity is directed at a reduction in excess adiposity and its associated risks. One should be sure to consistently use the proper terminology of “drugs for the treatment of obesity” which effectively identifies obesity as a disease and the objective of drug therapy as treatment of the disease. Archaic terminology, such as “weight-control drugs” which diminishes the importance of obesity as a health hazard, or the significance of the role of drug therapy, should be abandoned. In addition, correctly identifying obesity as a disease with significant morbidity and mortality (Working Group on Obesity, 2004) will facilitate patient access to effective therapy by reducing barriers for healthcare reimbursement. Currently, many healthcare plans do not provide reimbursement for treatment for obesity because it is not recognized as a disease. Facilitation of patient access to therapy for obesity will become more important in the next decade because of the anticipated development of more effective drugs.

Different Mechanisms for Treatment of Obesity and the Need for Flexibility: The current FDA draft guidance is reasonably well suited to the development of monotherapy for the treatment of obesity that are similar in mechanism, efficacy and potential risk to previously approved drug therapies. Currently approved drug monotherapies are limited in efficacy. Major breakthroughs can occur either by drugs aimed at novel targets or by combination therapy. As new scientific discoveries increase our understanding of the pathogenesis of obesity, its associated risks, and in potential treatment targets, this is an ideal opportunity to create a guidance which describes sound development principles and meaningful guidance without being excessively prescriptive or which narrowly address issues observed with previously approved drugs. The guidance should be forward-looking and flexible enough to facilitate the development of the broad range of pharmacotherapies, including combination therapies, that can be expected over the next decade, and beyond. The new guidance need not be limited by the assumptions that future treatments will be similar in any way to previously approved drugs.

2. GENERAL RATIONALE

Definitions of the Disease are Evolving: Excess adiposity presents a continuum of cardiovascular, metabolic and other risks to the patient, even with degrees of excess adiposity well below the currently used diagnostic BMI criteria (>30 kg/m²). This is particularly true for the risk of diabetes, for which the increased risk of excess adiposity begins even at BMI considered normal (<25 kg/m²) (Kopelman, 2000). Therefore, although widely used, the conventional classification of normal, overweight, obese and morbidly obese is somewhat arbitrary. The currently used BMI diagnostics criteria is not necessarily applicable to ethnic populations such as native Americans or Asians (Tanchoco et al., 2003), nor does it account for the risks of visceral adiposity, even at modest degrees of obesity. As knowledge of obesity and drug treatments of obesity evolves, it is likely that the currently described BMI criteria (>30 kg/m² without comorbidities or >27 kg/m² with comorbidities) will evolve, just as the diagnostic criteria and treatment goals for other chronic metabolic diseases such as hypertension, diabetes, and hyperlipidemia have evolved over the past 20 years. Although the current BMI criteria is a reasonable starting place for most

studies of occidental Caucasian populations, the guidance should anticipate the evolution in understanding of obesity and allow sponsors to choose criteria for inclusion in studies are based on the current knowledge of the relationship between risk and excess adiposity. Such criteria may not necessarily be based solely on body weight or BMI, but may also include waist circumference, other anthropomorphic measurements, or other assessments of excess adiposity that have been shown to be associated with excess risk.

3. POPULATION

Effect of Excess Adiposity on Different Populations: As described above, the diagnostic criteria for the study populations should be based on the risk associated with excess adiposity. While the BMI criteria of >30 kg/m² without comorbidities or >27 kg/m² with comorbidities is suitable for most studies of occidental Caucasian populations, there may be specific populations with lower BMI which are appropriate populations due increased risk of morbidity, such as Asian populations or populations with predominantly visceral adiposity (Tanchoco et al., 2003)

Childhood and Adolescent Obesity: Obesity in childhood and adolescence is emerging as an important public health issue. Diagnostic criteria and the role of pharmacotherapy will may be different in pediatric and adolescent populations still in an active growth and weight gain phase than in an adult population. Because of the increasing numbers of adolescents with obesity, sponsors should be encouraged to include studies of this patient population in their clinical development plan. Although specific guidance for the study of pediatric populations is beyond the scope of this guidance document, sponsors should be encouraged to include plans for addressing this growing public health concern in individual discussions with the Agency.

Population Diversity: Phase 3 studies should include diverse populations. Due to the smaller sizes and different objectives of Phase 1 and 2 studies, diverse populations should not be required in early development unless driven by a specific need (for example if the drug is metabolized by an enzyme known to have significant ethnic differences.)

4. PHASE 1 STUDIES

There are no unique aspects to Phase 1 studies of obesity treatments. This could be stated explicitly or this section deleted altogether. Sponsors should be encouraged to develop and use biomarkers for the early assessment of potential efficacy and to guide the selection of dose regimens for subsequent stages of drug development.

5. PHASE 2 STUDIES

There are no unique requirements for Phase 2 studies in the development of drugs for the treatment of obesity. The size, duration and population studied should be sufficient to support the design and dose selection for the Phase 3 studies. A specific study design cannot be prescribed as it will differ based on the rapidity of onset of the drug effect, the availability of one or more biomarkers, and the design of the subsequent Phase 3 study. For example, if a sponsor intends to include 3 active doses in Phase 3 studies of a rapidly acting compound with a good biomarker for efficacy, the Phase 2 study may only need to be large enough and long enough to define the no-effect dose based on the biomarker and to assure tolerability of the higher doses with chronic administration. On the other hand, if the sponsor intends to include only a single dose of a more slowly acting drug without a good efficacy

biomarker in Phase 3, the Phase 2 studies should be substantially larger and longer to assure that the dose selected for Phase 3 has the optimum benefit-risk characteristics.

6. PHASE 3 TRIALS

Trials to establish the safety and efficacy of a drug for the treatment of overweight and obesity should be randomized, double-blind, and placebo-controlled. Other interventions, such as dietary and activity regimens should be balanced across treatment groups. The total size of the exposed population required to demonstrate safety should be driven by specific objectives or safety issues. ICH guidelines describe the rational basis for safety exposure required by ICH and seem suitable for chronic use treatments for obesity. The current FDA draft requires size and duration of safety exposure far in excess of ICH requirements; however, it does not provide the rationale for such a requirement. While individual drugs may require safety exposure which is larger or longer than ICH guidelines if data from nonclinical toxicology studies or previous experience with similar drugs suggests an important potential safety issue which is known to be rare or significantly delayed in onset, it is not rational to impose this requirement on all drugs.

6.1 ENDPOINT EVALUATION

Weight Loss as a Surrogate of Loss of Fat: The objective of a treatment for obesity is reduction of excess adipose tissue and its associated risks. Accurate and precise direct measurement of adipose tissue is currently impossible or impractical in large Phase 3 studies. In most cases, weight can be established by an appropriate surrogate in Phase 2 or 3 by the use of body composition measurements in an appropriately designed study. If weight loss is shown to be appropriate surrogate for fat loss, it is not necessary to directly measure fat mass or body composition in every Phase 3 study. Actual weight loss should be reported. It is helpful to express weight loss in relative terms such as percent of body weight or percent of excess over ideal body weight or change in body mass index. For drugs that reduce visceral adiposity, another surrogate measure, such as waist circumference or mid-sagittal diameter, needs to be established as an appropriate endpoint for implementation in Phase 3.

In studies in which weight loss is the primary objective, the currently described requirements for statistically significant 5% decrease compared with placebo or statistically significant increase in the proportion of patients who achieve 5% weight loss compared to placebo remains appropriate. In addition, analyses of proportions of patients which achieve 10% or 15% weight loss would be important information.

In studies in which maintenance of weight loss or prevention of weight gain is the primary objective, the drug should show statistically significantly greater proportion of patients who maintain at least a 5% weight loss.

Reduction in Visceral Adiposity: For drugs which have primary effects on reducing visceral adiposity or which may enhance lean body mass in addition to reducing adipose mass, body weight loss may substantially underestimate the therapeutic effects of the drug, and the above criteria may not be appropriate measures of efficacy. In these cases, another valid endpoint will need to be established by the sponsor and agreed upon by the Agency prior to use in Phase 3 studies. For example, reduction in visceral adiposity could be established by reduction in waist circumference, by imaging methods, or by showing improvements in metabolic markers of visceral adiposity, such as reductions in serum lipids, blood pressure, serum C-reactive protein, or serum leptin, or increase in serum adiponectin. The combination of favorable improvements in metabolic markers should be taken as a whole,

and individual markers should not necessarily be expected to be as great as one would expect for a specific indications such as hypertesion or hyperlipidema.

Diet Run-In as Part of Study Design: The inclusion and duration of a diet run-in phase may depend on the objectives of the Phase 3 study. As most adults seeking medical treatment for obesity have already failed non-pharmacological treatment on multiple occasions, it is unnecessary to demonstrate within the course of the study that dietary intervention will fail to normalize body mass. At the most, an elicited history of failed dietary intervention should be sufficient. In all studies, the total weight loss from baseline includes the effect of drug and non-drug interventions, and the estimate of drug effect is obtained by comparing the drug treatment arms to placebo arms. In those studies in which a dietary or other intervention is included in the regimen prior to instituting drug therapy, weight loss from baseline should also be assessed from the beginning of the total regimen, not just from the start of drug treatment, and the estimate of drug effect is likewise derived from the comparison to placebo.

As our knowledge of obesity advance, it may be possible to identify patients who will not respond well to drug treatment. Whether they are identified by failure to respond to a diet run-in or by some biochemical marker, if entry into Phase 3 studies excludes patients who are not expected to respond, the same limitation should be reflected in the product label.

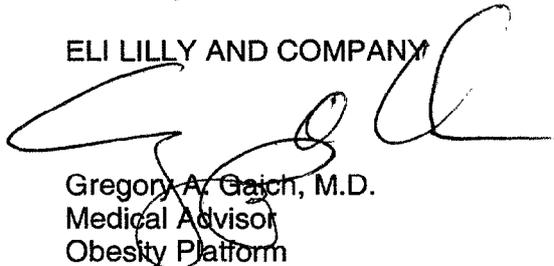
Obesity-Associated Cardiovascular and Metabolic Risk Factors: The protocol and analysis plans should describe the obesity-associated cardiovascular and metabolic risk factors (e.g., lipids, blood pressure and glucose tolerance) that would be measured; and the results of those analyses, whether positive, neutral, or negative, should be described in the label. It should not be necessary to show that the improvements in risk factors are independent of weight loss, as weight loss is the mechanism by which the risk factors are improved, and it is important for physicians and patients to understand the cardiovascular and metabolic effects of weight loss.

6.2 DURATION OF TRIALS

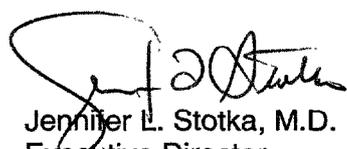
Obesity is a chronic metabolic disease; therefore, the duration of treatment should be sufficient to demonstrate efficacy and safety with chronic dosing, with initial trends established within the first 6 months and durability established with a primary endpoint at one year. Although the treatment of obesity requires demonstration of long-term weight loss, it is likely that drugs will be developed which are most useful in the induction of weight loss, after which a different weight maintenance regimen (either pharmacological or non-pharmacological) is instituted. In this case, even though the drug treatment induction may be relatively short (perhaps 3-6 months), the primary endpoint must still be at one-year, demonstrating the long-term benefit of the initial drug treatment.

Sincerely,

ELI LILLY AND COMPANY



Gregory A. Gaich, M.D.
Medical Advisor
Obesity Platform



Jennifer L. Stotka, M.D.
Executive Director
U.S. Regulatory Affairs

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