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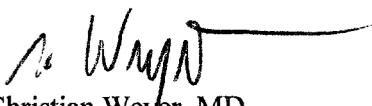
**RE: DOCKET NO. 2003D-0570: GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT-CONTROL DRUGS [69 Federal Register 3588-3589 January 26, 2004]**

Amylin Pharmaceuticals, Inc. is a biopharmaceutical company engaged in the discovery, development, and commercialization of drug candidates for the treatment of diabetes, obesity, and cardiovascular disease. The company's mission is to improve the lives of people with diabetes and other metabolic diseases through the discovery, development, and commercialization of innovative, cost-effective medicines. Because of its ongoing research in and commitment to obesity and obesity-related diseases, Amylin welcomes the opportunity to comment on the FDA draft guidance titled, "Guidance for the Clinical Evaluation of Weight-Control Drugs."

Amylin agrees that obesity is an urgent public health issue that requires more options for medical intervention. Recent scientific discoveries have greatly enhanced our understanding of the complex mechanism by which body weight is regulated. These discoveries have identified new potential therapeutic targets that hold promise of greater efficacy and safety than past weight loss medications. But there is a significant concern to any company that must decide whether to allocate millions of dollars to development of a drug for obesity due to the negative perception surrounding pharmacologic intervention. However, we are encouraged by the recent steps taken by the FDA to interact with industry to navigate the challenges, and better define the requirements, involved in the approval process for anti-obesity medications. Amylin recognizes that regulatory guidance on weight-loss drugs can only provide a framework, and not a "one size fits all" formula, for the development and approval process, and anticipates that the revised guidance will include language that encourages sponsors to discuss innovative approaches to arrive at conclusions that support safety and efficacy as a basis for drug approval. Specific comments to the guidance are attached. These comments are being provided electronically as directed in the Federal Register Notice.

Amylin Pharmaceuticals, Inc. appreciates the opportunity to submit these comments and looks forward to continuing dialogue with the Agency on this important issue. Should you have any questions concerning these comments, please contact me either by phone at (858) 642-7076 or by facsimile at (858) 334-1076.

Sincerely,

  
Christian Weyer, MD  
Director  
Clinical Research

CW/ch

2003D-0570

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**COMMENTS FROM  
AMYLIN PHARMACEUTICALS, INC.  
TO**

***GUIDANCE FOR INDUSTRY***

***GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT-CONTROL DRUGS  
(current draft guidance issued 1996)***

**26 April 2004**

**DOCKET NO. 2003D-0570  
69 Federal Register 3588-3589, January 26, 2004**

**AMYLIN PHARMACEUTICALS, INC.  
COMMENTS ON THE DRAFT GUIDANCE FOR  
THE CLINICAL EVALUATION OF WEIGHT-CONTROL DRUGS**

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**Comment # 1**

**Guidance Reference: Page 2, Section 2  
GENERAL RATIONALE**

Current guidance reads, "*FDA standards for weight-control drug approval anticipate the investigation of long-term safety and efficacy of weight-control drugs, leading to approval of drugs with indications for weight control using long-term or indefinite drug administration.*"

Some anti-obesity drug candidates may be most effective for inducing weight loss, while others may be most effective in weight loss maintenance. A clear definition of regulatory requirements for a short-term weight loss, long-term weight loss, and weight maintenance indication would be desirable.

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**Comment # 2**

**Guidance Reference: Page 2, Section 3  
EARLY CLINICAL TRIALS**

Current guidance reads, "*The mechanism of action of the drug should be established if possible.*"

Many of the parameters required to establish the mechanism of action of an anti-obesity drug are rather difficult to measure in humans (e.g., food intake, hunger, energy expenditure, body composition). Weight loss mechanisms in animals may or may not be applicable to humans. More specific guidance might be useful as to the requirements for including findings on the mechanism of action into the package insert.

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**Comment # 3**

**Guidance Reference: Page 3, Section 4  
DOSE RANGE FINDING**

Current guidance reads, "*Dose-finding should identify the lowest dose of the drug that safely achieves an optimal drug effect. Inclusion of at least 3 doses of drug in dose-finding efficacy studies will probably allow identification of a low dose that is inadequate, and also a dose that achieves the maximum benefit that can be obtained without toxicity.*"

It is understood that dosage levels should be selected that allow identification of a low dose that is inadequate and a dose that achieves the maximum benefit that can be obtained without toxicity in order to establish a dose-response relationship. However, for some classes of products (those that cause little to no toxicity or those where tolerability differs widely among individuals), it may not be possible to define a general, "one-fits-all" maximum dose. In these cases, the guidance should define a procedure/strategy that allows a sponsor to provide a scientific justification of the rationale for the doses selected for Phase 3 clinical trials.

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**Comment # 4**

**Guidance Reference: Pages 3-6, Section 5  
TRIALS TO ESTABLISH EFFICACY**

Current guidance reads, *“Subjects who meet the entry criteria with regard to obesity and risk factors may be entered into a program aimed at weight reduction, but without drug. Such a program might include calorie-restricted or controlled diet, behavior modification, and exercise. As a minimum, a modestly restricted diet and regular exercise should be actively encouraged. Placebo may be used during this period so that placebo responders are identified. Generally, this program should be continued for 6 weeks. Subjects should not be placed on drug as long as weight loss continues without drug, but may be randomized when weight has plateaued, as long as their weight remains above their goal for weight reduction (e.g. ideal body weight). Although subjects who are still losing or who reach ideal body weight on this program have no need for drug at that time, they may be kept on the weight program and randomized to placebo or study drug later if their success at weight loss evaporates.”*

In previous pivotal trials with anti-obesity agents (including sibutramine and orlistat), these guidelines were followed, and subjects, on average, lost weight prior to randomization. Thus, study medication was introduced at a stage when subjects had been in a negative energy balance for several weeks, and presumably had fully manifested the typical counterregulatory responses, e.g., activation of central orexigenic signals, decrease in metabolic rate. These compensatory responses may differentially interfere with the mechanism of action of different anti-obesity agents, possibly augmenting the effect of some agents, while diminishing the effect of others.

In clinical practice, most obese subjects have had many unsuccessful attempts to lose weight with diet and exercise alone, and by the time they seek drug treatment many will have recently (re-) gained weight (meaning that they will start study medication while in a positive, or neutral energy balance). In clinical practice, it is the exception, not the rule, that subjects will have lost several pounds of weight just prior to the time that drug treatment is initiated.

It therefore appears that the Phase 3 study design outlined in the 1996 guidance may not represent the scenario in which these drugs may later be used in the clinic. Thus, the requirement for a six-week run-in period where all subjects are encouraged to partake of a restricted diet and increase exercise intervention should be re-evaluated, as it is felt that this requirement may confound trial results and not reflect real world conditions.

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**Comment # 5**

**Guidance Reference: Pages 4-5, Section 5.2  
Procedures**

Current guidance reads, *“Measurement of obesity-associated cardiovascular risk factors (lipids, blood pressure and glucose tolerance) during drug administration is encouraged, as they may have a place in determining the balance of benefit vs. risk for the drug. If one or more of these factors deteriorates or is not improved, the risk associated with this deviation must be considered in making a benefit-to-risk decision for the drug.”*

It is well established that most health risks associated with obesity increase exponentially with increasing BMI (i.e., subjects with a BMI of 40 are at a much greater risk than subjects with a BMI of 30). While the effect of pharmacologically induced weight loss on cardiovascular risk has not yet been established in hard endpoint trials, it is conceivable, if not likely that the benefit of drug-induced weight loss (in terms of absolute risk reduction and number-needed-to-treat) also increases with increasing BMI. In contrast, the risk (safety) of a given anti-obesity agent may be constant across a wide range of BMI categories. Consequently, an anti-obesity agent may have a favorable risk/benefit profile (approvable) in more severely obese subjects (e.g., BMI>35), but a less favorable risk/benefit profile (perhaps non-approvable) in moderately obese subjects (e.g., BMI 27-30). Based on the 1996 guidance, it is unclear whether and how a drug candidate might be approved for a high-risk BMI subcategory.

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**Comment # 6**

**Guidance Reference: Pages 4-5, Section 5.2  
Procedures, Endpoint evaluation**

Currently, at least two weight loss demonstrations of efficacy are possible:

*a) demonstration that the drug effect is significantly greater than the placebo effect and the mean drug-associated weight loss exceeds the mean placebo weight loss by at least 5%.*

*b) demonstration that the proportion of subjects who reach and maintain a loss of at least 5% of their initial body weight is significantly greater in subjects on drug than in those on placebo.*

**Comment 1:** Efficacy in relation to initial BMI – The guidance does not consider or address possible subpopulation indications.

For example, a drug candidate, based on its mechanism of action, may be much more effective in severely obese than in overweight or moderately obese subjects. Consider a scenario where a drug causes 4% weight loss in subjects with a BMI of 27-45 (not meeting current efficacy criteria), but 7% weight loss in subjects with a BMI >35, and only 2% weight loss in subjects with a BMI of 27-35. From this example, it is unclear whether the drug can be approved for severely overweight patients (BMI >35). A revised guidance document should include more specific guidance on the appropriate clinical trial strategy (separate trial or prospectively defined subgroup analysis) for possible subpopulation indications or treatments.

**Comment 2:** Efficacy in relation to risk factors/safety – The guidance does not address if a risk/benefit analysis may provide a reduction in the 5% threshold if the drug is safe or reduces other obesity related risk factors.

Consider two drug candidates:

Drug A causes 5-7% weight loss accompanied by little improvement in obesity-related risk factors (e.g., blood pressure, glucose tolerance) and some safety concerns (CNS side effects); whereas, Drug B causes 3-4% weight loss and is associated with marked improvements in obesity-related risk factors and has virtually no safety concerns.

In this scenario, Drug B may have greater therapeutic benefit in preventing obesity-related comorbidities and is very safe, yet based on the current guidance, Drug A seems to have the better chance for approval because it achieves greater than a 5% weight loss.

The guidance should address whether the same “efficacy hurdle” be applied to all drug candidates regardless of their accompanying effect on risk factors and their safety profile.

**Comment 3:** Efficacy in conjunction with other, already approved drugs – Currently, the guidance only addresses monotherapy.

In type 2 diabetes, where a much larger armamentarium of drugs is available, and combination therapy is a standard treatment, Phase 3 trials are often designed in an add-on fashion. In obesity, where the number of currently marketed drugs is scarce, Phase 3 trials are typically designed as monotherapy trials. That is, every single drug candidate is required to cause at least a 5% weight loss on its own in order to reach the market. Obesity researchers tend to agree that it is unlikely that there will ever be a “magic bullet” that, in monotherapy, causes pronounced weight loss without side effects. Instead, the path for more pronounced, safe weight loss may lie in combination treatment with drugs that are moderately effective by themselves, but are more effective and safer when used in combination, possibly at lower doses (due to additive mechanism of actions and/or a synergy of effects).

A revised guideline should provide sufficient guidance on the regulatory/clinical trial strategy for the possible approval of an anti-obesity drug candidate for a combination therapy indication.

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#### **Comment # 7**

##### **Guidance Reference: Pages 5-6, Section 5.3** **Duration of Trials**

*Current guidance reads, “In order to obtain an adequate estimation of the safety of weight-control drugs for long-term administration, generally, about 1500 subjects are expected to complete 12 months with 200-500 of those subjects completing 24 months of study. Most often the double-blind status of the study is maintained for at least 1 year, at which time, placebo patients may be switched to drug and followed on open label for another 12 months to a total of 24 months for weight and development of obesity-related morbidities. For those who have dropped out of the study it is usually possible to obtain at least telephone contact at 24 months for self-reported weight, and morbidities.”*

Currently, the draft guidance recommends that pivotal trials include a second year of open-label extension, primarily for the collection of data related to long-term safety. In some instances long-term safety data may be available for drugs that are already marketed for another indication or for which extensive long-term safety data are available from previous development programs designed for related indications. Should this be the case and the dose for both development plans are comparable, use of this long-term data may be considered relevant.

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