
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

920 U.S. Highway 202, P.O. Box 300
Raritan NJ 08869

2003 1 APR 20 10 30

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1051
Rockville, MD 20852

FDA Docket No. 2003D-0570
Request for Comments on a Draft Guidance of the Clinical Evaluation of Weight-
Control Drugs

Dear Sir/Madam:

As leaders in the discovery, development, manufacturing and marketing of prescription medicines, the pharmaceutical business and research organizations in the Johnson & Johnson family of companies are committed to improving health and well being through innovative products and services. I am sending these comments on their behalf.

We fully support the FDA's interest in incorporating the latest scientific advances in the field of obesity and drug development into an amended obesity guidance document. The current epidemic of obesity in the U.S. needs to be addressed and it is encouraging that Tommy Thompson, Secretary of Health and Human Services (HHS) has kicked off a major initiative on obesity to convert opinion that obesity is a medical concern not a life style issue. Acting Commissioner Lester Crawford has stated that obesity-related deaths in the U.S. have increased to 400,000 per year, up from 300,000 two years ago. He predicted the number will exceed 500,000 deaths per year by the end of this decade and at that point will likely overtake tobacco as the leading cause of death in the U.S.

Although not a complete and total answer, pharmacological intervention has an integral role along side other treatments (e.g. bariatric surgery) and lifestyle modifications in curbing the obesity epidemic and reducing the incidence of associated diseases such as diabetes and hypertension that are well recognized as major contributors to the onset of cardiovascular morbidity and premature cardiovascular mortality. The treatment of obesity includes induction of weight loss, maintenance of weight loss and prevention of weight gain. As such, it needs to be recognized that available therapies may provide valuable benefit to one phase of the treatment paradigm.

The guidance should address the recent emergent environment associated with obesity such as metabolic syndrome and childhood obesity. With newer and novel therapeutic approaches to treat obesity and the associated morbidity and mortality, we encourage

2003D-0570

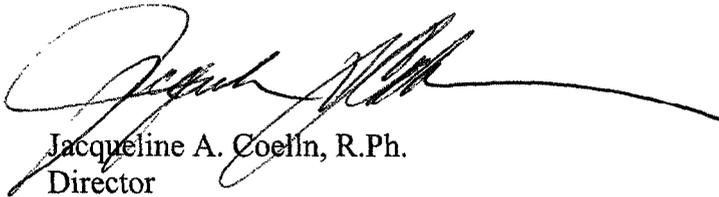
C8

FDA to take into account clinically relevant improvements in co-morbid disease biomarkers (HbA_{1c}, blood pressure, lipids etc.) whilst determining the benefit-risk of a new agent. We further encourage the Agency to utilize all resources at their disposal to expedite delivery of new therapeutic options to obese patients.

We believe the obesity guidance revision process will be greatly enhanced by broad consultation with experts in the field and therefore encourage the FDA to take full benefit of the larger scientific and medical community on developing solutions in the field of obesity research. As indicated in FDA's recently issued paper on Innovation Stagnation (US Department of Health and Human Services, March 2004), the FDA is uniquely positioned to help identify the challenges of development with the goal of promoting efficient development of safe and effective new medical treatments.

In closing, we appreciate the opportunity to comment on this very important draft guideline. We look forward to working alongside the FDA with the goal of promoting efficient development of safe and effective new medical treatments for obesity.

Sincerely,

A handwritten signature in black ink, appearing to read 'Jacqueline A. Coeln', with a long horizontal flourish extending to the right.

Jacqueline A. Coeln, R.Ph.
Director
Regulatory Affairs

GENERAL COMMENTS

Overall, this is a very important draft guideline that will have a significant impact on development of drugs for the treatment of obesity, a chronic metabolic disease. However, at this point, it requires major revisions and we fully support the current efforts to update this guidance. The document dates from 1996, so it could not be expected to address the recent emergent environment associated with obesity; metabolic syndrome, childhood obesity, or the fact that the epidemic of obesity continues to progress largely unchecked. Although not a complete and total answer, pharmacological intervention has an integral role along side other treatments (e.g. bariatric surgery) and lifestyle modifications in curbing the obesity epidemic and reducing the incidence of associated diseases such as diabetes and hypertension that are well recognized as major contributors to the onset of cardiovascular morbidity and premature cardiovascular mortality.

Control of obesity can result in a variety of health benefits and outcomes. It is well documented that even modest weight loss has been associated with clinically significant improvements in hypertension, lipid abnormalities, ischemic heart disease and reduced risk of developing type 2 diabetes (Clinical Guidelines of the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, The Evidence Report, NIH September 1998). These documented patient benefits need to be communicated to prescribers and patients, potentially forming the basis for label claims. With newer and novel therapeutic approaches to treat obesity and the associated morbidity and mortality, we encourage FDA to take into account these clinically significant improvements whilst determining the benefit-risk of a new agent. We further encourage the Agency to utilize all resources at their disposal to expedite delivery of new therapeutic options to obese patients.

It should be recognized that an obesity agent could provide a valuable benefit for only one stage of the treatment phases / potential indication statements for obesity, for example: induction of weight loss, maintenance of weight loss, prevention of weight gain, reduction in morbidity and/or mortality, e.g., cardiovascular disease, type 2 diabetes, malignancies, respiratory disorders, etc. Therefore FDA guidance should delineate recommended clinical development programs (e.g. trial designs, clinical endpoints (single endpoints and/or possible composite outcome measures), duration of treatment, etc) for each phase.

We believe the obesity guidance revision process will be greatly enhanced by broad consultation with experts in the field and therefore encourage the FDA to take full benefit of the larger scientific and medical community on developing solutions in the field of obesity research. As indicated in FDA's recently issued paper on Innovation Stagnation (US Department of Health and Human Services, March 2004), the FDA is uniquely positioned to help identify the challenges of development with the goal of promoting efficient development of safe and effective new medical treatments.

Below is the Johnson & Johnson family of companies comments directed at the wording in the 1996 draft obesity guidance; comments are provided for each section of the draft guidance.

1 INTRODUCTION

We suggest replacing the terminology “self-esteem” with “patient reported outcomes”, as “self-esteem” represents a very limited perspective and tends to understate the serious impact of the obese condition and the compelling need for treatment. “Patient reported outcomes” provide the broader understanding of the patient’s perception of their general functioning and well being including domains such as health status, symptoms, psychological and social functioning. This type of evaluation may be valuable to include in the product labeling, therefore, we recommend that the guidance address instruments (tools) that can be used to measure and report patient reported outcomes.

In addition, we recommend that reducing or maintaining body weight, or preventing body weight gain be added to reducing body fat as a demonstration of the safety and efficacy of obesity treatments.

We suggest replacing the terminology “weight-control drugs” with the description “drugs for the treatment of obesity”.

In addition, the WHO definition of the term obesity should be described in the introduction or general rationale sections:

- BMI $\geq 25\text{kg/m}^2$ for overweight (Pre-obese: BMI $\geq 25\text{-}29.9\text{ kg/m}^2$)
- BMI $>30\text{kg/m}^2$ for obesity:
 - Class I obese: BMI $30\text{-}34.9\text{kg/m}^2$ (Moderate)
 - Class II obese: BMI $35\text{-}39.9\text{kg/m}^2$ (Severe)
 - Class III obese: BMI 40kg/m^2 (Morbid)

Reference to “healthy obese” or “otherwise healthy” should be eliminated and replaced with “obesity uncomplicated by associated co-morbid disease”.

We generally agree with the BMI definitions for the population to be treated as outlined in the current guidance. However, given the growing body of scientific evidence that overweight patients are at increased risk for co-morbid diseases, including the observation of a J-Shaped relationship between body-mass index and overall mortality from the prospective Nurses’ Health Study that examined the health consequences of being mildly to moderately overweight in association with mortality, the FDA may wish to consider the relevance of modifying a portion of the criteria to include patients with a BMI $\geq 25\text{kg/m}^2$ with co-morbidities.

2 GENERAL RATIONALE

We strongly urge the FDA to discuss in this guidance the relationship of obesity with type 2 diabetes mellitus. The increasing prevalence of obesity is a major public health concern associated with increased incidence of hypertension (HTN), dyslipidemia and type 2 diabetes mellitus. Further, as childhood obesity is increasing there is evidence that the onset of type 2 diabetes is no longer limited to those in their fourth or fifth decade of life. Diabetes is associated with significant morbidity and mortality due to microvascular (retinopathy, nephropathy, and neuropathy and neuropathic complications) and macrovascular (cerebrovascular and cardiovascular diseases) complications. The association of obesity with diabetes is well established, and obesity is now accepted as a major risk factor for the development of type 2 diabetes; approximately 80% of patients with type 2 diabetes are overweight. As body weight increases, the risk of type 2 diabetes increases linearly. From the Diabetes Prevention Program (DPP), intensive lifestyle intervention led to weight loss and associated with that weight loss was a delay in the onset of diabetes by 58%.

In addition to the co-morbidities that result from excess weight, there are also decreases in patient perceptions of functioning and well being and changes in other patient-reported outcomes associated with obesity (e.g. symptoms). (Patrick, et al. Performance of two self-report measures for evaluating obesity and weight loss. *Obesity Res* 2004;12:48-57).

Furthermore, obesity imposes a significant economic burden on society. Annual medical expenditures of obese adults under 65 were estimated to be 36% higher than those of normal weight (R. Sturm "The Effects of Obesity, Smoking, and Drinking on Medical Problems and Costs", *Health Affairs* March/April 2002:245-253.) In 2002, \$92.6 billion of annual medical spending was attributable to being overweight or obese (E. A. Finkelstein et. al. "National Medical Spending Attributable To Overweight and Obesity: How Much, And Who's Paying?" *Health Affairs*, May 2003:219-226.) These estimates of the full societal economic effect are underestimated, as they do not include non-direct medical costs, such as losses in worker productivity.

Currently approved pharmacological therapies for the management of obesity are indicated for both weight loss and weight maintenance. It should be recognized that an obesity agent could provide a valuable benefit for only one phase of the treatment paradigm, and therefore specific (e.g.; trial duration, endpoint evaluation, etc.) guidance for each phase should be provided in the appropriate sections of this document. In addition, a separate discussion of the development of pharmaceuticals for the prevention of obesity and early treatment intervention, including childhood interventions should be included.

The current guidance document states that "weight is frequently (usually) regained promptly after it has been lost if the weight loss was induced by weight-control drugs and the drugs have been discontinued". This statement should be removed since it is common to have a rebound effect when either pharmacological intervention or non-pharmacological intervention is terminated (Clinical Guidelines of the Identification,

Evaluation, and Treatment of Overweight and Obesity in Adults, The Evidence Report, NIH September 1998). Weight maintenance interventions should be considered a chronic intervention with potentially life-long therapies in the same context as treatment of other metabolic and CV risk factors & diseases (dyslipidemia, hypertension). Thus suggesting that a new “set point” will be developed after the cessation of drug administration is not valid.

3 EARLY CLINICAL TRIALS

Consistent with the current PK guidelines, we support the inclusion of both healthy volunteers and obese patients without significant co-morbidity for evaluation in the early phase clinical trials. And while the statements regarding the inclusion of a minority and gender mix is valid, this comment is more applicable to larger Phase 2b and 3 studies for which useful clinical data may be obtained. In addition, the high prevalence of metabolic syndrome and co-morbidities in the obese population implies that concomitant use of antihypertensives, lipid lowering and hypoglycemic agents, among others, will occur. As such, for those concomitant drugs that may have a narrow therapeutic window and may have a potential for pharmacokinetic or pharmacodynamic interaction with the drug agent under development, consideration should be given to conducting early drug-drug interaction trials for co-morbid treatments.

The mechanism of action is an important consideration for the development of any new agent. However, it is a complex undertaking, which may not be feasible to fully elucidate in a short time frame, and therefore is frequently not practical to define in early clinical studies. It should be investigated thoroughly, and in parallel with the whole development program. In early mechanism probe trials, hypothesis generating studies for the mechanism(s) of action may be useful, such as investigating a dose dependent change in a biomarker that suggests a certain mechanism of action (e.g. reduction of food intake for appetite suppressing drugs, fecal fat content or postprandial triglyceride absorption for fat absorption inhibiting agents). Subsequently, if proven to correlate with and be reasonably interpreted as causative of the weight loss, these biomarkers can be used as surrogate markers of weight loss and be of clinical utility in early proof of clinical concept trials where study duration is too short to demonstrate weight loss.

If there is theoretical rationale for a differentiated response (exaggerated or diminished) to a drug in a certain cohort of patients, the study design should aim to identify and characterize this cohort (e.g. by using a pharmacogenomic approach).

4 DOSE RANGE FINDING

We agree with the general description of the design considerations as stated in the 1996 draft guidance for dose-range finding clinical trials. We do however recommend:

- That the identification of a lower dose needs to be “ a clinically relevant drug effect “ rather than the current wording of “ an optimal drug effect”

- That “similar instruction in diet, exercise and behavioral interventions” be replaced with, “standardized instruction in diet, exercise and behavioral interventions” to be given across sites within a study to eliminate the potential influence of site to site variability of ancillary interventions on weight loss response.
- Those patients with certain co-morbid risk factors (e.g. hypertension & dyslipidemia), which do not historically interfere with weight loss response, be included in phase 2b trials.
- Consideration be given to dose ranging in specific obese populations if these are to be the focus of a phase 3 development program (e.g. severe or morbid obese, obese subjects with type 2 diabetes).
- The population under study in dose-finding should be diagnosed as obese by accepted diagnostic convention and be broadly similar in demographic composition to the proposed phase 3 population. This population should therefore be considered similar demographically, ethnically and in terms of predicted drug response, to a representative US obese population.

The guidance should also address the following scenarios: the possibility of different dose regimens, such as continuous or intermittent treatment; dose ranging for weight loss, dose ranging for weight maintenance and dose ranging for use in combination with other weight control agents.

5 TRIALS TO ESTABLISH EFFICACY

As indicated in FDA’s recently issued paper on Innovation (US Department of Health and Human Services, March 2004), much more attention and creativity need to be applied to disease-specific trial design and endpoints intended to evaluate the effects of medical products.

As discussed earlier, weight loss, weight maintenance, as well as obesity prevention should be described, along with the general and specific parameters for consideration during drug development programs (e.g.; trial duration, dose selection, efficacy assessment tools (parameters), efficacy endpoints).

As also mentioned previously diet, exercise and behavioral interventions should be standardized within a study to eliminate the potential influence of variability of ancillary interventions on weight loss response. It is suggested that caloric content of the background hypocaloric diet should be assessed individually according to the subject’s calculated daily energy requirements. Because of the influence of body weight on this, these requirements should be recalculated periodically during long-term studies. Lower doses or a eucaloric diet should be considered when assessing long term weight maintenance following weight reduction.

We are encouraged by the FDA collaboration with NIH in addressing the need to improve the efficiency and effectiveness of the clinical trial process, including trial design, endpoints and analyses through its *Roadmap* initiative.

5.1 POPULATION

As provided for earlier in these comments, the WHO definition of the term obesity should be described as the guidance for patient populations to be studied:

- BMI $\geq 25\text{kg/m}^2$ for overweight (Pre-obese: BMI $\geq 25\text{-}29.9\text{ kg/m}^2$)
- BMI $>30\text{kg/m}^2$ for obesity:
 - Class I obese: BMI $30\text{-}34.9\text{kg/m}^2$ (Moderate)
 - Class II obese: BMI $35\text{-}39.9\text{kg/m}^2$ (Severe)
 - Class III obese: BMI 40kg/m^2 (Morbid)

Including consideration for modifying a portion of the criteria to include patients with a BMI $\geq 25\text{kg/m}^2$ with co-morbidities instead of $\geq 27\text{kg/m}^2$.

The sentence “It is often preferable to identify obesity by methods that measure body fat and its distribution”, suggests that this type of measure should replace weight or BMI as a primary endpoint measure. We agree that the measure of body fat and its distribution is an import factor and suggest the wording be modified to reflect fat assessment as an additive measure, rather than an a replacement measure to weight and BMI. Associated with this comment, a more detailed description regarding the identification of an appropriately powered subset of subjects with visceral obesity needs to be given. For instance, visceral obesity can be indirectly assessed through anthropometric assessments such as waist circumference or directly via more intensive imaging modalities such as CT scanning, DEXA or MRI. Often, assessment of a representative proportion of male subjects will allow a better opportunity for assessment of visceral fat in subject population with a greater degree of visceral obesity.

We question the value of including the demographics of “socioeconomic status and education level” of a subject as these factors do not have a causal relationship to the efficacy of an agent and should therefore be deleted.

5.1 PROCEDURES- SUBJECT SELECTION

We strongly disagree with the requirement for a 6-week non-pharmacological weight loss run-in period prior to study inclusion. As discussed in the General Rationale section of this document non-pharmacological weight loss while often successful in initial weight reduction is also commonly associated with weight re-gain over time. It is highly unusual for an obese subject to enter a study of an investigational agent unless they have

previously attempted other weight loss modalities, and these previous failed attempts can be ascertained through medical history.

From a study design perspective run in periods have revealed a minority of subjects that achieve a clinically relevant weight loss that would preclude intervention. This makes subjecting all subjects to this regimen of doubtful clinical benefit and adds unnecessary time and cost to study conduct. From the medical perspective are the unusual baseline conditions such run-in periods present. Subjects are usually placed on caloric restriction during this period resulting in significant metabolic changes. This includes lipid (particularly triglyceride) and glucose changes that make the interpretation of the baseline value (i.e. at the time of drug intervention) extremely difficult.

In addition this requirement presents an inconsistency with guidance for other chronic metabolic conditions (lipid-lowering, anti-hypertensive or anti-diabetic agents). We suggest the Agency consider a short (2-4 week) placebo weight maintenance run-in period to establish drug compliance and evaluate an accurate baseline metabolic status in a eucaloric setting.

5.1 PROCEDURES- ENDPOINT EVALUTION

We generally agree with the requirements for demonstration of a weight-loss or maintenance of at least 5% as stated in the current document. However, as stated previously, it would be more meaningful to separate weight loss from weight maintenance and to give consideration to weight prevention.

It is generally recognized that people with obesity experience a number of significant co-morbidities including diabetes and dyslipidemia. We recommend that for agents where a sponsor foresees a significant benefit in a particular co-morbidity in addition to weight loss, and has plans to study this particular obese population for a dual indication, dual primary endpoints be considered. Given that a number of co-morbid variables may show improvement in addition to weight loss and that this information would greatly benefit the prescribers of these agents, it is important to have this information available in the product label. As such, it should not be necessary to declare a co-morbid endpoint as a co-primary endpoint in order for inclusion in the product label. For multiple co-morbid endpoints, each can be listed as secondary endpoints, but a multiplicity adjustment rule would need to be specified.

Furthermore, we strongly urge the FDA to consider the balance of benefit versus risk for an agent that modifies a disease state primarily through a mechanism of weight loss. An agent should be considered efficacious with the opportunity for a primary indication for that specific comorbid disease (e.g. type 2 diabetes, hypertension) if the effects are:

- Clinically relevant for that disorder
- In line with accepted clinical practice for that disorder
- The magnitude and the durability of effect is consistent or superior to other approved agents for that disorder

- An acceptable safety profile for that disorder
- The added benefit of weight loss, rather than being considered a barrier to an indication for these conditions, often adds to the accepted standard of care (e.g. type 2 diabetes, where this is an elusive clinical attribute with current interventions).

With reference to potential indications, we suggest the FDA consider the potential for a prevention of other metabolic diseases associated with obesity, (e.g. type 2 diabetes, dyslipidemia) where the sponsor demonstrates a significant reduction in the conversion of subjects with obesity to the metabolic disease (e.g. subjects with obesity and impaired glucose tolerance/impaired fasting glycemia to type 2 diabetics through drug plus diet/exercise vs. diet/exercise alone).

In addition to the biomarkers currently listed in the guidance document it is suggested that the following additional CV biomarkers for assessment be considered where applicable for agents with potential to demonstrate benefit: left ventricular mass, inflammatory markers (e.g. C-reactive protein) and clotting factors (e.g. PAI-1 and fibrinogen).

It is suggested that in addition to the empirical assessment of body composition and body fat in all subjects through anthropometric measurements (e.g. waist circumference), these should also be adequately assessed in an appropriately powered subset of subjects via more accurate direct measurements (e.g. DEXA, CT, MRI, underwater weighing)

For drugs acting in the central nervous system, the potential for drug dependence or abuse should be discussed within the guidance.

5.3 DURATION OF TRIALS

Broadly we agree with the treatment durations and overall treatment exposures proposed in the guidance. However, if our previous suggestion is considered there should be guidance on the duration and exposure requirements for the weight loss and weight maintenance phase of obesity treatment, respectively. And this would be separate from the obesity or diabetes prevention requirements that should also be addressed.

It is suggested that maintenance of body weight be defined as relative to baseline and not relative to placebo, i.e. weight regain at the same trajectory, as placebo should not constitute maintenance. For a weight loss claim, a trial duration of 6 months would be adequate; for a weight maintenance claim, twelve months may be more than sufficient for the duration of the trial, since if the drug were not effective in maintaining the weight loss, this would become apparent early. For safety evaluation, a subset of patients may continue for a longer period (e.g. 24 months).

As per the current guidance *“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.”* This appears to envision combining data from the open label second year

with data from the randomized first year. Such combination of data may produce bias because the first year after study entry gets more protection from study entry criteria than does the second year. Additionally, such telephone follow-up requirements should be tailored for off-treatment monitoring of specific predefined safety concerns and not be used to assess post treatment weight or other efficacy parameters due to the potentially unreliable nature of data captured in this format. Consideration should also be given to historically poor compliance rates with such follow up strategies following study withdrawal.