

COMMENTS
FDA GUIDANCES FOR INDUSTRY
Developing Products for Weight Management

Richard L. Atkinson, M.D.

The FDA is to be congratulated on the draft of Guidance for Industry for weight management drugs. This Guidance is a marked improvement over the older Guidance and will help pharmaceutical companies bring new and better drugs to the marketplace for the treatment of obesity. However, there are several areas that I believe may be improved upon in this draft. My comments below have the current FDA language in bold and my comments or suggested language below that:

Page 1, Lines 22-25: “This guidance applies to products intended to be used for medical weight loss, which can be defined as a long-term reduction in fat mass with a goal of reduced morbidity and mortality through quantifiable improvements in biomarkers such as blood pressure, lipids, and HbA1c.”

This sentence is limiting. It implies that the only reason to lose weight and fat mass is to improve morbidity and mortality through improvements in biomarkers. This ignores two factors. It is valuable to individuals to lose weight and fat for reasons other than reducing biomarkers. Psychological benefits and social/economic benefits occur with weight/fat loss. Secondly, it has been shown that excess weight or fat, even without abnormalities in common biomarkers, is associated with mortality.

Page 3, Lines 117-123: “Lifestyle modification, consisting of changes in patterns of dietary intake, exercise, and other behaviors, is considered the cornerstone of overweight and obesity management. Because all drug and biological therapies impose some risk for adverse events, the use of a weight-management product should be contemplated only after a sufficient trial of lifestyle modification has *failed* and the risks of excess adiposity and the anticipated benefits of weight loss are expected to outweigh the known and unknown risks of treatment with a particular weight-management product.”

While no one would argue that diet, exercise, and lifestyle modification are important in treating obesity, there is a long history of failure of these behavioral treatments for obesity. The requirement that an individual fail behavioral treatment before pharmacologic agents are started is incompatible with the practice of medicine for other chronic disease that also respond quite nicely to behavioral treatment. For example, hypertension and Type 2 diabetes respond in about 80% of cases to exactly the same treatments that are suggested for obesity. However, an individual who is diagnosed with new onset hypertension or diabetes is virtually always started on drugs **at the same time** as the behavioral treatments. It is discriminatory to make significantly obese people **fail** a behavioral treatment first, when it has less than a 5% chance of being effective 3 years after initiation of treatment. If behavioral treatments do fail, the wasted time before starting drugs may allow the complications of obesity such as heart disease, cerebrovascular disease, diabetes, sleep apnea, etc, to progress further. The purported risks of

obesity drugs are in most cases less than the risks of anti-hypertensive or anti-diabetic agents, yet a similar prohibitive attitude against these agents is not taken.

Page 4, lines 125-133: “Patients with BMIs greater than or equal to 30 kg/m² or greater than or equal to 27 kg/m² if accompanied by weight-related comorbidities historically have been considered appropriate populations for treatment with weight-management medications (Clinical Guidelines on the Identification and Treatment of Overweight and Obesity in Adults 1998). Although these patient-selection criteria are to a degree arbitrary, and an argument may be made for criteria that are more or less restrictive, we believe that individuals with BMIs greater than or equal to 30 kg/m² or greater than or equal to 27 kg/m² if accompanied by weight-related comorbidities represent patient groups with sufficient baseline risk to justify inclusion in studies of investigational weight-management products.”

The use of a BMI of 27 kg/m² as a lower limit for weight reduction drugs has been accepted by many in the obesity field. However, this limit ignores the problem of racial differences in risk of overweight/obesity and the literature that has been published in recent years from other countries. Misra et al (1,2) have shown that a BMI of 22 puts an Indian at risk for diabetes and the morbidity/mortality rate begins to climb in Asians long before a BMI of 27. If minorities are to be included in clinical trials of obesity agents, some discretion on the part of the sponsor should be allowed.

In addition, nowhere in the Guidance does the possibility of using obesity drugs for weight maintenance surface. Thousands to millions of obese individuals have tried behavioral modalities to lose weight, some of them successful. It may be a very reasonable use of an obesity drug to treat a patient who has demonstrated major morbidities of obesity in the past, lost a large amount of weight, and is facing the inevitable weight regain that is so common (only about 5% of individuals in treatment programs keep off their weight for 5 years or more). Also, Anderson et al (3) and Astrup et al (4) have published meta-analyses that show that for every outcome variable tested, rapid weight loss (for example by very low calorie diets) produces similar or better results than does slow steady weight loss using a modest dietary regimen. However, rapid weight loss results in rapid weight gain in many individuals. Numerous studies have been done with all of the weight loss drugs approved since 1973 showing that they prevent weight regain better than behavioral treatment alone. Therefore, it may be a beneficial treatment of obesity to prescribe rapid weight loss followed by obesity drugs to prevent weight regain. A paragraph should be added to the guidance that sponsors who wish to gain approval of obesity agents for the **prevention** of weight gain may perform the appropriate clinical trials.

Page 4, lines 148-153 and 160-164: “For patients aged 2 to 7 years, the AAP recommends weight loss through lifestyle modification if the BMI is greater than or equal to the 95th percentile for age and sex with the presence of one or more comorbidities. For patients who are 7 years of age or older, weight loss through lifestyle modification is recommended if the BMI is between the 85th and 95th percentile for age and sex with the presence of one or more comorbidities or if the BMI is greater than or equal to the 95th percentile for age and sex regardless of the presence of comorbidities.” ... “The use of weight-management products in pediatric patients, as in adults, should be contemplated only after a sufficient

trial of lifestyle modification has *failed* and the risks of excess adiposity and the expected benefits of weight loss are believed to outweigh the known and unknown risks of treatment with a particular weight-management product. Such a population might include obese pediatric patients with weight-related comorbidities.”

Starting drugs that must be taken chronically is always an extremely difficult decision in children, particularly children younger than 7. However, it is discriminatory against obese children to preclude obesity drugs before age 7 and to require that children older than 7 fail behavioral therapy before drugs are started. For both situations, behavioral therapy before drugs should be the **preferred** action, but sole treatment with diet and exercise should not be mandatory if circumstances favor starting drugs. A child with severe hypertension or with a very elevated blood sugar would be extremely likely to be started on drugs along with behavioral therapy. Neither high blood pressure nor high blood sugar are themselves fatal. Similarly to obesity, both cause complications that may lead to major morbidity or mortality over time. The discrimination against obese children as compared to children with other chronic diseases cannot be justified. (Note that the rebuttal also applies to Page 11, lines 443-449).

Page 6, lines 216-226: “The number of subjects necessary to demonstrate the efficacy of a weight-management product will be smaller than the number needed to adequately assess safety. A reasonable estimation of the safety of a weight-management product upon which to base approval generally can be made when a total of approximately 3,000 subjects are randomized to active doses of the product and no fewer than 1,500 subjects are randomized to placebo for 1 year of treatment.” ...”For example, the above sample size will provide 80 percent power to rule out with 95 percent confidence an approximately 50 percent increase in the incidence of an adverse event that occurs at a rate of 3 percent in the placebo group (i.e., 4.5 percent versus 3 percent). This sample size also should allow for efficacy and safety analyses to be conducted within important subgroups such as sex, ethnicity, and baseline BMI.”

The necessity to prove a drug is safe is critical, especially drugs such as obesity drugs that may be taken by millions of people. However, the requirement that 3,000 people be tested is onerous when compared with drugs for other disorders. Testing 3000 people is exceedingly expensive and will limit the number of new applications that are submitted to the FDA for obesity drugs. The statistical example that is given makes sense on the surface and statistically, it is correct. However, consider the following quote from the literature regarding a drug for psoriasis, a disease that for the most part is not fatal:

Feldman SR. The design of clinical trials in psoriasis: lessons for clinical practice. *J Am Acad Dermatol.* 2003 Aug;49(2 Suppl):S62-5.

“However, we do not really know how safe Ipotet is with long-term use. Also, it could potentially cause fatal hepatotoxicity, aplastic anemia, or lymphoma in, say, 1 in 5,000 patients. While that would be a significant risk, we’d be unlikely to detect that low a risk in clinical trials that only involve hundreds, not thousands, of subjects. While clinical trials are an excellent way to assess efficacy and common adverse events, they are not very helpful for identifying rare events. Only after drugs are approved and many more patients are exposed to treatment can more complete safety information be obtained.”

Dr. Feldman states the case quite clearly. It is impossible to detect safety issues that occur rarely without doing thousands of subjects in Phase 3 trials. He notes that only after the drug is approved and used clinically can rare conditions be identified and complete safety information obtained. This puts a great burden on the FDA in the current era of litigious trial lawyers. Because of the great number of patients who will take obesity drugs, it is almost certain that someone will have an adverse reaction, even if the risk is 1:100,000 or greater. However, the FDA does a great disservice to the American people by requiring massive expenditures of money to protect individuals with very rare disorders while ignoring the plight of obese individuals who make up one third of the US population. More realistic numbers for Phase 3 trials, similar to those of other chronic diseases, are indicated. (Note that these comments also apply to Page 12, lines 489-494).

Page 6, lines 228-239:

3. Efficacy Endpoints

a. Primary efficacy endpoint

The efficacy of a weight-management product should be assessed by analyses of both mean and categorical changes in body weight.

- Mean: The difference in mean percent loss of baseline body weight in the active-product versus placebo-treated group.**

- Categorical: The proportion of subjects who lose at least 5 percent of baseline body weight in the active-product versus placebo-treated group.**

The disease of obesity is an excess of body fat. Body weight is an imperfect substitute for body fat. While weight is more easily obtained, the technology for assessment of body fat is available at modest cost, especially if bioelectrical impedance is used. While BIA is also imperfect and not a gold standard, it is suitable for groups of subjects. Air displacement or DEXA are more expensive and arguably represent gold standards, but if massive numbers of subjects are not required (see above), the costs are not prohibitive. The primary endpoint should be body fat, with visceral fat an allowed primary endpoint.

Page 9, lines 360-368: “We recommend that the efficacy and safety of fixed-dose combinations be compared with the individual product components of the combination and placebo in phase 2 trials of sufficient duration to capture the maximal or near-maximal weight-management effects of the products. We have not defined a minimum difference in weight loss between a fixed-dose combination and its individual component products that should be achieved for the combination to be considered more efficacious than either of its components when used alone. However, a fixed-dose combination that is associated with at least twice the weight loss observed with that of each of the individual components will be viewed more favorably than combinations that do not achieve this degree of relative weight loss.”

The implication that a combination should approach twice the weight loss of either component individually to be viewed favorably is too onerous at this point in the evolution of obesity drugs. While additive or synergistic weight losses are desirable, even phen-fen, which is the most effective combination described in the literature, only increased weight loss by about 50% over the individual components. The last sentence of the above statement could be profitably omitted in favor of a statement that some additive weight loss potential or a reduction in adverse events

from the combination must be seen for approval. Note that the side effects of the combination of phen-fen were less than the side effects from either agent alone (5).

Page 10, lines 413-418: “Serotonin syndrome, a potentially life-threatening condition characterized by akathisia, tremor, altered mental status, clonus, muscular hypertonicity, and hyperthermia (Boyer and Shannon 2005), has been observed in patients exposed to a single or two or more proserotonergic agents used in combination. Therefore, in general, weight-management products that act as agonists at serotonin receptors, particularly the 5-HT_{2A} subtype, should not be studied in combination with proserotonergic medications associated with weight gain.”

While the above statement is excellent guidance, it is stated too strongly and may inhibit beneficial combinations. Thousands of patients have been treated with two serotonergic agents, yet the occurrence of “serotonin syndrome” remains vanishingly small. The statement should be modified to recommend extreme caution when testing two serotonergic agents, not prohibit them altogether.

Page 12, lines 496-504: “B. Preventing Missing Data from Premature Subject Withdrawal Historically, there have been high rates of premature subject withdrawal in long-term trials of weight-management products. To allow for a true intent-to-treat (ITT) analysis, we encourage sponsors to obtain body weight measurements in all subjects who prematurely withdraw from late-stage preapproval trials near the calendar date at which they were scheduled to complete the trial (Simons-Morton and Obarzanek et al. 2006). For example, a subject who withdraws from a 12-month study after 6 months of treatment should have a body weight measurement at the time he or she would have completed 12 months of study participation.”

Intent to treat analyses are an important measure of drug effectiveness, but they contain problems. Many obese patients drop out of trials when it is apparent that the drug is not working, leaving only those for whom the drug is effective or “motivated” patients who are losing by behavioral efforts. Since obesity is a multifactorial disease, it is very unlikely that a single drug will treat all patients. If the standard analysis requires that everyone be included, without taking into account the response of those who complete the trial, drugs that may be useful for subgroups of obesity may be discarded. Completer analyses should also be examined by the FDA. A potential solution to the statistical problems that completers analyses raise is to re-randomize successful subjects after, for example, 6 months to determine if the drug is effective or if only “motivated” subjects remain. For virtually all the weight loss drugs studied to date, weight loss is maximal by 6 months, so the additional 6 months of a one year study only shows whether the drug is useful for maintenance. The FDA should consider requiring only 6 months of “efficacy” trials, then using extensive Phase 4 trials to ascertain safety after the drug is marketed.

Page 13, lines 553-563: “VIII. STAND-ALONE INDICATIONS FOR THE PREVENTION OR TREATMENT OF WEIGHT-RELATED COMORBIDITIES As mentioned earlier, weight loss through lifestyle modification is associated with improvements in blood pressure, lipid levels, glucose and insulin metabolism, and other physiometabolic endpoints. Improvements in these comorbidity are expected following

drug or biologic-induced weight loss, and from a regulatory perspective, they are considered part of the weight-management indication. Thus, for a weight-management product to obtain a stand-alone indication for the prevention or treatment of type 2 diabetes, dyslipidemia, hypertension, or any other weight-related comorbidity, it should be shown that the product effectively prevents or treats the comorbidity through a mechanism that is independent of weight loss.”

As a practicing physician, I do not care how improvements in health occurred, as long as they occurred. To require that a drug have an independent effect on a “comorbidity” of obesity cannot be justified if the reason to use drugs for a disease is to improve the disease. If a manufacturer wishes to gain approval for a weight loss drug as a treatment of a “comorbidity” of obesity, the drug should be held to the same standards as any other drugs for that “comorbidity.”

References:

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Richard L. Atkinson, M.D.
Clinical Professor of Pathology
Virginia Commonwealth University;
Director, Obetech Obesity Research Center
800 East Leigh St., Suite 50
Richmond, VA 23219
1-804-344-5360
Email: ratkinson2@vcu.edu