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April 23, 2004

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane Rm 1061  
Rockville MD 20852

Re: FDA Guidance for the Clinical Evaluation of Weight Control Drugs  
**Docket 2003D-0570**

Dear Sir/Madam:

Nastech Pharmaceutical Company, Inc. respectfully submits the following comments on the FDA Guidance for the Clinical Evaluation of Weight Control Drugs:

**Recommendation to change the focus of the Guidance to "Treatment of Obesity and Overweight":**

We agree with the comments submitted by the American Obesity Association that the emphasis of the document should be shifted from "weight control" to "...the treatment of obesity and overweight." "Weight control" connotes cosmetic improvement; in fact the current Guidance mentions "self esteem" in the first sentence and "relatively healthy subjects" in Section 4. Therefore, as written, the Guidance seems to suggest that obesity is simply a "lifestyle" issue, and is somehow less medically important. Changing the focus of the document to "...the treatment of obesity and overweight" emphasizes the severe medical consequences now recognized to be caused by these conditions (for example, the March 9, 2004 announcement of a study from the HHS' Centers for Disease Control and Prevention showing obesity and overweight may overtake smoking as the leading preventable cause of death<sup>1</sup>).

**On safety evaluation of pharmaceuticals intended for the treatment of obesity and overweight:**

We propose that the safety requirements in the Guidance be harmonized with the ICH E1A Guideline: Total exposure including short term exposure of 500-1500 patients; 300-600 patient exposure for 6 months; and an additional 100 patient exposure for 1 year. We respectfully suggest that this level of exposure is already conservative, as the E1A

<sup>1</sup> <http://www.hhs.gov/news/press/2004pres/20040309.html>

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Guideline is subtitled “For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions” – and few would now argue that obesity and overweight are “non-life-threatening conditions.” The Weight Control Guidance as currently written suggests a much larger safety database is required, with 1500 subjects completing 12 months and 200-500 completing 24 months. We suggest that such a large safety database should not be required for pharmaceuticals intended for an urgent and unmet medical need, unless signals of specific adverse events are identified during the development program.

We understand that following the unexpected cardiac valvular lesions encountered in patients taking the fen-phen combination, the Agency may have particular concern about drugs with a serotonin-associated mechanism of action. However, even for such drugs, data clearly indicate a signal for aortic regurgitation (adjusted odds ratio of 1.5 compared with controls and 4 cases of moderate-severe AR) in a randomly-selected sample of 313 patients on drug for 90-180 days and a statistically significant increase in prevalence of aortic regurgitation (adjusted odds ratio of 2.4 compared with controls ( $p=0.0002$ ), and 5 cases of moderate-severe AR) in a randomly-selected sample of 415 patients on drug for 181-360 days (see Jollis et al. Fenfluramine and Phentermine and Cardiovascular Findings: Effect of Treatment Duration on Prevalence of Valve Abnormalities. *Circulation* 2000; 101:2071-2077). Therefore even in the case of drug-induced cardiac valvulopathy, the ICH E1A guidance of 300-600 patients on study for 6 months would be sufficient to generate a signal of an adverse event.

We also respectfully suggest that the safety requirements be tailored to the particular active moiety. For example, an endogenous peptide might be held to a different standard than a new molecular entity or a class of drugs known to cause specific adverse events. In other words, “one size fits all” may not be appropriate regarding the required safety database.

### **On efficacy evaluation of pharmaceuticals intended for the treatment of obesity and overweight:**

#### **Section 5.1 Population**

The current Guidance requires that subjects with a body mass index (BMI) of 27 to 30 have at least one co-morbidity (hypertension, hyperlipidemia, glucose intolerance, cardiovascular disease, sleep apnea or other obesity-related condition). With the recognition that obesity is the second most common (and soon to be most common) cause of preventable death among Americans, and that many of the co-morbidities require years of obesity to appear and/or can be associated with irreversible conditions (osteoarthritis, for example) we respectfully request that the requirement of co-morbidities be removed. Furthermore, since the products are labeled for the treatment of patients who are overweight and/or obese and since overweight is defined by all academic associations as a BMI from 25.0 to 29.9, there is no medical basis for setting the lower limit of treatment at a BMI of 27.0. By so doing, treatment is denied to millions of Americans with BMI values between 25 and 27.

Section 5.2: We have a concern regarding the requirement for a drug-free 6 week (or longer if weight loss continues) “run in” period. We believe that having a “run in” period, during which time weight loss does not count toward the efficacy of a pharmaceutical for the treatment of obesity and overweight, is neither a realistic measure of the overall efficacy of the combination of diet, exercise, lifestyle intervention and pharmaceutical, nor is it a standard that other classes of drugs are held to. There is, for example, no such requirement for pre-treatment diet and exercise regimens for cholesterol reduction before initiating statin treatment nor is there a requirement for intensive psychotherapy for depression before beginning SSRI administration. A fixed duration “run in” period does not provide useful data to practicing physicians who are confronted with the initiation of therapy in a given patient. Moreover, strictly speaking, a pharmaceutical for the treatment of obesity and overweight is not labeled for “post run in period” efficacy; therefore, the study design should not be so constrained.

We thank the Agency for the opportunity to comment on this Guidance, and look forward to a continuing dialog on the issue of pharmaceutical development for the treatment of obesity and overweight.

Respectfully submitted,

A handwritten signature in black ink that reads "Gordon Brandt MD". The signature is written in a cursive, flowing style.

Gordon Brandt MD  
Executive Vice President, Clinical Development and Medical Affairs  
Nastech Pharmaceutical Company, Inc.