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

Re: Docket No. 2007D-0040, CDER 2006156. Draft Guidance for Industry on
Developing Products for Weight Management; Availability.

Dear Sirs:

This letter is submitted in response to the request for comments included in the above referenced draft release. My primary objection to the Draft Guidance is that it continues to regard obesity as a single disease, rather than a manifestation of a number of possible underlying conditions. This could have the very deleterious effect of preventing products which could benefit many overweight and obese individuals from ever coming to market. For example, it appears that impaired incretin response causes many individuals to be overweight. Possibly this is 10-30% of all overweight individuals.

If drugs were required to only address symptoms such as: “pain” or “fever” or “sore throat” rather than the underlying causes, probably no antibiotic could ever have been approved. Obesity is a symptom of other conditions, just as fever could be a symptom of numerous diseases.

In September 1996 the FDA issued *Guidance for the Clinical Evaluation of Weight-Control Drugs*. The recommendations it contained were reasonable given the state of knowledge about the causes of obesity at the time. The draft *GUIDANCE FOR INDUSTRY DEVELOPING PRODUCTS FOR WEIGHT MANAGEMENT* (Docket No. 2007D-0040, CDER 2006156. Draft) issued in February 2007 which, when finalized will replace the September 1996 guidance, falls short, in terms of what will best serve the overweight population in a number of important areas.

The 2007 draft guidance states “The pathogenesis obesity involves the interaction of genetic, environmental and behavioral factors.” In the last two decades tremendous advances have been made in identifying the specific genes and the hormones expressed by those genes which determine body weight. No acknowledgement is made of these advances in the 2007 draft guidance, nor is there any indication that the FDA has taken these advances into account in revising its draft guidance. To some extent, the 2007 draft guidance tends to perpetuate the pernicious misperception that obesity is more often a

matter of will power and that genetics are rarely the cause. The draft's statement: "Before therapeutic intervention, pediatric patients should receive a medical assessment to identify genetic (e.g., Prader-Willi syndrome) or endocrinologic (e.g., Cushing's syndrome) causes of their obesity", could be construed to insinuate that absent special circumstance, the causes of obesity are environmental or behavioral.

Previously, it did not matter whether anyone, including the medical profession, considered obesity to be the result of individual sloth and gluttony, or was aware that it was actually the consequence of one or more genetic variations. The only thing medical science had to offer the obese essentially was advice to eat less and/or exercise more. Now we are on the verge of developing products that may be able to address the specific genetic causes of many individuals obesity. However, an outmoded approach to the clinical evaluation of weight-control drugs might prevent many of these products from ever reaching those who could greatly benefit from them.

The biggest obstacle stems from the misperception that obesity is a "failure of willpower" rather than the consequence of one or more genetic variations. If obesity has just one cause, then the proper method to evaluate the efficacy of any treatment is the average weight loss for the population receiving the treatment. However, if the obese population consists of individuals with various different genetic causes of their obesity, a treatment that is very effective against one of the possible genetic causes, but not any of the others will not appear very powerful when averages of the entire population are measured.

The 2007 draft guidance neglects the situation where products for weight management may be very effective for certain subsets of the population. For example Byetta (Exenatide) has enabled many type 2 diabetics to lose significant weight, where all other attempts to lose weight had failed. Many overweight individuals are deficient in GLP-1, which Byetta addressed. The FDA guidance should explicitly allow clinical trials for weight management products to be conducted on identifiable subsets, such as obese individuals deficient in GLP-1.

There are already 58 genes known to be related to obesity, appetite, or the conversion of food into energy. As techniques such as resequencing allow more individual's genetic variations to be identified, drugs which address specific genetic variations which cause obesity will be more important. The 2007 guidance should provide for the possibility that a drug will be very effective for a small portion of the trial sample, and then the use of techniques such as resequencing can be used to determine if those individuals for whom the drug was very effective had an identifiable genetic trait. A drug that is very effective for an identifiable subset of the obese population would be a great advance, but not be approvable under the present FDA guidance.

The 2007 draft guidance regarding the metabolic syndrome is particularly unfortunate. Five hundred generations ago, prior to inception of agriculture, what we now call the metabolic syndrome was a naturally selected trait that enhanced survival prospects. Paleolithic hunter-gatherers, who were genetically disposed to eat voraciously whenever food was available, were more likely to survive those periods when food was scarce. That such individuals were more likely to develop diabetes and related cardiovascular diseases later in life, was of no consequence. Life expectancies were short

anyway, and it only mattered that they reached reproductive ages, for their genes to be passed on.

One way for natural selection to promote the propagation of those predisposed to metabolic syndrome was to have genetic strains evolve that under expressed hormones such as GLP-1 which naturally counteract the metabolic syndrome. The 2007 draft guidance would seem to preclude approval of products that prevented those with genetic tendencies to under express GLP-1 from becoming obese and diabetic. In the case of products that restore the incretin effect, the 2007 draft guidance would essentially require that those deficient in incretins would actually have to become diabetic before they could be treated the incretin deficiency. This is unfortunate since the causality relationship is first a reduced incretin effect, which causes obesity, then diabetes.

Thanks,

Lance Brofman, Ph.D.