

the label statement be surrounded by a box to ensure proper prominence. This requirement was established under section 409(c)(3)(B) of the act (21 U.S.C. 348(c)(3)(B)), which prohibits approval of a food additive if the proposed use would result in misbranding of food (61 FR 3118 at 3160). The legal authority and scientific basis that underlaid the requirement for this label statement are reviewed in detail in the next section of this document.

A. Basis for Requiring the Label Statement—1996 Decision

1. Legal Authority for the 1996 Label Statement

Under section 403(a)(1) of the act, a food is deemed to be misbranded if its labeling is false or misleading in any particular. Section 201(n) of the act amplifies what is meant by “misleading.” Section 201(n) of the act states that in determining whether labeling is misleading, the agency shall take into account not only representations made or suggested about the product, but also the extent to which the labeling fails to reveal facts material in light of such representations or material with respect to consequences which may result from use under the conditions of use prescribed in the labeling or under such conditions of use as are customary or usual (*see* 21 CFR 1.21). Thus, the omission of such material fact from the label or labeling of a food causes the product to be misbranded within the meaning of sections 201(n) and 403(a)(1) of the act.

2. GI Issues Associated With Olestra

As noted, olestra is not digested or absorbed, and it passes through the GI tract intact. The petitioner conducted a number of studies to address issues of potential concern with respect to the effect of olestra as it passes through the GI tract (61 FR 3118 at 3152–3159). For example, during studies designed primarily to assess potential effects of olestra on absorption of fat-soluble dietary components present in the gut at the same time, the petitioner also assessed the potential for olestra to elicit GI symptoms such as cramping, bloating, loose stools, and diarrhea-like symptoms by collecting reports from participants in the studies. In two human nutritional studies² (88 and 100 subjects respectively), the entire diet of

the subjects was controlled during the length of an 8-week study period. The studies were parallel, double-blind, and placebo-controlled, with olestra dosages of 0 (placebo), 8, 20, and 32 grams per day (g/d).³ The diets were formulated so that the total digestible fat (triglyceride) content was the same for all treatment groups. Triglyceride was added into the diets in the form of butter, margarine, or vegetable oil to compensate for the amount of fat replaced by olestra in the olestra-containing foods. Olestra was added to various food items by substituting olestra for triglyceride in recipes or in cooking oils. Therefore, the total amount of lipid-like material (digestible triglyceride plus olestra) increased with increasing olestra dose. Each meal contained olestra or the corresponding placebo (triglyceride). Subjects were questioned daily about changes in their health, including GI symptoms. To facilitate collection of GI symptom data, a questionnaire provided a list of common GI symptoms along with general definitions of each and was completed by each subject to capture data about the type, severity, and duration of symptoms experienced. As noted in the 1996 final rule (61 FR 3118 at 3152), the petitioner stated that the two 8-week studies were not intended to examine GI symptoms under real-life consumption conditions where snacks are not consumed every day with every meal and where people may moderate intake if they experience GI symptoms.

FDA's analysis of the data from the two 8-week studies (61 FR 3118 at 3152–3154) showed that there was a dose-response effect for olestra with respect to two endpoints, reported diarrhea/loose stools and fecal urgency. Reporting of diarrhea was based on subjects' perception of diarrhea. FDA found no evidence that study subjects experiencing olestra-related symptoms described as “diarrhea” also experienced significant fluid or significant electrolyte loss. The effect of olestra on stool consistency is similar to that produced by liquid petrolatum, which softens fecal contents. FDA recognized that the effect observed was not diarrhea in the clinical sense, but used that term in the 1996 final rule, and is using that term here, because it is the term used in the study report. FDA also found that these GI symptoms cease soon after olestra is no longer consumed.

The petitioner also conducted a study, the Fecal Parameters Study, designed to

examine fecal composition of stools from subjects who reported diarrhea when consuming olestra (61 FR 3118 at 3155). The study consisted of two phases, a screening phase and a study phase. The screening phase was conducted to identify subjects who reported GI symptoms from olestra consumption. During the study phase, the identified subjects ate different amounts of olestra, and GI symptoms were recorded and fecal measurements were made. From the initial screening phase, eighteen subjects reported an increase in the frequency, severity, or duration of GI symptoms during the olestra period, relative to the placebo period. These 18 subjects were selected to take part in the study phase, and 15 completed the study. The study phase was a crossover, placebo-controlled, single-blind (subject) design with three treatment groups, 0, 10, and 20 g/d olestra. Each subject received each treatment for 7 days. The treatment periods were separated by 7-day washout periods. Subjects ate all treatment meals under supervision at the clinical site, and ate their habitual diets at home during the washout periods. Study subjects recorded GI symptoms daily. Total fecal collections were made the last 3 days of each treatment period. Daily stool collections were measured for wet weight, volume, and density, and the pooled three day samples were analyzed for water concentration, dry weight, olestra content, sodium (Na), potassium (K), chloride (Cl), total and individual bile salts, free fatty acids, triglycerides, and total lipids.

Measurements of the concentration of stool water and electrolytes (Na, K, and Cl) suggested that these parameters did not differ in the stools of persons reporting “diarrhea” during the olestra 20 g/d period from those in the nondiarrheal stools (during the placebo period) of the same persons. However, it was not possible to analyze stool electrolyte values by individual stools or by individual days because the stools were pooled from the 3-day collection period, as is normally done when measuring fecal parameters. FDA noted that there appeared to be an increased weight of stools in those subjects reporting “diarrhea” when eating 20 g/d olestra that is not completely accounted for by the presence of olestra in the stools. FDA concluded that the results of this study indicated that there is no difference in stool composition (*e.g.*, water and electrolyte content) when subjects consumed olestra versus placebo (61 FR 3118 at 3155).

FDA found that the number of subjects in the Fecal Parameters Study

² In evaluating olestra's nutritional effects, the petitioner conducted two 8-week clinical studies, the 8-week clinical dose response study (8-week DR), and the 8-week clinical vitamin restoration study (8-week VR) (61 FR 3118 at 3133–3134). In this document, when discussing the combined results of these studies, they will be called the two 8-week studies.

³ By comparison, FDA concluded that the estimated lifetime-averaged daily intake at the 90th percentile of olestra consumption would be 7.0 grams per person per day (g/p/d) (61 FR 3118 at 3124).