

does not cause diarrhea, but simply adds bulk and softening to the stool.

FDA reviewed the data from this study and agrees with the petitioner's analysis, although some of the agency's analytical strategies differed from those of the sponsor (Ref. 17). FDA concludes that both comparisons of the mean after treatment and of changes from baseline showed dose responsive increases in stool characteristics (total output, water output, consistency, frequency and increases in water content) that were not clinically significant (Ref. 18).

Using a 7-point scale to rate consistency of bowel movements (1 = watery, diarrhea; 4 = normal; 7 = hard, constipation), subjective ratings of stool consistency showed that subjects who ate 40 g/d olestra perceived their stools to be looser (mean rating 2.4) compared to those who ate 20 g/d olestra (mean rating 3.1). By comparison, placebo subjects had a mean score of 3.9 whereas those subjects in the 40 g/d sorbitol group had a mean score of 1.5 (mean scores determined for days subjects consumed snacks according to their randomly assigned treatment group). When stool consistency was measured by peak force value for extrusion, both olestra groups had a lower mean stool consistency than placebo and the 40 g/d olestra group was lower than the 20 g/d group. These dose responsive findings seen among subjects eating olestra resulted from gradual stool softening effects observed after several consecutive days of olestra consumption. Although subjects characterized these viscosity changes as "diarrhea," the changes were not associated with an increase in stool water.

FDA examined the percentage of symptom days for cramping and found that although the 40 g/d olestra group reported an increased incidence of abdominal cramping compared to those in the 20 g/d olestra group (35.8 percent compared to 9.8 percent), this difference did not rise to statistical significance. The percentage of subjects reporting abdominal cramping in the 20 g/d olestra group appeared to decrease when compared to baseline or placebo (9.8 percent compared to 20.5 percent or 18.3 percent). The 40 g/d sorbitol group had the highest percentage (69.8 percent) of reports of cramping. Subjects rated symptom severity on a scale of 0 to 5, with 0 representing none and 5 extreme. The severity of cramps reported by subjects in the olestra 40 g/d group was less severe than that reported by subjects in the 40 g/d sorbitol group (0.72 compared to 2.3). No significant olestra effects were found for GI symptom severity, although one

individual in the 20 g/d olestra group reported severe urgency at a rating higher than any other report in any of the other groups (Refs. 10 and 18).

5. Comments Regarding the GI Studies

FDA received comments about the new GI studies. FDA considered these comments and responds in the following paragraphs. Comments regarding the label statement for GI effects will be discussed in section V of this document.

(Comment 5) A comment from CSPI to the current petition criticized the Rechallenge Study. The comment stated that the study subjects were not screened for sensitivity to olestra, as was done in the preapproval Fecal Parameters Study. The comment also asserted that the Rechallenge Study contained a strong likelihood of bias because only 10 percent of those contacted agreed to participate in the rechallenge and those that did participate consumed olestra on only 2 days, at least 1 week apart, which reduced the sensitivity of the study. CSPI asserted that the Rechallenge Study also assumed that those sensitive to olestra would respond to it 100 percent of the time. The comment contended that those experiencing adverse reactions may only do so under certain circumstances, not 100 percent of the time.

FDA does not agree that the selection of study subjects biased the Rechallenge Study nor does CSPI provide such evidence. FDA has determined that the subjects who participated in the Rechallenge Study were adequately representative of those persons who contacted the postmarketing surveillance system in terms of severity of initial symptoms and amount of olestra reportedly consumed prior to the initial symptom episode (Ref. 11). Further, CSPI provided no basis for its assertion that additional subject screening is necessary to accomplish the objectives of the Rechallenge Study.

CSPI states that the sensitivity of the Rechallenge Study was reduced because participants consumed olestra on only 2 days, at least 1 week apart. The conditions of the study were designed to be similar to the conditions under which the subjects originally reported effects that they attributed to consuming an olestra-containing snack. FDA found that for nearly three-quarters of the subjects, the amount of olestra consumed in the study was comparable to, or greater than, the amount associated with their initial symptom episode (Ref. 11). In addition, more than three-quarters of the subjects reported that their initial symptom episode

occurred after a single eating occasion. Therefore, subjects were challenged with 2 oz of olestra chips on two occasions separated by a week, providing a dose and number of exposures comparable to, or greater than, those associated with many of the subjects' initial symptom episodes.

CSPI's comment did not reference where FDA or the petitioner assumed that those sensitive to olestra would respond to it 100 percent of the time, nor is FDA aware of anyone who has put forth such a position. Indeed, FDA agrees that even if an individual experiences a reaction to olestra, that individual may not experience such reaction after every exposure. The Rechallenge Study shows that subjects exposed to olestra containing-chips were no more likely to report GI symptoms than when exposed to an equal amount of triglyceride chips. Thus, the study subjects' reactions to olestra containing-chips are not so frequent that they can be distinguished from their reactions to regular chips under the conditions of the test.

(Comment 6) A comment from CSPI to the current petition criticized the Acute Consumption Study. CSPI's comment relies on its published letter²⁷ commenting on a published study (Ref. 12.) that reports data from the Acute Consumption Study. CSPI stated that the study may have failed to detect the true incidence of GI effects due to a lack of statistical power or inadequate controls. For example, with the incidence of "any GI event" of about 15 percent, 550 subjects in each group would have provided only about a 50 percent probability of detecting a 5 percent actual increase in the treatment group. Along the same lines, diarrhea and loose stools were increased less than 1 percent in the olestra group compared to baseline levels of 2.6 percent and 1.1 percent, respectively. The comment asserted that maintaining 80 percent power to detect a 1 percent increase over a 2 percent baseline requires about 4,000 subjects per group. The comment also contends that the darkened movie theater may potentially cause exposure misclassification (some "olestra eaters" may have eaten few or none of their chips; some "non-olestra eaters" may have eaten friends' olestra chips). The comment also stated that it took up to 10 days after consumption to assess symptoms. CSPI also pointed out that non-olestra eaters consumed one-third more chips than the olestra eaters.

The criticism by CSPI of the Acute Consumption Study does not negate the

²⁷ CSPI's published letter was included in the comment as an attachment (Ref. 19).