

movements over the course of the 42 day study compared to females in the triglyceride group. For males in the olestra group, the analysis showed an increase of 0.24 more symptom days for more frequent bowel movements compared to males in the triglyceride group.

FDA then examined the relationship between the amount of product consumed and symptoms reported for all study subjects (males and females), and found there were associations between olestra consumption and reports of "any GI symptom" ( $p=0.03$ ), loose stools ( $p=0.006$ ), and more frequent bowel movements ( $p=0.002$ ). No such associations were observed between the consumption of the control chips (triglyceride chips labeled as olestra) and any measured symptom. When analyzed separately by gender, both sexes showed trends for an association between the consumption of olestra and loose stools (males  $p=0.001$ , females  $p=0.018$ ), and more frequent bowel movements (males  $p=0.001$ , females  $p=0.042$ ), but only males also showed a trend for an association between the consumption of olestra and "any GI symptom" ( $p=0.001$ ).

FDA examined the relationship between the consumption of olestra-containing foods and reports of abdominal cramping. FDA found no difference in the frequency of reported abdominal cramping between the olestra group and the triglyceride group. FDA analyzed the olestra and triglyceride groups separately by gender for reports of abdominal cramping and found no difference between males or females in the olestra group as compared to the triglyceride group. FDA agrees with the petitioner that there was no observed difference in the incidence or association of reported abdominal cramps between the olestra group and the triglyceride group (Ref. 10).

#### 4. Stool Composition Study

The Stool Composition Study was sponsored<sup>26</sup> by the petitioner as a followup to the preapproval Fecal Parameters Study (discussed previously in section II.A.2 of this document). The study was designed to establish whether consumption of olestra-containing foods is associated with changes in clinical measures of diarrhea (water and electrolyte loss), effects which may be harmful, or stool consistency alone, which may result from adding bulk to the stool and which is not harmful. In addition, the study was designed to determine the relationship between

objective measures of clinical diarrhea (e.g., stool water output and bowel movement (BM) frequency) and subjective reports of "diarrhea" from study subjects. The effects of olestra were compared to a placebo, triglyceride chips, and to sorbitol, an osmotically active sugar alcohol that was chosen as a positive control to ensure that the study methodology was adequately sensitive to detect increases in stool water output.

The study was a single-site, randomized, double-blind, placebo-controlled parallel clinical trial. Sixty-six subjects, ages 18 to 74, were housed on a metabolic ward for 12 days and consumed meals ad libitum. The meals conformed to the American Heart Association Step I diet guidelines (no more than 30 percent of calories from fat). Beverages were available ad libitum. All study subjects had to consume 5 oz of potato chips eaten as two afternoon snacks. A serving of potato chips was either olestra (test) or triglyceride (placebo). All subjects were also required to consume 1.5 oz of candy made either with sorbitol (test) or sucrose (placebo) as a morning snack. The first two days (study days 1 and 2) were a lead-in period during which subjects were acclimated to the living conditions and the diet, and consumed placebo snacks (triglyceride potato chips and sucrose candies). Stool samples were not collected during the lead-in period. The next 4 days (study days 3 to 6) comprised the baseline period, in which subjects continued to consume placebo snacks, and all stool samples, BM ratings, and GI symptoms were collected. For the final 6 days (study days 7 to 12), subjects consumed snacks according to their randomly assigned treatment group, and all stool samples, bowel movement ratings, and GI symptom reports were collected. There were two olestra test groups (20 g and 40 g olestra) and two control groups (positive control of 40 g sorbitol and placebo). The placebo group consumed two servings of placebo (triglyceride) potato chips and placebo (sucrose) candy. The positive control group consumed two servings of placebo potato chips and test candy (40 g sorbitol). The 20 g olestra test group consumed one serving of test potato chips (olestra), one serving of placebo potato chips, and placebo candy. The 40 g olestra group consumed two servings of test chips and placebo candy.

The petitioner noted that in the study the doses of olestra were threefold to sixfold more than the estimated daily intake, and 10 to 20 times more than the observed intake at the 90th percentile level in the Active Surveillance Study

(see section III.D.1 of this document). The high dose, 40 g/d, was higher than the highest dose used in the preapproval nutrition studies (32 g/d) described previously in section II.A.3 of this document, in which the high dose group experienced an increase in GI symptoms, specifically in reported diarrhea/loose stools. In that preapproval study, FDA concluded that the reported diarrhea was not diarrhea in the medical sense because there was no evidence of subjects experiencing significant fluid or electrolyte loss (hemoconcentration, electrolyte imbalance; 61 FR 3118 at 3152-3154).

The petitioner concluded that with regard to the critical parameters that are medically relevant in defining diarrhea, the objective measures showed that olestra did not meaningfully change either the total stool output or stool water output, while sorbitol produced large effects on both parameters. Compared to baseline, mean stool water output increased 9 g/d and 37 g/d for the 20 and the 40 g/d olestra groups respectively, and 325 g/d for the 40 g/d sorbitol group. Stool water output decreased 28 g/d for placebo. The measured mean stool water content for the sorbitol group was nearly 10 times greater than the group consuming the highest level of olestra and the number of watery BMs was 140 in the sorbitol group, one in the 40 g/d olestra group, none in the 20 g/d, and one in placebo. While sorbitol significantly increased the severity of abdominal cramping compared to placebo, olestra did not. The petitioner found that olestra consumption did not result in any clinically meaningful increases in objective measures of diarrhea, namely, total stool output, bowel movement frequency, and stool water and electrolyte output. The mean number of BMs for the olestra 40 g/d group was increased compared to placebo but was not increased compared to the olestra 20 g/d group. Subject reports of "watery, difficult to control diarrhea" did not necessarily correlate with measured viscosity of the stool. Olestra did increase stool weight in proportion to the amount eaten, and daily consumption of olestra gradually softened stool in a dose-responsive manner. The sponsor found that there was increased reporting of "diarrhea" in the olestra treatment groups during the treatment phase without an increase in total water output outside the normal range, i.e., the range observed during the baseline period and in the placebo group.

P&G concluded, based upon the study results, that the consumption of olestra

<sup>26</sup> The GI consultant to the study was Dr. R. Gianella, University of Cincinnati.