

subjects in the study experienced high rates of water loss through their stool. The comment also stated that the definition of diarrhea used in the Stool Composition Study was too narrow and is not consistent with the definition used by the Centers for Disease Control and Prevention (CDC; three or more loose stools in a 24 hour period). The comment asserted that self-reporting is usually considered sufficient to conclude that people experience diarrhea regardless of demonstrated loss of electrolytes.

In contrast to the Acute Consumption Study, the Home Consumption Study, and the Rechallenge Study, the Stool Composition Study was designed to extend the understanding of olestra's effect on stool characteristics that would potentially represent a safety concern. For this reason, the Stool Composition Study was conducted under conditions most likely to elicit GI effects. The highest dose of olestra provided in the Stool Composition Study (40 g/d) was greater than the 32 g/d used in the preapproval 8-week studies which was shown to cause an increase in GI symptoms (specifically in reported diarrhea/loose stools) and was twice as high as the highest dose given in the preapproval Fecal Parameters Study (20 g/d). Additionally, subjects' stool samples were collected for all 6 days of the treatment period in the Stool Composition Study, compared to only three days of the 7-day treatment periods in the Fecal Parameters Study. The Stool Composition Study does not negate the preapproval studies, but the results of the preapproval studies must be considered in light of those from the Stool Composition Study.

The results of the Stool Composition Study show that olestra consumption does not result in any clinically meaningful increases in the objective measures of diarrhea. Importantly, the Stool Composition Study assessed the effects of olestra consumption using objective parameters such as total stool output, bowel movement frequency,³¹ and stool water and electrolyte output rather than a subject's subjective assessment of whether he or she experienced diarrhea. The use of objective measures of diarrhea is necessary to assess whether the "diarrhea" experienced by study subjects represents a safety concern.

FDA was concerned with the potential for olestra to cause diarrhea because diarrhea of medical significance is associated with excessive water loss and electrolyte loss, which may raise safety concerns. The Fecal Parameters Study memorandum cited by the comment states that the stool water concentration of subjects who reported having diarrhea during the olestra 20 g/d period did not differ from that of their nondiarrheal stools during the placebo period. The memorandum also states that although the percent of water in the stools may not have differed, it is possible that absolute water loss was greater in subjects reporting olestra-associated diarrhea because of the greater mass (weight) of stool passed. FDA concluded in the 1996 final rule that the loose stools experienced in the preapproval clinical studies were not diarrhea in the medical sense because they were not associated with loss of water or electrolytes (61 FR 3118 at 3159). The agency also stated that even those subjects in the 8-week studies who experienced loose stools or diarrhea continuously for several weeks during olestra consumption did not show any evidence of fluid loss such as hemoconcentration or electrolyte imbalance. Thus, the agency determined that olestra-related GI effects were not adverse health effects (61 FR 3159). The results of the Stool Composition Study confirm the agency's 1996 decision that the GI effects resulting from olestra consumption do not represent adverse health effects, regardless of the terminology (diarrhea or otherwise) used to describe these effects.

D. A Study Regarding Nutritional Effects—Active Surveillance

As discussed previously in section II of this document, olestra is neither digested nor absorbed, and as such, passes intact through the digestive tract where it can interact with fat-soluble dietary components present in the gut at the same time. Fat-soluble nutrients and components tend to partition or dissolve into the olestra, thereby reducing the absorption efficiency of these substances (61 FR 3118 at 3144–3149). Olestra does not interfere with the absorption of macro-nutrients (protein, carbohydrates, and fats) or water-soluble nutrients (61 FR 3118 at 3149–3152). The clinical studies conducted in support of the 1996 final rule examining the effect of olestra on fat-soluble components of the diet were performed under conditions that maximized the interaction of olestra with these dietary components, *i.e.*, olestra was incorporated into foods eaten at every meal. These studies were not designed

to examine effects from the usual or customary consumption of savory snacks made with olestra (see section II.A.3 of this document).

To compensate for the effect of olestra on the absorption of the fat-soluble vitamins A, D, E, and K, FDA required that these vitamins be added to olestra-containing foods. The level of addition was chosen to ensure that there would be neither a reduction in the absorption of fat-soluble vitamins from the diet, nor an increase in vitamin levels due to the presence of the added vitamins in the olestra-containing foods (see section II.A.3 of this document). Although FDA noted that olestra interferes with the absorption of carotenoids, FDA found no scientific basis for requiring the addition of any carotenoid to olestra-containing foods (61 FR 3118 at 3147–3149).

As outlined by the petitioner in its January 24, 1996, letter to the agency, P&G established a program of active surveillance. A report of this surveillance with results and analysis from the first year at the sentinel site was submitted to the agency on April 15, 1998. Additionally, the agency has continued to review and evaluate new data and information that bear on the safe use of olestra, such as new data and information on the health significance of carotenoids.

1. Active Surveillance Study by P&G

The petitioner provided funding to investigators at the Fred Hutchinson Cancer Research Center in Seattle, WA, to design and implement a multi-year, Active Surveillance Study to monitor patterns of use of olestra-containing savory snack products and to collect blood samples to measure nutrient status (Ref. 23). The study had three specific goals: (1) To monitor adoption and patterns of use of olestra-containing savory snack products in representative samples of the U.S. population; (2) to assess the association between the introduction of olestra-containing savory snacks and serum concentrations of carotenoids and fat-soluble vitamins in representative cross-sectional samples of the U.S. population; and (3) to assess the long-term association between consumption of olestra-containing savory snacks and serum concentrations of carotenoids and fat-soluble vitamins among a cohort of olestra consumers.

The study has three components corresponding to the three specific aims. The first component, called the population cross-section, was a telephone survey used to monitor the prevalence and patterns of olestra-containing savory snack consumption,

³¹ FDA notes that the mean bowel movement frequencies in the olestra-consuming groups were less than three bowel movements per day. The mean bowel movement frequencies were 1.6 ± 0.2 BM/d (mean \pm standard error) in the 20 g/d olestra group and 2.0 ± 0.2 BM/d (mean \pm standard error) in the 40 g/d olestra group (Ref. 18).