Food

Agency Response Letter GRAS Notice No. GRN 000286

CFSAN/Office of Food Additive Safety

September 4, 2009

Constance Francis Ph.D., R.D.
GTC Nutrition
523 Park Point Drive, Suite 300
Golden, CO 80401

Re: GRAS Notice No. GRN 000286

Dear Dr. Francis:

The Food and Drug Administration (FDA) is responding to the notice, dated March 6, 2009, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; Apri 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on March 11, 2009, filed it on March 12, 2009, and designated it as GRAS Notice No. GRN 000286.

The subject of the notice is galacto-oligosacharides (GOS). The notice informs FDA of the view of GTC Nutrition (GTC) that GOS is GRAS, through scientific procedures, for use as an ingredient in term infant formula and follow-on formula at a level of 7.2 grams GOS per liter (g/L).

As part of its notice, GTC includes the report of a panel of individuals (GTC's GRAS panel) who evaluated the data and information that are the basis for GTC's GRAS determination. GTC considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. GTC's GRAS panel evaluated the method of manufacture, product specifications, analytical data, consumption estimates, published and unpublished literature, and its intended use. Based on this review, GTC's GRAS panel concluded that GOS, that meets food grade specifications and is manufactured in accordance with good manufacturing practices, is GRAS under the conditions of its intended use.

GTC provides information about the identity and composition of GOS. GOS is a spray-dried white powder produced from food-grade lactose via a transgalactosylation enzyme reaction. The final product contains at least 90 percent GOS (dry weight basis), with the remaining material characterized primarily as lactose, water, and trace amounts of dextrose and galactose. The GOS component is a mixture of β-linked GOS in various β(1-3), β(1-4), β(1-6) configurations, having a degree of oligomerization ranging between 3 and 5.

GTC describes the method of manufacture for GOS. GOS is produced through enzymatic conversion of lactose with β-galactosidase from *Bacillus circulans*.[1] GTC notes that all materials and processing aids used in the manufacture of GOS are food-grade. Lactose is dissolved in heated water and the pH is adjusted to mildly acidic conditions with sodium hydroxide or hydrochloric acid as required. β-Galactosidase is added to the solution and saccharification occurs until the desired oligosaccharide content is equal to 50 percent (weight to volume). The enzyme is then inactivated by heating and removed via filtration. The filtrate is decolorized and impurities are removed via an ionic exchange process. The resulting filtrate is then concentrated and purified by chromatographic separation. The oligosaccharide containing fraction (greater than 90 percent GOS) is further refined through additional ion exchange, activated carbon, and evaporative concentration treatments to produce a syrup, which is then spray dried, resulting in a white powder.

GTC includes specifications for GOS. Specifications include GOS (90 to 92 percent on dry weight basis (DB)), lactose (7 to 10 percent DB), galactose (0 to 0.5 percent DB), and dextrose (0 to 1 percent DB). GTC also specifies limits for moisture (less than 10 percent), lead (less than 0.01 milligrams per kilogram (mg/kg)), arsenic (less than 1 mg/kg), and microbiological contaminants.

GTC estimates the daily intake of GOS. Based on the intended use levels and data available from the 2003–2004 National Health and Nutrition Examination Survey, GTC estimates the mean intake in infants ages 0 to 6 months as 5.9 grams per person per day (g/p/d) and the 90th percentile as 8.5 g/p/d; for infants ages 7 to 12 months, the mean intake as 5.2 g/p/d and the 90th percentile as 7.9 g/p/d, and for toddlers ages 1 to 2 years, the mean intake as 2.8 g/p/d and the 90th percentile as 6.6 g/p/d.

GTC discusses absorption, distribution, metabolism, and excretion (ADME) of GOS. Published information regarding the indigestibility of GOS by humans has shown that GOS is not hydrolyzed by human salivar amylase or pancreatic juices. GOS passes undigested and unabsorbed to the colon where it is metabolized by colonic microflora to normal metabolites of fermentation (short-chain fatty acids, carbon dioxide, methane and hydrogen gases). GTC states that any unfermented dietary GOS will be excreted in the feces. GTC notes that GOS has been shown to be non-genotoxic in published *in vitro* and *in vivo* genetic toxicity studies. In addition, GTC discusses published animal studies, including a 90 day rodent study, and published human studies.

To further support its view that GOS is safe for the intended use, GTC discusses published human studies in infants that show that 7.2 g/L GOS in combination with 0.8g/L fructooligosaccharide (FOS) have no adverse effects. The notifier includes an in-depth discussion of their rationale for including the GOS:FOS combination studies in their safety determination for the intended use of GOS. As part of its rationale, GTC discuses the structural similarity of GOS and FOS, the equivalence of their ADME profiles, as well as information regarding the interaction with the microflora of the large intestine. Based on the totality of the scientific evidence, GTC considers GOS safe for its intended use at a level of 7.2 g/L.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic Act (FFDCA), a food is misbranded if its labeling is false or misleading in any particular. Section 403(r) of the FFDCA lays out the statutory framework for the use of labeling claims that characterize the level of a nutrient in a food or that characterize the relationship of a nutrient to a disease or health-related condition. In describing the intended use of GOS and in describing the information that GTC relies on to conclude that GOS is GRAS under the conditions of its intended use, GTC raises a potential issue under these labeling provisions of the FFDCA. If products that contain GOS bear any claims on the label or in labeling, such claims are the purview of the Office of Nutrition, Labeling, and Dietary Supplements (ONLDS) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety neither consulted with ONLDS on this labeling issue nor evaluated the information in your notice to determine whether it would support any claims made about GOS on the label or in labeling.

Intended use in infant formula

Under section 412 of the FFDCA, a manufacturer of a new infant formula must make a submission to FDA, providing required assurances about the formula, at least 90 days before the formula is marketed. GTC should be aware that FDA's response to GTC's GRAS notice does not alleviate the responsibility of any infant formula manufacturer who intends to market an infant formula that contains GOS to make the submission required by section 412.

Section 301(ll) of the FFDCA

The Food and Drug Administration Amendments Act of 2007, which was signed into law on September 27, 2007, amends the FFDCA to, among other things, add section 301(ll). Section 301(ll) of the FFDCA prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FFDCA, a biological product licensed under section 351 of the Public Health Service Act, or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)-(4 applies. In its review of GTC's notice that GOS is GRAS for use in various food products, FDA did not consider whether section 301(ll) or any of its exemptions apply to foods containing GOS. Accordingly, this response should not be construed to be a statement that foods that contain GOS, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information provided by GTC , as well as other information available to FDA, the agency has no questions at this time regarding GTC's conclusion that GOS is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of GOS. As always, it is the continuing responsibility of GTC to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter responding to GRN 000286, as well as a copy of the information in this notice that conforms to the information in the GRAS exemption claim (proposed 21 CFR 170.36(c)(1)), is available for public review and copying via the FDA home page at http://www.fda.gov. To view or obtain an electronic copy of the text of the letter, follow the hyperlinks from the "Food" topic to the "Food Ingredients and Packaging" section to the "Generally Recognized as Safe (GRAS)" page where the GRAS Inventory is listed.

Sincerely,

Mitchell A. Cheeseman, Ph.D.
Acting Director
Office of Food Additive Safety
Center for Food Safety and Applied Nutrition

[1] β-Galactosidase is the enzyme used in the production of GOS. The bacterial species used to make the β-galactosidase preparation is *Bacillus circulans* strain LOB 377. GTC states that this microorganism is non-toxigenic and non-pathogenic.

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