Claire Kruger, Ph.D., D.A.B.T.
ChromaDex Spherix Consulting, Inc.
11821 Parklawn Drive
Suite 310
Rockville, MD 20852

Re: GRAS Notice No. GRN 000721

Dear Dr. Kruger:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000721. We received the notice that you submitted on behalf of Vitalus Nutrition, Inc. (Vitalus) on August 8, 2017 and filed it on August 21, 2017. Vitalus submitted amendments to the notice on August 21, 2017 and October 31, 2017 that clarified the intended food categories and contained additional safety information, respectively.

The subject of the notice is galacto-oligosaccharides (GOS) for use as an ingredient in milk-based, non-exempt infant formula for term infants at a level up to 7.2 g GOS/L of reconstituted or ready-to-feed formula; and in milk and milk products, soups, bakery products, cereals, fruit and vegetable juices, jellies and jams, and nonalcoholic beverages at a maximum level up to 33.4%.[1] The notice informs us of Vitalus' view that these uses of GOS are GRAS through scientific procedures.

Vitalus describes the identity and composition of GOS. GOS is a clear to slight-yellow syrup that contains ≥ 62% galacto-oligosaccharides on a dry matter (DM) basis; the remainder is primarily lactose, glucose, and galactose. Vitalus states that GOS is a mixture of β-linked di- to octasaccharides with one to seven galactose units linked to glucose at the reducing end, with the trisaccharide as the predominant constituent.

Vitalus describes the method of manufacture for GOS from lactose derived from cow's milk whey,[2] which is dissolved in water, heated with agitation, and pH adjusted. A β-galactosidase preparation purified from *Aspergillus oryzae*[3] is added to the solution to catalyze the hydrolysis of lactose and the transgalactosylation reaction to form GOS. A β-galactosidase preparation from *Kluyveromyces lactis*[3] is then added to hydrolyze the remaining lactose. Both enzymes are heat-inactivated; the resulting mixture is filtered, subjected to an adsorption resin, and concentrated by evaporation. The resulting GOS syrup is heated and then passed through a screen to produce a homogenous finished product. Vitalus states that GOS is manufactured using food-grade materials.

[1] Vitalus states that GOS is not intended for use in products under the U.S. Department of Agriculture's jurisdiction.
[2] Vitalus states that an analysis of GOS did not detect casein.
[3] Vitalus states that the *A. oryzae* and *K. lactis* production strains are non-pathogenic and non-toxigenic.

Vitalus provides specifications for GOS, which include minimum levels of galacto-oligosaccharides (≥ 62% DM) and galactose (≥ 1% DM), a range for total DM (74% to 76%), and limits on lactose (≤ 16% DM), glucose (≤ 22% DM), protein (≤ 0.2% DM), lead (≤ 0.2 mg/kg), arsenic (≤ 0.4 mg/kg), cadmium (≤ 0.06 mg/kg), and mercury (≤ 0.005 mg/kg). Specifications also include limits on microbial contaminants, including Salmonella (not detected in a 25 g sample). Vitalus provides analyses quarterly confirming the absence of *Cronobacter sakazakii* and *Bacillus cereus* in GOS. Vitalus provides the results of five non-consecutive batch analyses to demonstrate that GOS can be manufactured to meet specifications.

Vitalus estimates the dietary exposure to GOS. Vitalus states that the intended uses of GOS are consistent with those described in GRN 000334;[4] therefore, dietary exposures to GOS are not expected to change. In GRN 000334, the estimated dietary exposures to GOS are based on food consumption data from the 2003-2004 National Health and Nutrition Examination Survey. Vitalus reports the mean and 90th percentile exposures to GOS for the U.S. population, users only, to be 12.2 g/person/day (0.28 g/kg body weight (bw)/day) and 25.3 g/person/day (0.7 g/kg bw/day), respectively, and the mean and 90th percentile exposures to GOS for infants up to one year old to be 1.44 and 2.42 g/kg bw/day, respectively.

Vitalus discusses the safety of GOS and states that a literature search was conducted through October 2017. Vitalus concluded that GOS was safe based on a published 90-day toxicology study using the GOS syrup that is the subject of this notice; this published study identified a no-observed-adverse-effect-level of 4.1 g/kg bw/day (2.0 g GOS/kg bw/day), the highest level tested. Vitalus supports the safety of this GOS product through published and unpublished, subchronic, developmental, reproductive, and genotoxicity studies conducted on other GOS-containing products.

Vitalus considers that GOS has a long history of safe use worldwide. In the European Union, the safety of GOS was reviewed by the Scientific Committee on Food in 2003 and is approved for use in infant and toddler formulas at levels up to 7.2 g/L. In Australia and New Zealand, the safety of GOS was reviewed by the Food Standards of Australia and New Zealand in 2008 and is permitted in infant and toddler formulas at levels up to approximately 8 g/L. Vitalus references prior GRAS notices, including use in infant and toddler formulas at levels up to 7.8 g/L, in support of its safety conclusion.[4]

Vitalus includes the statement of a panel of individuals (Vitalus' GRAS panel). Based on its review, Vitalus' GRAS panel concluded that GOS is safe under the conditions of its intended use.

On the basis of the information presented in the notice, Vitalus concluded that GOS is GRAS under the conditions of its intended use.

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[4] GRNs 000236, 000285, 000286, 000334, 000484, 000489, 000495, 000518, 000569, and 000620 describe the use of GOS in infant formula and conventional food. We evaluated these GRNs and responded with letters stating that we had no questions at those times regarding the notifiers' GRAS conclusions.

Standards of Identity

In the notice, Vitalus states its intention to use GOS in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, and Cosmetic (FD&C) Act, a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C Act lays out the statutory framework for labeling claims characterizing a nutrient level in a food or the relationship of a nutrient to a disease or health-related condition (also referred to as nutrient content claims and health claims). The notice raises a potential issue under these labeling provisions. Vitalus cites studies that describe GOS as having certain health benefits. If products containing GOS bear any nutrient content or health claims on the label or in labeling, such claims are subject to the applicable requirements and are under the purview of the Office of Nutrition and Food Labeling (ONFL) in the Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety (OFAS) did not consult with ONFL on this issue or evaluate any information in terms of labeling claims. Questions related to food labeling should be directed to ONFL.

Allergen Labeling

The FD&C Act requires that the label of a food that is or contains an ingredient that contains a "major food allergen" declare the allergen's presence (section 403(w)). The FD&C Act defines a "major food allergen" as one of eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. GOS from cow's milk-derived whey may require labeling under the FD&C Act because it may contain protein derived from milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Biotechnology and GRAS Notice Review in OFAS. Questions related to food labeling in general should be directed to ONFL.

Intended Use in Infant Formula

Under section 412 of the FD&C Act, 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. Our response to Vitalus' GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing GOS to make the submission required by section 412. Infant formulas are the purview of ONFL.

Section 301(ll) of the FD&C Act

Section 301(ll) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act, 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 our evaluation of Vitalus' notice concluding that GOS is GRAS under its intended conditions of use, we did not consider whether section 301(ll) or any of its exemptions apply to foods containing GOS. Accordingly, our response should not be construed to be a statement that foods containing GOS, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Vitalus provided, as well as other information available to FDA, we have no questions at this time regarding Vitalus' conclusion that GOS is GRAS under its intended conditions of use. This letter is not an affirmation that GOS is GRAS under 21 CFR 170.35. Unless noted above, our review did not address other provisions of the FD&C Act. Food ingredient manufacturers and food producers are responsible for ensuring that marketed products are safe and compliant with all applicable legal and regulatory requirements.

In accordance with 21 CFR 170.275(b)(2), the text of this letter responding to GRN 000721 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 2.9.2342.19200300.100.1.1=1300042713, cn=Michael A. Adams -S
Date: 2017.12.19 16:03:10 -05'00'

Dennis M. Keefe, Ph.D.
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