U.S. FOOD & DRUG ADMINISTRATION
Human Foods Program

Dietrich Conze, Ph.D.
Spherix Consulting Group
751 Rockville Pike
Unit 30-B
Rockville, MD 20852

Re: GRAS Notice No. GRN 000236

Dear Dr. Conze:

The Food and Drug Administration (FDA, we) completed our evaluation of the supplement that you submitted on behalf of FrieslandCampina Ingredients (FrieslandCampina) to GRN 000236. We received the supplement on June 26, 2024. The supplement addresses additional manufacturing steps that produce different forms of the subject of GRN 000236. FrieslandCampina submitted information on October 7, 2024, and November 4, 2024, that clarified the manufacturing and specifications.

We previously responded to GRN 000236 on July 28, 2008. We stated that we had no questions at that time regarding Friesland Foods Domo's conclusion that galacto-oligosaccharides (GOS) is GRAS for the intended uses in infant formula for term infants at a level of 5 g/L and in other food categories at levels shown in Table 1 of that letter. Additionally, we responded to a supplement to GRN 000236 on April 24, 2014. We stated that we had no questions at that time regarding Friesland Campina Domo B.V.'s conclusion that GOS is GRAS for use as an ingredient in baby cereals at a level of 3 g/serving, adult cereals at a level of 5 g/serving, milk drinks (yogurt drinks and fermented milk drinks including kefir) at a level of 7.5 g/serving, dairy based desserts (puddings, custards, and mousses) at a level of 3 g/serving, and juices at a level of 5 g/serving; and in term infant formula at a level up to 7.2 g/L. In the supplement dated June 24, 2024, FrieslandCampina informed us of its view that GOS is GRAS, through scientific procedures, for use as an ingredient in the same food categories and at the same use levels as in GRN 000236.

In GRN 000236, FrieslandCampina describes the manufacturing method and specifications for GOS in a syrup form. This supplement describes the manufacturing process and specifications for additional forms of GOS that is the subject of GRN 000236, including three GOS syrups and one GOS powder. FrieslandCampina states that the differences in the manufacturing method for these GOS syrups and GOS powder compared to the GOS syrup that was the subject of GRN 000236 and its April 24, 2014, supplement are limited to either the source of lactose or the processes used to refine the finished substances. In the manufacturing method for the first GOS syrup (Syrup 1), lactose undergoes an additional filtration step with activated carbon to remove residual

milk proteins. The second GOS syrup (Syrup 2) is manufactured using lactose obtained from milk produced by cows grown on farms in compliance with 7 CFR Part 205. In the manufacturing method for the third GOS syrup (Syrup 3), following the addition of citric acid, the GOS-containing solution is subjected to size exclusion chromatography to remove glucose and galactose. The resulting solution is concentrated to yield Syrup 3 or spray-dried to yield GOS powder. FrieslandCampina states that all raw materials and processing aids are used in accordance with applicable U.S. regulations, are GRAS for the intended use, or are the subject of an effective food contact notification.

FrieslandCampina compares the specifications for GOS produced using the manufacturing method described in GRN 000236 and the April 24, 2014, supplement and GOS produced using the modified manufacturing methods described in this supplement (Table 1).

Table 1. Specification Comparison.

Parameter	**GOS Syrup GRN 000236**	**GOS Syrup GRN 000236 Supplement (2014)**	**GOS Syrup 1**	**GOS Syrup 2**	**GOS Syrup 3**	**GOS Powder**
Dry matter, total	74-76%	74-76%	74-76%	74-76%	74-76%	NS
GOS	≥ 57% on DM	≥ 57% on DM	≥ 57% on DM	≥ 57% on DM	≥ 68% on DM	≥ 66%
Lactose	≤ 23% on DM	≤ 23% on DM	NS	NS	NS	NS
Lactose (and other disaccharides)	NS	NS	≤ 23% on DM	≤ 23% on DM	≤ 29% on DM	≤ 28%
Glucose	≤ 22% on DM	≤ 22% on DM	≤ 22% on DM	≤ 22% on DM	NS	NS
Galactose	≥ 0.8% on DM	≥ 0.8% on DM	≥ 0.8% on DM	≥ 0.8% on DM	NS	NS
Monosaccharides	NS	NS	NS	NS	≤ 7% on DM	≤ 7%
Moisture	NS	NS	NS	NS	NS	≤ 5%
Scorched particles	NS	NS	NS	NS	NS	Disc A
Sulphated ash	≤ 0.3% on DM	≤ 0.3% on DM	≤ 0.3% on DM	≤ 0.3% on DM	≤ 0.3% on DM	≤ 0.3%
Nitrogen	≤ 0.016% on DM	≤ 0.032% on DM	NA	≤ 0.1% on DM	≤ 0.032% on DM	≤ 0.1%
Nitrite	≤ 2 mg/kg on DM	≤ 2 mg/kg on DM	≤ 2 mg/kg on DM	≤ 2 mg/kg on DM	≤ 2 mg/kg on DM	≤ 1 mg/kg
Nitrate	NS	NS	NS	NS	≤ 50 mg/kg on DM	≤ 50 mg/kg
Viscosity	1000-5000 cPs	1000-5000 cPs	1000-5000 cPs	1000-5000 cPs	1000-5000 cPs	NA

Parameter	GOS Syrup GRN 000236	GOS Syrup GRN 000236 Supplement (2014)	GOS Syrup 1	GOS Syrup 2	GOS Syrup 3	GOS Powder
pH	3.2-3.8 (as is)	2.8-3.8 (as is)	2.8-3.8 (as is)	2.8-3.8 (as is)	2.8-3.8 (as is)	2.8-4.5 (10% solution)
Beta-lactoglobulin	NS	NS	≤0.2 mg/kg	NS	NS	NS
Aerobic Mesophilic Count (30°C)	≤ 3000 cfu/g	≤ 3000 cfu/g	≤ 3000 cfu/g	≤ 3000 cfu/g	≤ 3000 cfu/g	≤ 1000 cfu/g
Enterobacteriaceae	ND in 1 g	ND in 1 g	ND in 1 g	ND in 1 g	ND in 1 g	ND in 10 x 10 g
Escherichia coli	ND in 5 g	ND in 5 g	ND in 5 g	ND in 5 g	ND in 5 g	ND in 10 g
Yeasts	≤ 50 cfu/g	≤ 50 cfu/g	≤ 50 cfu/g	≤ 50 cfu/g	≤ 50 cfu/g	≤ 10 cfu/g
Molds	≤ 50 cfu/g	≤ 50 cfu/g	≤ 50 cfu/g	≤ 50 cfu/g	≤ 50 cfu/g	≤ 10 cfu/g
Coagulase-positive Staphylococci	ND in 1 g	ND in 1 g	ND in 1 g	ND in 1 g	ND in 1 g	ND in 1 g
Salmonella	ND in 25 g	ND in 25 g	ND in 125 g	ND in 125 g	ND in 125 g	ND in 1500 g
Cronobacter spp.	NS	NS	ND in 100 g	ND in 100 g	ND in 100 g	ND in 30 x 10 g
Listeria monocytogenes	NS	NS	ND in 25 g	ND in 25 g	ND in 25 g	ND in 25 g
Arsenic	< 0.4 mg/kg	< 0.4 mg/kg	< 0.02 mg/kg	< 0.02 mg/kg	< 0.02 mg/kg	< 0.02 mg/kg
Cadmium	< 0.06 mg/kg	< 0.06 mg/kg	< 0.05 mg/kg	< 0.05 mg/kg	< 0.05 mg/kg	< 0.05 mg/kg
Lead	< 0.2 mg/kg	< 0.2 mg/kg	< 0.1 mg/kg	< 0.1 mg/kg	< 0.1 mg/kg	< 0.1 mg/kg
Mercury	< 0.5 mg/kg	< 0.5 mg/kg	< 0.02 mg/kg	< 0.02 mg/kg	< 0.02 mg/kg	< 0.02 mg/kg

Abbreviations: cfu - colony forming units; NS - Not specified; ND - Not detected; DM - dried matter; cPs - centipoise.

FrieslandCampina provides the results from three non-consecutive batch analyses to demonstrate that GOS Syrups 1, 2, 3 and GOS powder can be manufactured to meet these specifications. FrieslandCampina states that GOS Syrups 1, 2, 3 and GOS powder are stable up to 2 years.

FrieslandCampina states that the intended uses of GOS Syrups 1, 2, 3 and GOS powder are substitutional for the uses described in the April 24, 2014, supplement; therefore, the dietary exposure from the intended uses in this supplement is expected to remain the same.

FrieslandCampina conducted an updated literature search through June 2024, and

discussed new published toxicity and clinical studies surrounding the safe use of GOS. FrieslandCampina did not identify any data or information that would contradict its safety conclusion from GRN 000236.

Based on the totality of the data and information described above, FrieslandCampina concludes that GOS is GRAS for its intended use.

Standards of Identity

In the notice, FrieslandCampina states its intention to use GOS in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. 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, & 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). 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 Nutrition Center of Excellence. The Office of Pre-Market Additive Safety (OPMAS) 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 nine foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans, and sesame) or a food ingredient that contains protein derived from one of those foods. GOS 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 Food Ingredients in OPMAS. Questions related to food labeling in general should be directed to ONFL.

Intended Use in Infant Formulas

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 FrieslandCampina's 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 the Office of Critical Foods in the Nutrition Center of Excellence.

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 FrieslandCampina's supplement 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 FrieslandCampina provided, as well as other information available to FDA, we have no questions at this time regarding FrieslandCampina's 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 the supplement to GRN 000236 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Mical E. Honigfort -S

Digitally signed by Mical E. Honigfort -S
Date: 2024.11.25 15:28:31 -05'00'

For Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Pre-Market Additive Safety
Office of Food Chemical Safety, Dietary Supplements, and Innovation