U.S. FOOD & DRUG ADMINISTRATION

Human Foods Program

Wing Yu
CIRS GROUP USA INC
4250 Fairfax Drive, Suite 600
Arlington, VA 22203

Re: GRAS Notice No. GRN 001299

Dear Ms. Yu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001299. We received the notice that you submitted on behalf of Synaura Biotechnology (Shanghai) Co., Ltd. (Synaura) on July 18, 2025, and filed it on January 23, 2026. Synaura submitted an amendment to the notice on March 31, 2026, that clarified the specifications, manufacturing, and aspects of the safety narrative.

The subject of the notice is 3′-sialyllactose sodium salt (3′-SL), produced via fermentation using production strain *Escherichia coli "SLIS109*," for use as an ingredient in foods, including infant formula, at the maximum levels shown in Table 1. Synaura states that 3′-SL is not intended for use in products under the U.S. Department of Agriculture's jurisdiction, in alcoholic beverages, and in foods for which standards of identity do not permit its addition. The notice informs us of Synaura's view that these uses of 3′-SL are GRAS through scientific procedures.

**Table 1: Intended food categories and use levels for 3′-SL**

| **Food Categories** | **Maximum Use Levels (g/kg or g/L)** |
|---|---|
| Non-exempt infant formula for term infants[1] | 0.28 |
| Formula-type drinks for young children | 0.28 |
| Meal replacement and nutritional drinks (milk- and non-milk-based) | 0.9 |
| Sports, isotonic, and "energy" drinks | 0.45 |
| Enhanced or fortified waters | 0.45 |
| Soft drinks (regular and diet) | 0.25 |
| Cappuccino, non-fat, with milk, sweetened | 0.52 |
| Herbal tea, presweetened with low calorie sweetener or sugar | 12.9 |
| Imitation milk | 0.12 |
| Non-dairy yogurt | 0.55 |

[1] Synaura states that the use of 3′-SL in non-exempt infant formula is not restricted to any specific protein base (e.g., cow milk-based, soy-based).

| | |
|---|---|
| Frozen yogurt | 1.7 |
| Cereal and granola bars | 2.5 |
| Meal replacements bars, for weight management | 25.9 |
| Other drinks for young children | 0.15 |
| Milk-based meal replacement beverages for children | 0.9 |
| Instant cereals for infants and young children | 1.66 |
| Other foods for infants and young children | 1.25 |
| Unflavored pasteurized and sterilized milk | 0.25 |
| Buttermilk | 0.25 |
| Flavored milk | 0.25 |
| Yogurt | 2.5 |
| Fruit flavored drinks and ades | 0.25 |
| Herbal extract sugar substitutes | 100 |
| Enteral tube feeding formulas (≥11 years) | 1.5 |

Synaura provides information on the identity and composition of 3′-SL. Synaura describes 3′-SL as a white to off-white powder consisting of ≥88% 3′- SL on a dry weight (DW) basis and small quantities of other related carbohydrates (*N*-acetyl-D-neuraminic acid, 3′-sialyllactulose, and D-lactose). 3′-SL (CAS Registry Number 128596-80-5) is a trisaccharide composed of D-glucose, D-galactose, and *N*-acetyl-D-neuraminic acid. Synaura states that 3′-SL has the same molecular weight, molecular formula, and chemical structure as the human milk-derived 3′-SL sodium salt, as confirmed by various chromatography and spectroscopy techniques.

Synaura describes the production organism used in the manufacturing process for 3′-SL. The production strain *E. coli* "SLIS109" was constructed through genetic engineering of the *E. coli* BL21(DE3) host strain to enable efficient synthesis of 3′-SL from D-glucose, D-glycerol, and D-lactose. Synaura states that the sequence integrity of the genome was verified by whole genome sequencing and that the strain is non-pathogenic and non-toxigenic.

Synaura describes the two-stage manufacturing process, which includes an upstream fermentation stage and a downstream purification stage. In the first stage, 3′-SL is produced by fermentation with *E. coli* "SLIS109" under controlled conditions and is secreted into the fermentation medium. After fermentation is complete, the production organism is removed from the fermentation medium using solid-liquid separation techniques, such as centrifugation, flocculation, or membrane filtration. The filtrate containing 3′-SL is then further purified. First, the filtrate undergoes an ultrafiltration process to remove proteins, endotoxins, and DNA, and then the filtrate is heated to denature any residual proteins and inactivate microbial contaminants. The resulting solution is purified using activated carbon followed by filtration to remove the activated carbon and any associated impurities. The solution is then subjected to cation and anion exchange columns to remove salts, amino acids, pigments, and other impurities. 3′-SL is eluted from the ion exchange column using water and sodium acetate. The eluant is desalinated and concentrated using nanofiltration and the resulting solution is filtered

to remove residual impurities. The concentrated solution is spray dried to obtain the final 3′-SL powder. Synaura states that 3′-SL is manufactured according to current good manufacturing practices, and that all raw materials and processing aids are food-grade and are used in accordance with applicable U.S. regulations, are GRAS for their intended uses, or are the subject of an effective food contact notification.

Synaura provides specifications for 3′-SL, which include the minimum content of 3′-SL (≥88% DW) and limits on *N*-acetyl-D-neuraminic acid (≤1.5%), 3′-sialyllactulose (≤5%), D-lactose (≤3%), moisture (≤10.5%), sodium (≤4,200 mg/kg), protein (≤100 mg/kg), heavy metals (including lead (≤0.05 mg/kg)), cereulide (<0.1 µg/kg), and microorganisms, including *Salmonella* serovars (absent in 25 g), *Listeria monocytogenes* (absent in 25 g), and *Cronobacter sakazakii* (absent in 100 g). Synaura provides the results from three non-consecutive batch analyses to demonstrate that 3′-SL can be manufactured to meet the specifications. Synaura states that, except for lactose, none of the raw materials are derived from major allergens.

Synaura states that the intended uses of 3′-SL are substitutional for those described in GRN 001074[2] and incorporates the dietary exposure estimates from GRN 001074 into the notice based on food consumption data from the 2017-2018 National Health and Nutrition Examination Survey. Synaura states that the estimated eaters-only dietary exposure to 3′-SL is 0.28 g/person (p)/d (41 mg/kg body weight (bw)/d) at the mean and 0.53 g/p/d (66 mg/kg bw/d) at the 90$^{th}$ percentile for infants aged 0-6 months, and 0.48 g/p/d (52 mg/kg bw/d) at the mean and 0.89 g/p/d (96 mg/kg bw/d) at the 90$^{th}$ percentile for infants aged 7-12 months. For children aged 1-3 years, the estimated eaters-only dietary exposure to 3′-SL is 0.23 g/p/d (17 mg/kg bw/d) and 0.42 g/p/d (33 mg/kg bw/d) at the mean and 90$^{th}$ percentile, respectively. For the U.S. population aged 2 years and older, the estimated eaters-only dietary exposure to 3′-SL is 0.39 g/p/d (6 mg/kg bw/d) and 0.71 g/p/d (12 mg/kg bw/d) at the mean and 90$^{th}$ percentile, respectively. Synaura notes that the most recent cumulative dietary exposure to 3′-SL is reported in GRN 001052,[2] which considers all current uses, including those from GRN 001074, and incorporates those cumulative dietary exposure estimates into the notice. Synaura states that because the intended uses are substitutional, an increase in the cumulative dietary exposure to 3′-SL is not expected.

Synaura discusses data and information supporting the safety of 3′-SL and states that the subject of the notice is structurally and chemically identical to that found in human milk, as well as other 3′-SL ingredients previously concluded to be GRAS. Synaura incorporates safety data and information into the notice and provides summaries of published studies discussed in GRNs 000766, 000880, 000921, 001015, 001052, and 001074.[2] Synaura states that 3′-SL is resistant to digestion in the gastrointestinal tract and only a small amount is absorbed intact, while the majority of 3′-SL is unabsorbed and either fermented by colonic bacteria or excreted unchanged. Synaura discusses

[2] 3′-SL was the subject of GRNs 000766, 000880, 000921, 0001015, 001052 and 001074. We evaluated these notices and responded in letters dated September 26, 2018, February 21, 2020, October 30, 2020, July 15, 2022, April 18, 2023, and April 05, 2023, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

published genetic and subchronic toxicity studies in rats, which demonstrated no evidence of toxicity up to the highest doses tested. Synaura summarizes published clinical studies evaluating the consumption of 3′-SL in healthy term infants and adults where 3′-SL was demonstrated to be safe and well tolerated. Synaura states that a literature search conducted through March 2026 did not identify any published studies that would contradict its GRAS conclusion.

Based on the totality of the data and information, Synaura concludes that 3′-SL is GRAS for its intended use.

**Standards of Identity**

In the notice, Synaura states its intention to use 3′-SL 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 3′-SL 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 (NCE). 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. 3′-SL from lactose 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 Synaura's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing 3′-SL to make the submission required by section 412. Infant formulas are the purview of the Office of Critical Foods in NCE.

**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 Syaura's notice concluding that 3′-SL 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 3′-SL. Accordingly, our response should not be construed to be a statement that foods containing 3′-SL, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

**Conclusions**

Based on the information that Synaura provided, as well as other information available to FDA, we have no questions at this time regarding Synaura's conclusion that 3′-SL is GRAS under its intended conditions of use. This letter is not an affirmation that 3′-SL 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 001299 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

SUSAN J. CARLSON -S

Digitally signed by SUSAN J. CARLSON -S
Date: 2026.05.13 10:05:59 -04'00'

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
Human Foods Program