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 001262

Dear Ms. Yu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001262. We received the notice that you submitted on behalf of Zhuhai Long Health Biotechnology Co., Ltd. (Long Health) on February 24, 2025, and filed it on July 28, 2025. Long Health submitted amendments to the notice on October 6, 2025, November 28, 2025, January 22, 2026, March 26, 2026, and March 31, 2026, containing additional information regarding the production organism, manufacturing process, specifications, dietary exposure, and safety narrative.

The subject of the notice is 2'-fucosyllactose (2'-FL) for use as an ingredient in non-exempt infant formula[1] for term infants and formula for young children (>12 months) at a maximum use level of 2.4 g/L, as consumed, and in other food categories at the maximum levels as shown in Table 1. Long Health states that 2'-FL is not intended for use in foods where standards of identity would preclude such use, alcoholic beverages, or in products under the jurisdiction of the U.S. Department of Agriculture. The notice informs us of Long Health's view that these uses of 2'-FL are GRAS through scientific procedures.

Table 1: Intended food categories and use levels for 2'-FL

Food Categories	Maximum Use Levels (g/L or g/kg)
Breads and baked goods[2]	48
Carbonated beverages	1.2
Enhanced or fortified waters	1.2
Sports, isotonic, and "energy" drinks	6
Hot breakfast cereals, prepared	31

[1] Long Health states that the use of 2'-FL in non-exempt infant formula is not restricted to any specific protein base (e.g., cow milk-based, soy-based).

[2] The response letter for GRN 001051 listed this food category as breads and baked goods, gluten-free; however, we note that based on information provided in the dietary exposure assessment this category included breads and baked goods, including gluten-free. The subject of GRN 001051 was 2'-FL. We evaluated this notice and responded in a letter dated November 21, 2023, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

Food Categories	**Maximum Use Levels (g/L or g/kg)**
Ready-to-eat (RTE) cereals, puffed	80
RTE cereals, high fiber	40
RTE cereals, biscuit type	40
Coffee and tea[3]	10
Milk substitutes	1.2
Beverage whiteners (powdered)	600
Beverage whiteners (liquid)	80
Non-dairy yogurt	12
Frozen dairy-based desserts	17
Puddings, custard and mousses	17
Fruit pie filling	14.1
Fruit filling in bars, cookies, yogurt, and cakes	30
Non-exempt infant formula for term infants	2.4
Formula intended for young children (>12 months)	2.4
Hot cereals for infants and young children, prepared (from dry instant) and ready-to-serve	12
Other foods for infants and young children (yogurt, fruits, vegetables, “toddler” meals, desserts	12
Other drinks for infants and young children (juice and yogurt drinks)	10
Baby snacks (crackers, pretzels, cookies, and other dry snack items)	57
Jams and jellies, fruit preserves, and fruit butters	60
Meal replacement bars, general use	30
Cereal bars including snack, granola, and breakfast bars	30
Meal replacement bars, for weight management	40
Meal replacement drinks (including nutritional drinks, smoothies) for general use, milk and non-milk based	5
Meal replacement drinks for weight management, milk and non-milk based	12
Milk-based meal replacement beverages for children (e.g., pediatric nutritional drinks)	12
Unflavored pasteurized and sterilized milk	1.2
Buttermilk	1.2
Flavored and fermented milks	1.2
Yogurt	12
Fruit juices and nectars	1.2
Fruit-flavored drinks and ades	1.2
Vegetable juices and nectars	1.2
Sugar substitutes: table-top sweeteners	300

[3] The category of coffee and tea includes ready-to-drink (e.g., bottled, flavored, presweetened) coffee and tea and powder mixes used to prepare coffee and tea. For dietary exposure estimates, it is assumed that the intended uses of 2'-FL do not include plain brewed coffee or tea.

Food Categories	Maximum Use Levels (g/L or g/kg)
Syrups used to flavor milk beverages	7
Nutritional drinks for pregnant women	12
Oral and enteral tube feeding formulas for ages ≥11 years	20

Long Health provides information on the identity and composition of 2'-FL. Long Health describes 2'-FL as a white to off white powder containing a minimum of 94% 2'-FL (dry-weight basis (DW)). Long Health states that 2'-FL is a trisaccharide composed of L-fucose, D-galactose, and D-glucose. The chemical name for 2'-FL is α-L-fucopyranosyl-(1→2)-ß-D-galactopyranosyl-(1→4)-D-glucose and the CAS registry number is 41263-94-9. Long Health states that 2'-FL is identical to the 2'-FL in human milk, as confirmed by nuclear magnetic resonance spectroscopy and high-resolution mass spectrometry.

Long Health describes the production organism used in the manufacturing process for 2'-FL. The production organism, *Escherichia coli* CCTCC M 20242108, is constructed through genetic engineering of the *E. coli* B21 (DE3) parent strain using CRISPR/Cas9 to knock out or replace 14 genes and insert six genes to allow for the efficient production of 2'-FL. Long Health states that all genetic modifications are verified by polymerase chain reaction (PCR) and whole genome sequencing, and that the strain is non-pathogenic and non-toxigenic.

Long Health describes the two-stage manufacturing process, including fermentation and purification. In the first stage, 2'-FL is produced from D-lactose and D-glucose during fermentation with *E. coli* CCTCC M 20242108 under controlled conditions. After fermentation is complete, the fermentation liquid is passed through a ceramic membrane to remove the production organism. The clear filtrate containing 2'-FL undergoes a series of purification steps, including decolorization, desalination, concentration, chromatography, and ultrafiltration to remove pigments, endotoxin, salts, carbohydrate impurities, proteins, and other impurities. The resulting liquid is concentrated by evaporation concentrator and spray dried to produce the final 2'-FL powder. Long Health states that 2'-FL is manufactured according to current good manufacturing practices, and 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.

Long Health provides specifications for 2'-FL, which include the minimum content of 2'-FL (≥94% DW) and limits on D-lactose (≤5% DW), 3,2'-difucosyl-D-lactose (≤5% DW); L-fucose (≤3% DW), D-glucose (≤3% DW); D-galactose (≤3% DW), 2'-fucosyl-D-lactulose (≤2% DW), water content (≤9%); residual proteins (≤100 mg/kg), ash (≤0.5%), pH (3.5-6.5), heavy metals, including lead (≤0.05 mg/kg), cereulide (<0.2 µg/kg), and microorganisms, including *Salmonella* serovars (absent in 25 g), *Listeria monocytogenes* (absent in 25 g) and *Cronobacter sakazakii* (absent in 10 g). Long Health provides the results from the analyses of three non-consecutive batches to demonstrate that 2'-FL can be manufactured to meet the specifications.

Long Health states that the intended uses of 2'-FL are substitutional for those described in GRN 001051[4] and incorporates into the notice those dietary exposure estimates. Long Health states that the estimated dietary exposure to 2'-FL is 2.4 g/person (p)/d (360 mg/kg body weight (bw)/d) at the mean and 4.4 g/p/d (578 mg/kg bw/d) at the 90th percentile for infants aged 0-6 months, and 4.3 g/p/d (474 mg/kg bw/d) at the mean and 7.7 g/p/d (812 mg/kg bw/d) at the 90th percentile for infants aged 7-12 months. For children aged 1-2 years, the estimated dietary exposure to 2'-FL is 2.9 g/p/d (237 mg/kg bw/d) and 5.7 g/p/d (477 mg/kg bw/d) at the mean and 90th percentile, respectively. For the U.S. population aged 2 years and older, dietary exposure to 2'-FL is 4.2 g/p/d (65 mg/kg bw/d) and 9.1 g/p/d (146 mg/kg bw/d) at the mean and 90th percentile, respectively. Long Health notes that the intended uses are substitutional for the current uses of other sources of 2'-FL, and an increase in the cumulative dietary exposure to 2'-FL is not expected.

Long Health provides data and information supporting the safe use of 2'-FL. Long Health states that the 2'-FL that is the subject of this notice is chemically identical to 2'-FL derived from human milk. Thus, Long Health concludes that the absorption, distribution, metabolism, and excretion profile of 2'-FL is expected to be the same as naturally occurring 2'-FL. Long Health states that the global average concentration of 2'-FL in mature breast milk is about 2.30 g/L, accounting for 15% to 46% of breast milk oligosaccharides. Long Health also states that the composition of 2'-FL is very similar to the test article used in published toxicological studies of 2'-FL, and discusses these pertinent studies referenced in GRNs for 2'-FL that have been previously evaluated by FDA and for which FDA had no questions about the notifers' GRAS conclusions. Based on their evaluation, Long Health concludes that 2'-FL is not genotoxic, did not demonstrate adverse effects based on oral toxicological studies in rats, and is safe and well tolerated by infants and adults. Long Health discusses new studies identified through a comprehensive literature search through September 2025 and concludes that no new publicly available data and information would contradict their GRAS conclusion.

Based on the totality of the data and information, Long Health concludes that 2'-FL is GRAS for its intended use.

Standards of Identity

In the notice, Long Health states its intention to use 2'-FL 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, and Cosmetic Act (FD&C Act), a food is misbranded if its labeling is false or misleading in any way. Section 403(r) of the FD&C

[4] 2'-FL was the subject of GRN 001051. We evaluated this notice and responded in a letter dated November 21, 2023, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

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 2'-FL 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. 2'-FL 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 in NCE.

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 Long Health's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing 2'-FL 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 Long Health's notice concluding that 2'-FL 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 2'-FL. Accordingly, our response should not be construed to be a statement that foods containing 2'-FL, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Long Health provided, as well as other information available to FDA, we have no questions at this time regarding Long Health's conclusion that 2'-FL is GRAS under its intended conditions of use. This letter is not an affirmation that 2'-FL 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 001262 accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

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