



Timothy Murbach
CIRS Group USA Inc.
4250 Fairfax Drive, Suite 600
Arlington, VA 22203

Re: GRAS Notice No. GRN 001273

Dear Dr. Murbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001273. We received the notice that you submitted on behalf of Shenzhen Long Health Biotechnology Co., Ltd. (Long Health) on April 22, 2025, and filed it on August 29, 2025. Long Health submitted an amendment to the notice on January 9, 2026, and April 1, 2026, containing additional information regarding the manufacturing process, specifications, and safety narrative.

The subject of the notice is lacto-*N*-tetraose (LNT) for use as an ingredient in non-exempt infant formula for term infants¹ at a maximum level of 0.8 g/L as consumed, and in other food categories at the maximum levels as shown in Table 1, excluding use in foods for which standards of identity do not permit its addition, alcoholic beverages, and foods under the jurisdiction of the United States Department of Agriculture. The notice informs us of Long Health's view that these uses of LNT are GRAS through scientific procedures.²

Table 1: Intended food categories and use levels for LNT

Food Categories	Serving Size³	Maximum use levels (g/serving)	Maximum use levels (g/kg or g/L)
Meal replacement drinks, for weight management	240 mL	0.48	2.0
Sports, isotonic, and "energy" drinks	360 mL	0.36	1.0
Soft drinks	360 mL	0.36	1.0
Enhanced or fortified waters	360 mL	0.36	1.0
Fruit-based ades	360 mL	0.36	1.0

¹ Long Health states that the use of LNT in infant formula is not restricted to any specific protein base (e.g., cow milk-based, soy-based).

² Long Health states that the intended uses of LNT are substitutional for the intended uses evaluated in GRN 001068.

³ Long Health states that the intended serving sizes are based on the Reference Amounts Customarily Consumed (RACC) per eating occasion established in 21 CFR 101.12.

Food Categories	Serving Size³	Maximum use levels (g/serving)	Maximum use levels (g/kg or g/L)
Infant formula, non-exempt	100 mL ⁴	0.08	0.8
Formula-type drinks for young children (>12 months of age)	100 mL ⁴	0.06	0.6
Other drinks for young children	120 mL	0.07	0.6
Baby foods for infants and young children	7 to 170 g	0.04 – 0.85	5.0
Meal replacement bars, for weight management	40 g	0.8	20
Cereal and granola bars	40 g	0.4	10
Unflavored pasteurized and sterilized milk	240 mL	0.24	1.0
Buttermilk	240 mL	0.24	1.0
Flavored milk	240 mL	0.24	1.0
Yogurt	170 g	1.7	10

Long Health provides information on the identity and composition of LNT (CAS Registry Number 14116-68-8). Long Health describes LNT as an off-white to white powder that is $\geq 80\%$ LNT on a dry matter (DM) basis, with small amounts of D-lactose, lacto-*N*-triose II, lacto-*N*-hexaose II, and other related saccharides. The molecular formula of LNT is $C_{26}H_{45}NO_{21}$ and the molecular weight is 707.6 g/mol. LNT is an oligosaccharide, found in human milk, that is comprised of galactose, glucose, and *N*-acetylglucosamine. The chemical name of LNT is β -D-galactopyranosyl-(1 \rightarrow 3)-2-acetamido-2-deoxy- β -D-glucopyranosyl-(1 \rightarrow 3)- β -D-galactopyranosyl-(1 \rightarrow 4)-D-glucopyranose.

Long Health describes the production organism, *Escherichia coli* CCTCC M 20242456, used in the manufacture of LNT. The production organism is genetically engineered from the parent strain, *E. coli* BL21 star (DE3), using λ -Red homologous recombination to knock out four genes and CRISPR-associated transposon (CAST) system to insert three genes⁵ that encode enzymes to allow for the efficient production of LNT. Long Health states that all gene insertions and deletions were verified by polymerase chain reaction. Long Health states that the production organism does not contain any helper plasmids or antibiotic resistance genes introduced into the genome. Long Health states that *E. coli* CCTCC M 20242456 is non-pathogenic and non-toxicogenic and is deposited in the China Center for Type Culture Collection under the deposit number CCTCC M 20242456.

⁴ Long Health notes that RACCs are not established in CFR 101.12 for infant formula and formula for young children and a value of 100 mL is used as an approximation to describe the intended use level.

⁵ Long Health states that the modifications to the parent strain, *E. coli* B21 star (DE3), to produce *E. coli* CCTCC M 20242456 include the insertion of chemically synthesized genes that encode β -1,3-*N*-acetylglucosaminyltransferase, UDP-galactose-4-epimerase, and β -1,4-galactosyltransferase.

Long Health states that LNT is manufactured in two main stages. In the fermentation stage, the production organism is grown in a medium containing glycerol and glucose as carbon sources, ammonium sulfate as a nitrogen source, and D-lactose as a substrate for the synthesis of LNT. In the post-fermentation stage, the LNT is isolated, purified and concentrated via a series of filtration, sterilization, deionization, decolorization, and drying steps. Long Health states that LNT is manufactured following current good manufacturing practices and all materials used in the manufacturing processes are food-grade and are used in accordance with applicable U.S. regulations, are concluded to be GRAS for their respective use, or are the subject of an effective food contact notification.

Long Health provides specifications for LNT that include the minimum content of LNT ($\geq 80\%$ DM) and limits for lacto-*N*-triose II ($\leq 5\%$, as-is basis), D-lactose ($\leq 5\%$, as-is basis), lacto-*N*-hexaose II ($\leq 5\%$, as-is basis), and the sum of D-galactose and D-glucose ($\leq 5\%$, as-is basis), and other carbohydrates ($\leq 15\%$). Long Health also provides specifications for protein (≤ 100 mg/kg), ash ($\leq 0.5\%$), moisture ($\leq 9\%$), heavy metals, including lead (≤ 0.05 mg/kg), cereulide (<0.2 $\mu\text{g}/\text{kg}$), and microorganisms, including *Cronobacter sakazakii* (absent in 100 g), *Listeria monocytogenes* (absent in 25 g), and *Salmonella* serovars (absent in 25 g). Long Health provides the results from the analyses of three nonconsecutive batches to demonstrate that LNT can be manufactured to meet these specifications.

Long Health states that its intended uses of LNT in infant formula and conventional foods are substitutional for the intended uses described in GRN 000833⁶ and subsequently in GRN 001068. As such, Long Health incorporates into the notice estimates of dietary exposure to LNT from these prior notices that are based on the intended uses and food consumption data from the 2013-2014 National Health and Nutrition Examination Survey (NHANES). In addition, Long Health concludes that the cumulative dietary exposure to LNT is not expected to change.

Long Health states that LNT is structurally identical to LNT found in breastmilk and provides a structural analysis on their article of commerce in support of this statement. Long Health discusses data and information pivotal to the safety of LNT previously reviewed for GRNs 000833, 000923, 001017, and 001068⁶ and from a literature search conducted through December 2025. Data and information incorporated into this discussion includes a published genotoxicity testing battery (two bacterial reverse mutation tests, and two *in vitro* mammalian micronucleus tests), published absorption, distribution, metabolism and excretion studies, and two published 90-day repeated dose oral toxicity studies in rats. Long Health also reports and summarizes a number of unpublished toxicology studies for LNT and two published clinical studies in healthy term infants for LNT in mixture, that the notifier considers supportive of their

⁶ The subject of GRNs 000833, 000923, 001017, and 001068 is lacto-*N*-tetraose. We evaluated these GRNs and responded in letters dated, April 13, 2020, February 2, 2021, August 23, 2022, and June 5, 2023, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

conclusion. Long Health states that none of the publicly available data and information would contradict the conclusion that the proposed uses of LNT are safe.

Based on the totality of the data and information, Long Health concludes that LNT is GRAS for its intended uses.

Standards of Identity

In the notice, Long Health states its intention to use LNT 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 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 LNT 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. LNT 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 the OPMAS. Questions related to food labeling in general should be directed to the 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 LNT 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 LNT 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 LNT. Accordingly, our response should not be construed to be a statement that foods containing LNT, 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 LNT is GRAS under its intended conditions of use. This letter is not an affirmation that LNT 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 001273 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

**Susan J.
Carlson -S**

 Digitally signed by Susan J. Carlson -S
Date: 2026.04.08 11:40:24 -04'00'

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Director
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