



Wing Yu  
CIRS Group USA Inc.  
4250 Fairfax Drive, Suite 600  
Arlington, VA 22203

Re: GRAS Notice No. GRN 001272

Dear Ms. Yu:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001272. We received the notice that you submitted on behalf of Shenzhen Long Health Biotechnology Co., Ltd. (Long Health) on April 17, 2025, and filed it on August 29, 2025. Long Health submitted an amendment to the notice on December 19, 2025, and April 3, 2026, containing additional information regarding the production organism, specifications, and safety narrative.

The subject of the notice is lacto-*N*-neotetraose (LNnT). The notice informs FDA of Long Health's view that LNnT is GRAS, through scientific procedures, for use as an ingredient in non-exempt infant formula for term infants<sup>1</sup> at up to 0.6 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 in foods under the jurisdiction of the United States Department of Agriculture).<sup>2</sup>

Table 1: Intended food categories and use levels for LNnT

<b>Food Category</b>	<b>Serving size<sup>3</sup></b>	<b>Use level (g/serving)</b>	<b>Maximum Use Level (g/kg or g/L)</b>
Meal replacement drinks, for weight reduction	240 mL	0.6	2.5
Sports, isotonic, and "energy" drinks	240 mL	0.14	0.58
Imitation milks	240 mL	0.14	0.58
Non-dairy yogurts	225 g	0.6	2.67
Infant formula	100 mL <sup>4</sup>	0.06	0.6

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

<sup>2</sup> Long Health states that the intended uses of LNnT are substitutional for the intended uses evaluated in GRN 001067. LNnT was the subject of GRN 001067. We evaluated this notice and responded in a letter dated April 4, 2023, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

<sup>3</sup> 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.

<sup>4</sup> 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.

Food Category	Serving size <sup>3</sup>	Use level (g/serving)	Maximum Use Level (g/kg or g/L)
Formula-type drinks for young children (>12 months of age)	100 mL <sup>4</sup>	0.06	0.6
Baby foods for infants and young children	7 to 170 g	0.02 to 0.68	3.0
Drinks for infants and young children	120 mL	0.07	0.58
Meal replacement bars, for weight reduction	30 g	0.6	20.0
Unflavored pasteurized and sterilized milk	240 mL	0.14	0.58
Buttermilk	240 mL	0.14	0.58
Flavored milk	240 mL	0.14	0.58
Milk-based meal replacement drinks, for weight reduction	240 mL	0.6	2.5
Yogurt	225 g	0.6	2.67
Fruit juices and nectars	240 mL	0.14	0.58

Long Health provides information on the identity and composition of LNnT. Long Health describes LNnT as a white to off-white powder containing  $\geq 92\%$  LNnT. Long Health reports that the final LNnT product may also contain other carbohydrates, including D-lactose, lactose-*N*-triose II, fructo-lacto-*N*-neotetraose, and *para*-lacto-*N*-neohexaose. LNnT is a tetrasaccharide composed of D-galactose, *N*-acetyl-D-glucosamine, and D-glucose. LNnT has the CAS registry number 13007-32-4 and the chemical name  $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-2-acetamido-2-deoxy- $\beta$ -D-glucopyranosyl-(1 $\rightarrow$ 3)- $\beta$ -D-galactopyranosyl-(1 $\rightarrow$ 4)-D-glucopyranose. Long Health states that LNnT is chemically and structurally identical to the LNnT found in human milk, as confirmed by nuclear magnetic resonance spectroscopy, distortionless enhancement by polarization transfer, and liquid chromatography-mass spectrometry.

Long Health describes the production organism, *Escherichia coli* CCTCC M 20242455, used in the manufacture of LNnT. The production organism is genetically engineered from the parent strain, *E. coli* BL21 star (DE3), using  $\lambda$ -Red homologous recombination to knock out four genes and CRISPR-associated transposon (CAST) system to insert four genes<sup>5</sup> that encode enzymes to allow for the efficient production of LNnT. Long Health states that all gene insertions and deletions were verified by polymerase chain reaction, Sanger sequencing, and whole genome sequencing. 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 20242455 is non-pathogenic and non-toxigenic and is deposited in the China Center for Type Culture

<sup>5</sup> Long Health states that the modifications to the parent strain, *E. coli* B21 star (DE3), to produce *E. coli* CCTCC M 20242455 include the insertion of chemically synthesized genes that encode  $\beta$ -1,3-*N*-acetylglucosaminyltransferase, UDP-galactose-4-epimerase,  $\beta$ -1,4-galactosyltransferase, and LNnT transport protein.

Collection under the deposit number CCTCC M 20242455.

Long Health states that LNnT 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, ammonia salts as nitrogen sources, and D-lactose as a substrate for the synthesis of LNnT. The LNnT is secreted across the cell membrane by transport proteins encoded by inserted genes in the production organism. In the post-fermentation stage, the LNnT is isolated, purified and concentrated via a series of filtration, sterilization, deionization, decolorization, and drying steps. Long Health states that LNnT may undergo an optional crystallization step in which methanol is added to the concentrated liquid prior to the drying step to precipitate LNnT that is subsequently dissolved in water prior to spray drying. Long Health states that 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, and that LNnT is manufactured following current good manufacturing practices.

Long Health provides specifications for LNnT that include the minimum content of LNnT ( $\geq 92\%$  on a dry matter basis (DM)) and total human milk-identical saccharides<sup>6</sup> ( $\geq 95\%$  DM), and limits for D-lactose ( $\leq 3\%$ ), lacto-*N*-triose II ( $\leq 3\%$ ), *para*-lacto-*N*-neohexaose ( $\leq 3\%$ ), fructo-lacto-*N*-neotetraose ( $\leq 1\%$ ), moisture ( $\leq 9\%$ ), ash ( $\leq 0.4\%$ ), methanol ( $\leq 100$  mg/kg),<sup>7</sup> heavy metals, including lead ( $\leq 0.05$  mg/kg), protein ( $\leq 100$  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* spp. (absent in 25 g). Long Health provides the results from the analyses of three non-consecutive batches each of LNnT produced with or without the optional crystallization step to demonstrate that LNnT can be manufactured to meet these specifications. Long Health discusses the results of an accelerated stability study conducted with three batches of LNnT stored for 3 months at 37 °C and 75% relative humidity. Long Health concludes that the results of this study demonstrate that LNnT is stable under the conditions tested, and Long Health expects the shelf-life of LNnT to be up to two years.

Long Health discusses the estimated dietary exposure to LNnT and states that the intended uses are the same as described in GRN 001067<sup>2</sup>, and, therefore, Long Health does not expect the dietary exposure to LNnT to change. The notifier of GRN 001067 and Long Health incorporate into their notices information on the estimated dietary exposure to LNnT from GRN 000547<sup>8</sup> and GRN 000659.<sup>8</sup> Long Health discusses the estimates of dietary exposure to LNnT presented in GRN000547 for infants and young children based on the intended uses and food consumption data from the 2009-2010

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<sup>6</sup> Long Health states that the sum of human milk-identical saccharides includes LNnT, D-lactose, lacto-*N*-triose II, and *para*-lacto-*N*-neohexaose.

<sup>7</sup> Long Health notes that the specified limit for methanol only applies to LNnT produced using the optional crystallization step.

<sup>8</sup> LNnT is the subject of GRNs 000547, 000659, 000895, 000919, and 001059. We evaluated these notices and responded in letters dated October 2, 2015, November 23, 2016, November 30, 2020, October 30, 2020, and December 2, 2022, respectively, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

National Health and Nutrition Examination Survey (NHANES). Long Health reports the mean and 90<sup>th</sup> percentile eaters-only dietary exposure to LNnT for infants up to 6 months of age to be 0.82 and 1.60 g/person (p)/d, respectively. The mean and 90<sup>th</sup> percentile eaters-only dietary exposure to LNnT for infants 7 to 12 months of age are reported to be 1.50 and 2.69 g/p/d, respectively. The mean and 90<sup>th</sup> percentile eaters-only dietary exposure to LNnT for children aged 1 to 3 years are reported to be 0.67 and 1.21 g/p/d, respectively. Long Health also provides estimates of dietary exposure to LNnT presented in GRN 000659 for the total population based on the intended uses and food consumption data from the 2011-2012 NHANES. The mean and 90<sup>th</sup> percentile eaters-only dietary exposure to LNnT for the total population (all ages) are reported to be 304 and 646 mg/p/d, respectively.

Long Health discusses the publicly available data and information supporting safety of LNnT. Long Health states that their LNnT ingredient is structurally and chemically equivalent to LNnT found in human milk, and compositionally similar to other LNnT ingredients. Thus, Long Health incorporates the publicly available data and information discussed in GRNs 000547, 000659, 000895, 000919, 001059,<sup>8</sup> and 001067<sup>2</sup> into their notice. Long Health summarizes information on the absorption, distribution, metabolism, and excretion of LNnT, noting that data suggests that the majority of LNnT is not digested, but instead is metabolized by the gut microbiome in the colon, and excreted. Additionally, Long Health summarizes published genotoxicity and subchronic toxicity studies performed in rats. Across all studies, results consistently demonstrated no test article-related adverse effects. To further support the safe use of LNnT, Long Health discusses unpublished genotoxicity, acute toxicity, and subchronic toxicity studies using their LNnT ingredient as the test article. Long Health notes that no test-article related adverse effects were observed in the toxicity studies, nor was LNnT found to be mutagenic or genotoxic in a bacterial reverse mutation assay or an *in vivo* mammalian micronucleus assay.

Long Health states that an updated literature search through December 2025 did not identify any new animal toxicological studies; however, Long Health discusses several new human studies published on LNnT in infants. Additionally, Long Health summarizes human studies with LNnT in infants, children, and adults that have previously been reviewed in GRAS notices for LNnT. Long Health notes that the human studies were done with either LNnT alone or in combination with other human milk oligosaccharides and ranged in duration from 1 week up to 12 months. Long Health concludes that these clinical studies demonstrate that LNnT is well-tolerated and safe in infants and adults.

Based on the available data and information, Long Health concludes that LNnT is GRAS for its intended uses.

### **Standards of Identity**

In the notice, Long Health states its intention to use LNnT 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 LNnT 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. LNnT 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 LNnT 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 LNnT is GRAS under its intended conditions of use, we did not consider whether section

301(l) or any of its exemptions apply to foods containing LNnT. Accordingly, our response should not be construed to be a statement that foods containing LNnT, if introduced or delivered for introduction into interstate commerce, would not violate section 301(l).

## 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 LNnT is GRAS under its intended conditions of use. This letter is not an affirmation that LNnT 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 001272 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

**Susan J.  
Carlson -S**

Digitally signed by Susan  
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