Christoph Röhrig, Ph.D.
Glycom A/S
Kogle Allé 4
2970 Hørsholm
DENMARK

Re: GRAS Notice No. GRN 000659

Dear Dr. Röhrig:

The Food and Drug Administration (FDA, we) completed our evaluation of the supplement that you submitted on behalf of Glycom A/S (Glycom) to GRN 000659. We received the supplement on July 29, 2021. The supplement addresses changes in the method of manufacture for the subject of GRN 000659. Glycom submitted information on December 1, 2021, December 2, 2021, and December 10, 2021, clarifying the updated literature search, manufacturing, and dietary exposure.

We previously responded to GRN 000659 on November 23, 2016. We stated that we had no questions at that time regarding Glycom's conclusion that lacto-N-neotetraose (LNnT) is GRAS for use as an ingredient in non-exempt infant formulas for term infants at a maximum use level of 600 mg/L and in beverages and beverage bases, dairy product analogs, milk (whole and skim), milk products, processed fruits and juices, grain products and pastas, infant foods, and toddler foods (including formulas for children >12 months of age) at use levels ranging from 0.02 to 0.68 g/serving. In the supplement dated July 26, 2021, Glycom informs us of its view that LNnT is GRAS, through scientific procedures, for the same uses described in GRN 000659.

In GRN 000659, Glycom describes the two-stage manufacturing process for LNnT that includes upstream (fermentation) and downstream (purification) processing. The first stage involves the production of LNnT by fermentation using the *Escherichia coli* K-12 MP572 production strain.[1] In this supplement, Glycom generates a secondary production strain, *E. coli* K-12 MP572b,[2] in which the plasmid-based β-1,4-galactosyltransferase gene and a transporter gene are integrated into the chromosome of the production strain. Additionally, Glycom deletes genes involved in mixed-acid fermentation. Glycom states that the second stage of the manufacturing process is the same as described in GRN 000659.

[1] We reviewed the available information and determined that *E. coli* K-12 is a non-pathogenic, non-toxigenic, and safe production strain when used in accordance with good manufacturing practices (55 FR 10932 at 10934; March 23, 1990). *E. coli* K-12 MDO (the parent strain of E. coli K-12 MP572) is derived from *E. coli* K-12 DH1, a nalidixic acid-resistant strain altered by seven genetic modifications.
[2] *E. coli* K-12 MP572b is equipped to biosynthesize LNnT using sucrose as the carbon source.

Glycom states that the specifications for LNnT produced using *E. coli* K-12 MP572b are the same as described in GRN 000659. Glycom provides the results of three non-consecutive batch analyses to demonstrate that LNnT can be manufactured to meet the specifications in GRN 000659. Glycom states that the changes to the production organism described in the supplement do not introduce unknown proteins, thus no new potential allergens, or result in new secondary metabolites or by-products in LNnT. In GRN 000659, Glycom provides dietary exposure estimates to LNnT based on the intended uses. In the supplement, Glycom states that the intended uses are the same; therefore, no changes in dietary exposure are expected.

Glycom conducted an updated literature search through July 2021 and discusses newer publications relevant to its safety conclusion, including studies conducted in healthy, term infants, pre-term infants, infants and children with allergies, and in older children and adults. Glycom states that upon review of these publications, it did not identify any data or information that would contradict the safety conclusion from GRN 000659.

Based on the totality of information discussed above, Glycom concludes that LNnT is GRAS for its intended use.

Standards of Identity

In the supplement, Glycom 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, & 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 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 Center for Food Safety and Applied Nutrition. The Office of Food Additive Safety 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.

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 Glycom's supplement 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 ONFL.

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 Glycom's supplement concluding that LNnT 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 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(ll).

Conclusions

Based on the information that Glycom provided, as well as other information available to FDA, we have no questions at this time regarding Glycom'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 the supplement to GRN 000659 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.12.22 09:54:46 -05'00'

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Director
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