James T. Heimbach, Ph.D., F.A.C.N.
JHeimbach LLC
923 Water Street #66
Port Royal, VA 22535

Re: GRAS Notice No. GRN 001127

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001127. We received the notice that you submitted on behalf of Danisco USA, Inc. (Danisco) on October 13, 2022, and filed it on May 10, 2023. Danisco submitted amendments to the notice on August 3, 2023, September 13, 2023, and November 14, 2023, that clarified the specifications, intended use, estimates of dietary exposure, and details of the literature search.

The subject of the notice is *Lactiplantibacillus plantarum* ATCC-202195[1] for use in non-exempt cow milk- or soy-based infant formula for term infants, non-exempt partially hydrolyzed cow milk-based infant formula for term infants, exempt extensively hydrolyzed cow milk-based infant formula for term infants, and formula for young children (>12 months) at a level up to 10^8 colony forming units (CFU)/g of powdered formula; in juices and drinks, cereal and grain products, ready-to-eat cereals, puffs and melts, and fruit and vegetable purees for infants and young children at a level up to 2 x 10^{10} CFU/serving; and in flavored milk beverages, dairy and non-dairy yogurt and smoothies, soy products, powdered meal replacement beverages, fruit juices and nectars, fruit-based beverages, candy, and cereal and nutrition bars at a level up to 2 x 10^{10} CFU/serving.[2] The notice informs us of Danisco's view that these uses of *L. plantarum* ATCC-202195 are GRAS through scientific procedures.

Danisco describes *L. plantarum* ATCC-202195 as a Gram-positive, obligate hetero-fermentative, lactic acid bacterium. Danisco states that the strain was isolated from human infant feces and is deposited in the American Type Culture Collection (ATCC). Danisco discusses the results of phenotypic and genotypic characterization used to confirm the strain identity and includes whole genome sequencing of *L. plantarum* ATCC-202195. Danisco discusses the results of genotypic and phenotypic analyses

[1] Danisco states that *Lactiplantibacillus plantarum* was formerly classified as *Lactobacillus plantarum*, as reported in Zheng, J., et al. (2020). A taxonomic note on the genus *Lactobacillus*: Description of 23 novel genera, emended description of the genus *Lactobacillus* Beijerinck 1901, and union of *Lactobacillaceae* and *Leuconostocaceae*. International Journal of Systematic and Evolutionary Microbiology, 70(4), 2782–2858. https://doi.org/10.1099/ijsem.0.004107

[2] Danisco states that *L. plantarum* ATCC-202195 is not intended for use in products under the jurisdiction of the U.S. Department of Agriculture or in food where standards of identity preclude its use.

performed on *L. plantarum* ATCC-202195 and concludes that the strain is non-pathogenic and non-toxigenic.

Danisco describes the manufacture of *L. plantarum* ATCC-202195 by fermentation of a pure culture under controlled conditions. Danisco states that the fermentation media does not contain allergens or substances derived from allergenic sources. After fermentation, the fermentate containing *L. plantarum* ATCC-202195 cells is cooled and concentrated by centrifugation. Cryoprotectants are added to the concentrate and the mixture is pelletized in liquid nitrogen. The pellets are then freeze dried, milled, and blended to obtain the final *L. plantarum* ATCC-202195 product. Danisco states that *L. plantarum* ATCC-202195 is manufactured under current good manufacturing practices using food grade materials that are approved for their respective uses.

Danisco provides specifications for *L. plantarum* ATCC-202195 that include total viable cell count (4.0 to 7.5 x 10^{11} CFU/g), and limits for microorganisms, including *Escherichia coli* (<3 CFU/10 g), *Cronobacter sakazakii* (absent in 25 g), *Salmonella* serovars (absent in 25 g), *Staphylococcus aureus* (<10 CFU/g), *Listeria monocytogenes* (absent in 25 g), and heavy metals, including lead (<0.05 mg/kg). Danisco provides the results from the analyses of three non-consecutive batches to demonstrate that *L. plantarum* ATCC-202195 can be manufactured to meet these specifications.

Danisco discusses the results of stability studies conducted with *L. plantarum* ATCC-202195 under controlled conditions. *L. plantarum* ATCC-202195 was stored in a foil sachet at 4 °C and at 25°C and 60% relative humidity over a 24-month period. Danisco concludes that the results of the studies demonstrate that *L. plantarum* ATCC-202195 is stable under the conditions tested. Danisco notes that the viability of microbial cultures used in processed food products may decrease during storage depending on the nature of the food matrix, water activity, and pH of the final product.

Danisco provides estimates of dietary exposure to *L. plantarum* ATCC-202195 based on the intended uses, food consumption data from the National Health and Nutrition Examination Survey (NHANES), and published estimates of food consumption. Based on 2015-2016 NHANES food consumption data for infant formula, Danisco estimates the 90th percentile dietary exposures for infants up to 6 months of age and infants aged 6 to 12 months to be 1.67 x 10^{10} and 1.48 x 10^{10} CFU/person (p)/day (d), respectively. Based on 2007-2016 NHANES food consumption data, Danisco estimates that children up to 2 years of age consume approximately six servings of food and two servings of beverages (as milk) per day that would result in a dietary exposure of 8 x 10^{10} CFU/p/d based on an assumption that half of these servings contain *L. plantarum* ATCC-202195 at the maximum use level. Alternatively, Danisco estimates the dietary exposure in children up to 2 years of age to be 6.7 x 10^{10} CFU/p/d based on assumptions that half of daily food servings contain *L. plantarum* ATCC-202195 and that daily beverage servings are formula for young children that contain *L. plantarum* ATCC-202195. Danisco also provides an estimate of dietary exposure to *L. plantarum* ATCC-202195 from its use in conventional foods based on the assumption that a healthy individual consumes approximately 20 servings of food per day and that half of those servings contain *L. plantarum* ATCC-202195 at the maximum use level. Danisco states that the maximum

dietary exposure to *L. plantarum* ATCC-202195 from use in conventional foods is 2 x 10^{11} CFU/p/d.

Danisco discusses publicly available data and information to support the safety of *L. plantarum* ATCC-202195, including the history of consumption of *L. plantarum* and other lactic acid bacteria in foods. Danisco presents data to demonstrate that *L. plantarum* AC-202195 does not produce antimicrobials or secondary metabolites that would pose a safety concern. Danisco notes that *L. plantarum* ATCC-202195 is resistant to aminoglycosides, but this resistance is a characteristic of most *Lactiplantibacillus* species due to the presence of certain enzymes. Danisco describes published toxicity studies on other strains of *L. plantarum* and notes that no significant safety concerns were identified, including potential translocation of bacteria. Danisco performed a literature search through October 2022 and notes that no serious adverse effects from consumption of *L. plantarum* were identified. Danisco describes published clinical studies with both infants and adults consuming *L. plantarum* ATCC-202195, as well as other strains of *L. plantarum*, and states that no adverse effects were reported.

Based on the totality of evidence, Danisco concludes that *L. plantarum* ATCC-202195 is GRAS for its intended use.

Standards of Identity

In the notice, Danisco states its intention to use *L. plantarum* ATCC-202195 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 *L. plantarum* ATCC-202195 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 Danisco's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an

infant formula containing *L. plantarum* ATCC-202195 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 Danisco's notice concluding that *L. plantarum* ATCC-202195 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 *L. plantarum* ATCC-202195. Accordingly, our response should not be construed to be a statement that foods containing *L. plantarum* ATCC-202195, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Danisco provided, as well as other information available to FDA, we have no questions at this time regarding Danisco's conclusion that *L. plantarum* ATCC-202195 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. plantarum* ATCC-202195 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 001127 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2024.02.01 14:19:00 -05'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition