Winnie Ng, Ph.D., DABT
Chr. Hansen A/S
Boege Alle 10-12
2970 Hoersholm
DENMARK

Re: GRAS Notice No. GRN 001113

Dear Dr. Ng:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001113. We received Chr. Hansen A/S (Chr. Hansen)'s notice on August 10, 2022, and filed it on March 20, 2023. Chr. Hansen submitted an amendment to the notice on March 26, 2023, that clarified the dietary exposure.

The subject of the notice is *Lactiplantibacillus plantarum* NCIMB 30562 for use as an ingredient in non-exempt infant formula for term infants[1] at a level up to 1.1 x 10^8 colony forming units (CFU)/g of powdered formula, as well as in conventional foods at levels up to 1.0 x 10^{11} CFU/serving.[2] The notice informs us of Chr. Hansen's view that this use of *L. plantarum* NCIMB 30562 is GRAS through scientific procedures.

Chr. Hansen describes *L. plantarum* NCIMB 30562 as a white to off-white powder. Chr. Hansen states that *L. plantarum* NCIMB 30562[3] is a Gram-positive, non-spore forming, catalase-negative, non-motile, non-pathogenic, and non-toxigenic bacterium. The strain was isolated from a human infant and is deposited in the National Collection of Industrial, Food, and Marine Bacteria (NCIMB) culture collection under accession number NCIMB 30652. Chr. Hansen discusses the results of phenotypic and genotypic characterization used to confirm the strain identity and states that they performed whole genome sequencing of *L. plantarum* NCIMB 30562. Chr. Hansen states that *L. plantarum* NCIMB 30562 contains one plasmid and that the strain does not contain any antibiotic resistance genes.

Chr. Hansen describes the manufacture of *L. plantarum* NCIMB 30562 by fermentation

[1] Chr. Hansen states that the use of *L. plantarum* NCIMB 30562 in infant formula is not restricted to any specific protein base (e.g., cow milk-based, soy-based, etc.).
[2] Chr. Hansen states that *L. plantarum* NCIMB 30562 is not intended for use in products under the U.S. Department of Agriculture's jurisdiction.
[3] Chr. Hansen notes that recent taxonomic changes to the genus *Lactobacillus* includes the nomenclature of this organism from *Lactobacillus plantarum* to *Lactiplantibacillus plantarum* (Zheng et al., 2020).

of a pure culture under controlled conditions and states that *L. plantarum* NCIMB 30562 is manufactured under current good manufacturing practices with food-grade raw materials suitable for human consumption. After fermentation, the *L. plantarum* NCIMB 30562 cells are harvested from the fermentation medium by centrifugation to remove water-soluble material and to concentrate the cells. Chr. Hansen states that food-safe cryoprotectants are added to the concentrated cell mixture that is then frozen, lyophilized, and ground. Chr. Hansen notes that powdered *L. plantarum* NCIMB 30562 can be sold as-is, or blended with other food-grade microbial ingredients, carriers, or food-grade materials appropriate for their intended use.

Chr. Hansen provides specifications for *L. plantarum* NCIMB 30562 that include limits for *L. plantarum* NCIMB 30562 ($\geq 4 \times 10^{11}$ CFU/g), lead (<0.05 mg/kg), and other microorganisms, including yeast and mold (<10 CFU/g); *Enterobacteriaceae* and *Cronobacter* spp. (both negative in 10 g); and *Salmonella* serovars and *Listeria* spp. (both negative in 25 g). Chr. Hansen provides the results of three non-consecutive batch analyses to demonstrate that *L. plantarum* NCIMB 30562 can be manufactured to meet these specifications.

Chr. Hansen provides an estimate of dietary exposure to *L. plantarum* NCIMB 30562 in conventional foods based on the assumption that a healthy individual consumes ~20 servings/d of *L. plantarum* NCIMB 30562-containing foods. Chr. Hansen states that the maximum use level of *L. plantarum* NCIMB 30562 is 10^{11} CFU/serving; however, the typical use level is 10^{9} CFU/serving. Therefore, Chr. Hansen states that the maximum dietary exposure attributed to use in conventional foods is 2.0×10^{10} CFU/person (p)/d. Chr. Hansen also provides estimates of dietary exposure to *L. plantarum* NCIMB 30562 from consuming infant formula based on the maximum intended use level of 1.1×10^{8} CFU/g of powdered formula, published estimates of caloric requirements for infants, and a reconstitution rate of 14.1 g/100 mL for infant formula with a caloric density of 0.67 kcal/mL. Chr. Hansen reports the maximum dietary exposures to be 2.0×10^{10} CFU/p/d for male infants and 1.8×10^{10} CFU/p/d for female infants.

Chr. Hansen discusses data and information used to support the safety of *L. plantarum* NCIMB 30562, including a history of safe use of *L. plantarum* in fermented foods and dairy products. Chr. Hansen cites published clinical studies in which infants, children, and adults ingested other strains of *L. plantarum* and states that the species was well tolerated. Chr. Hansen discusses data showing that *L. plantarum* NCIMB 30562 does not have hemolytic activity, is non-cytotoxic, and does not produce biogenic amines.

Based on the totality of the data and information, Chr. Hansen concludes that *L. plantarum* NCIMB 30562 is GRAS for its intended use.

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 *L. plantarum* NCIMB 30562 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 (OFAS) 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. *L. plantarum* NCIMB 30562 may require labeling under the FD&C Act because it may contain protein derived from milk from the fermentation process. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in OFAS. Questions related to food labeling in general should be directed to ONFL.

Infant Formula

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 Chr. Hansen's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *L. plantarum* NCIMB 30562 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 Chr. Hansen's notice concluding that *L. plantarum* NCIMB 30562 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* NCIMB 30562. Accordingly, our response should not be construed to be a statement that foods containing *L. plantarum* NCIMB 30562, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Chr. Hansen provided, as well as other information

available to FDA, we have no questions at this time regarding Chr. Hansen's conclusion that *L. plantarum* NCIMB 30562 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. plantarum* NCIMB 30562 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 001113 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.07.20 16:51:20 -04'00'

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