Kate Urbain
Chr. Hansen, Inc.
9015 West Maple Street
Milwaukee, WI 53214-4298

Re: GRAS Notice No. GRN 001013

Dear Ms. Urbain:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001013. We received Chr. Hansen, Inc. (Chr. Hansen)'s notice on June 24, 2021, and filed it on September 1, 2021.[1] Chr. Hansen submitted amendments on October 29, 2021, November 23, 2021, and December 2, 2021, that clarified the manufacturing and specifications.

The subject of the notice is *Lactobacillus rhamnosus* DSM 33156 for use as an ingredient in conventional foods[2] at a maximum use level of 1.0×10^{11} colony forming units (CFU)/serving and in cow milk-, soy milk-, and partially hydrolyzed protein-based, non-exempt infant formula for term infants at a use level of 1.0×10^{8} CFU/g. The notice informs us of Chr. Hansen's view that these uses of *L. rhamnosus* DSM 33156 are GRAS through scientific procedures.

Chr. Hansen describes *L. rhamnosus* DSM 33156 as a Gram-positive, non-motile, non-spore forming, rod-shaped bacterium. *L. rhamnosus* DSM 33156 was isolated from the human gut and is deposited in the German Collection of Microorganisms and Cell Cultures (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH) under the accession number DSM 33156. Chr. Hansen discusses the results of phenotypic and genotypic characterization to confirm strain identity and states that *L. rhamnosus* DSM 33156 is non-pathogenic and non-toxigenic, is not genetically engineered, does not produce biogenic amines, and does not carry any transposable elements that could be transferred to the commensal microbiome.

Chr. Hansen describes the manufacture of *L. rhamnosus* DSM 33156 by fermentation of a pure culture under controlled conditions. After fermentation, the *L. rhamnosus* DSM 33156 cells are separated from the medium and concentrated by centrifugation. Chr.

[1] In an update provided to us on August 31, 2021, Chr. Hansen noted that the representative who signed the original notice no longer works for the company and Ms. Urbain would be the new signee on the notice.
[2] In the October 29, 2021, amendment, Chr. Hansen clarified that *L. rhamnosus* DSM 33156 uses do not include categories where standards of identity apply.

Hansen states that cryoprotectants (i.e., carbohydrates and amino acids) are added to the concentrated cell mixture that is then frozen into pellets and lyophilized. Chr. Hansen states that *L. rhamnosus* DSM 33156 is manufactured under current good manufacturing practices with food-grade raw materials that comply with FDA regulations for such use. Chr. Hansen notes that milk may be used in the fermentation medium, and the final product may contain milk allergens. Chr. Hansen states that it also manufactures dairy-free forms of *L. rhamnosus* DSM 33156.

Chr. Hansen provides specifications for *L. rhamnosus* DSM 33156 in conventional foods that include limits for total cell count (≥ 5×10^{10} CFU/g), *Enterobacteriaceae* (< 1 CFU/g), coagulase-positive staphylococci (< 1 CFU/g), yeasts and molds (< 1 CFU/g), *Salmonella* serovars (absent in 25 g), and lead (≤ 0.05 mg/kg). Chr. Hansen provides specifications for *L. rhamnosus* DSM 33156 in infant formula that include limits for total cell count (> 1.7×10^{10}), *Enterobacteriaceae* (absent in 10 samples of 10 g each), *Bacillus cereus* (< 100 CFU/g), *Cronobacter* spp. (absent in 10 samples of 10 g each), *Staphylococcus aureus* (< 10 CFU/g), yeasts and mold (≤ 100 CFU/g), *Salmonella* serovars (absent in 10 samples of 10 g each), and lead (≤ 0.05 mg/kg). Chr. Hansen provides the results of three non-consecutive batch analyses for microorganisms and lead to demonstrate that *L. rhamnosus* DSM 33156 can be manufactured to meet these specifications.

Chr. Hansen estimates the dietary exposure to *L. rhamnosus* DSM 33156 from the intended use in conventional foods to be a maximum of 1.0×10^{11} CFU/d based on the assumption that a healthy individual consumes 20 servings/d of *L. rhamnosus* DSM 33156-containing foods. Chr. Hansen estimates the dietary exposure to *L. rhamnosus* DSM 33156 from the intended use in infant formula to be 9.9×10^{9} CFU/d for infants 1 month of age and 1.4×10^{10} CFU/d for infants 6 months of age, based on the intended use level, published caloric requirements for infants 1 and 6 months of age, and a reconstitution rate of 14.1 g/100 mL for infant formula with a caloric density of 0.67 kcal/mL.

Chr. Hansen discusses data and information used to support the safety of *L. rhamnosus* DSM 33156, including a history of safe use of *L. rhamnosus* DSM 33156 in dairy products and infant formulas in European markets. Chr. Hansen incorporates into the notice summaries of surveillance studies from GRN 000231[3] showing that no increases in *Lactobacillus* bacteremia were evident with increased *L. rhamnosus* DSM 33156 consumption. Chr. Hansen also discusses newly published reports of adverse events associated with consuming *L. rhamnosus* DSM 33156 and incorporates into the notice previous adverse case reports from GRN 000231. Chr. Hansen concludes that adverse events were rare and occurred only in subjects with an underlying disease or health condition. Chr. Hansen also states that *L. rhamnosus* DSM 33156 is recognized by the European Food Safety Authority with a Qualified Presumption of Safety.

Based on the totality of the data and information, Chr. Hansen concludes that *L.*

[3] *Lactobacillus casei* subsp. *rhamnosus* strain GG was the subject of GRN 000231. We evaluated this notice and responded in a letter dated May 29, 2008, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

rhamnosus DSM 33156 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. rhamnosus* DSM 33156 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.

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 (effective January 1, 2023)) or a food ingredient that contains protein derived from one of those foods. *L. rhamnosus* DSM 33156 requires labeling under the FD&C Act because it contains protein derived from milk.

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 Chr. Hansen's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *L. rhamnosus* DSM 33156 to make the submission required by section 412. Infant formulas are the purview of the 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. rhamnosus* DSM 33156 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. rhamnosus* DSM 33156. Accordingly, our response should not be construed to be a statement that foods containing *L. rhamnosus* DSM 33156, 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. rhamnosus* DSM 33156 is GRAS under its intended conditions of use. This letter is not an affirmation that *L. rhamnosus* DSM 33156 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 001013 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.12.15 16:25:01 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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and Applied Nutrition