



Emily Gregoire  
Chr. Hansen, Inc.  
9015 West Maple Street  
Milwaukee, WI 53214

Re: GRAS Notice No. GRN 000950

Dear Ms. Gregoire:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000950. We received Chr. Hansen, Inc. (Chr. Hansen)'s notice on June 2, 2020, and filed it on October 1, 2020.<sup>1</sup> Chr. Hansen submitted amendments to the notice on December 9, 2020,<sup>2</sup> and January 13, 2021, that clarified the specifications, manufacturing, dietary exposure, literature cited, and removed all confidential information and markings.

The subject of the notice is *Bifidobacterium longum* subsp. *infantis* DSM 33361 (*B. longum* DSM 33361) for use as an ingredient in cow milk-, soy-, and partially hydrolyzed protein-based, non-exempt infant formula for term infants at a level up to  $1 \times 10^{10}$  colony forming units (CFU)/g, and in conventional foods, including but not limited to milk and dairy products; plant-based dairy alternatives; beverages; bars; confectionery; and cereals and at a use level up to  $2.8 \times 10^{10}$  CFU/serving. The notice informs us of Chr. Hansen's view that these uses of *B. longum* DSM 33361 are GRAS through scientific procedures.

Chr. Hansen describes *B. longum* DSM 33361<sup>3</sup> as a light beige, finely ground powder. The notice describes *B. longum* DSM 33361 as a Gram-positive, non-motile bacterium that is long, curved, and irregularly shaped; it is deposited in the German Collection of Microorganisms and Cell Cultures (Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH) under the accession number DSM 33361. Chr. Hansen discusses the results of phenotypic and genotypic characterization to confirm strain identity and states that *B. longum* DSM 33361 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.

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<sup>1</sup> Chr. Hansen clarified information on the intended infant formula protein base in an update on October 1, 2020.

<sup>2</sup> Chr. Hansen submitted the December 9, 2020, amendment with confidential markings. In the January 13, 2021, amendment, Chr. Hansen removed the confidential markings and used publicly available data only to respond to FDA's questions.

<sup>3</sup> FDA notes that *B. longum* is a member of the lactic acid bacteria (LAB) classification, a group characterized by the production of lactic acid as the major end-product of carbohydrate metabolism and by other common physiological traits.

Chr. Hansen describes the manufacture of *B. longum* DSM 33361 by fermentation of a pure culture under controlled conditions. After fermentation, the *B. longum* DSM 33361 cells are separated from the medium and concentrated by centrifugation. Chr. Hansen states that cytoprotectants (i.e., carbohydrates and amino acids) are added to the concentrated cell mixture that is then lyophilized and milled to a powder. Chr. Hansen states that *B. longum* DSM 33361 is manufactured under current good manufacturing practices with food-grade raw materials that comply with FDA regulations for such use. Chr. Hansen notes that skimmed milk powder 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 *B. longum* DSM 33361.

Chr. Hansen provides specifications for *B. longum* DSM 33361 that include limits for total aerobic bacteria ( $\leq 2000$  CFU/g), yeast and mold ( $\leq 100$  CFU/g), *Enterobacteriaceae* (absent in 10 g), *Staphylococcus aureus* (absent in 0.1 g), *Bacillus cereus* ( $< 100$  CFU/g), *Salmonella* serovars (absent in 10 g), *Cronobacter* spp. (absent in 10 g), and heavy metals, including lead ( $< 0.05$  mg/kg). Chr. Hansen provides the results of three and four non-consecutive batch analyses for heavy metals and microorganisms, respectively, to demonstrate that the *B. longum* DSM 33361 can be manufactured to meet these specifications.

Chr. Hansen estimates the dietary exposure to *B. longum* DSM 33361 from consuming infant formula to be  $1.18 \times 10^{12}$  CFU/day based on the intended use level, published estimates of infant formula consumption by infants 0 to 6 months of age, and a reconstitution rate of 14.1 g powder/100 mL of formula as consumed. Chr. Hansen estimates the dietary exposure to *B. longum* DSM 33361 from consuming conventional foods to be approximately  $1 \times 10^{11}$  CFU/day based on the assumption that the number of servings of *B. longum* DSM 33361-containing foods consumed by healthy individuals is half of the approximately 20 servings of all combined food consumed per day.

Chr. Hansen discusses data and information used to support the safety of *B. longum* DSM 33361, including a history of safe use of *Bifidobacterium* spp. in fermented milks and food products. Additionally, *Bifidobacteria* occur naturally in food and in the digestive tract of humans. Chr. Hansen provides summaries of published clinical trials in which infants and adults consumed *B. infantis* and states that the results of these clinical studies suggest *B. infantis* is well-tolerated and unlikely to cause adverse effects. Based on published literature, Chr. Hansen concludes that infections with *Bifidobacterium longum* subsp. *infantis* are rare and that the risk from consuming *Bifidobacteria*-containing products is negligible; this includes consumers who are immunocompromised. Chr. Hansen also states that *B. infantis* 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 *B. longum* DSM 33361 is GRAS for its intended use.

## **Standards of Identity**

In the notice, Chr. Hansen states its intention to use *B. longum* DSM 33361 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 *B. longum* DSM 33361 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 eight foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, and soybeans) or a food ingredient that contains protein derived from one of those foods. *B. longum* DSM 33361 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 (DFI) in OFAS. Questions related to food labeling in general 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 Chr. Hansen’s GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. longum* DSM 33361 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 *B. longum* DSM 33361 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 *B. longum* DSM 33361. Accordingly, our response should not be construed to be a statement that foods containing *B. longum* DSM 33361, 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 *B. longum* DSM 33361 is GRAS under its intended conditions of use. This letter is not an affirmation that *B. longum* DSM 33361 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 000950 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Susan J. Carlso

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Susan Carlson, Ph.D.

Director

Division of Food Ingredients

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

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