



Jayne Chalfin Davies  
Global Regulatory Affairs  
Danisco, USA Inc.  
DuPont Experimental Station – E320  
200 Powder Mill Road  
Wilmington, DE 19803

Re: GRAS Notice No. GRN 000985

Dear Ms. Davies:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000985. We received Danisco USA, Inc.'s (Danisco's)<sup>1</sup> notice on December 15, 2020 and filed it on April 7, 2021. Danisco submitted amendments to the notice on June 23, 2021, July 8, 2021, and September 1, 2021 that provided clarification on the identity of the strain, specifications, methods used to ensure conformance to the specifications, additional data on the dietary exposure, and an updated literature search.

The subject of the notice is *Bifidobacterium longum* subsp. *infantis* strain ATCC SD 6720 (*B. longum* ATCC SD 6720) for use as an ingredient in cow milk- and soy-based, non-exempt powdered infant formula for term infants and powdered toddler formula<sup>2</sup> at a use level up to 10<sup>8</sup> colony forming units (CFU)/g of powdered formula. The notice informs us of Danisco's view that this use of *B. longum* ATCC SD 6720 is GRAS through scientific procedures.

Danisco describes *B. longum* ATCC SD 6720 as a white to cream powder. Danisco states that *B. longum* ATCC SD 6720 is a Gram-positive, non-pathogenic, non-toxicogenic, non-motile, non-spore forming, rod or Y-shaped bacterium. The strain was isolated from a human and is deposited in the strain collection of the American Type Culture Collection (ATCC) in Manassas, Virginia. Danisco discusses the results of the phenotypic and genotypic characterization used to confirm the strain's identity.

Danisco describes the manufacture of *B. longum* ATCC SD 6720 by batch fermentation of a pure culture under controlled conditions. Once the fermentation enters the stationary phase, the fermenter is cooled to stop the fermentation process. The cooled

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<sup>1</sup>When the notice was submitted, the notifier was doing business as DuPont Nutrition and Biosciences (DuPont). In an email received on April 1, 2021, the notifier explained that DuPont has since been acquired by International Flavors & Fragrances Inc. (IFF), that Danisco USA, Inc. (Danisco) is owned by IFF, and the notifier's current affiliation is as Danisco.

<sup>2</sup> While we do not have a regulatory definition for "toddler formula," we recognize it as formula intended for children > 12 months of age. Formulas for older infants (e.g., 9-12 months of age) would be included in the category of infant formula and must comply with the infant formula regulations under Section 412 of the Federal Food, Drug, and Cosmetic Act.

fermentate is centrifuged to concentrate the bacterial culture and to remove the fermentation medium. Following this, cryoprotectant is added to the cooled, concentrated bacterial culture and the mixture is then pelletized by immersing droplets of concentrate into liquid nitrogen. The resulting pellets are then freeze-dried, milled to a powder, and blended with food-grade excipients. Danisco states that the manufacturing process is monitored for contamination, and that *B. longum* ATCC SD 6720 is manufactured under current good manufacturing practices using food-grade materials. Danisco states that no components of the fermentation media are allergens or are derived from allergenic sources.

Danisco provides specification for *B. longum* ATCC SD 6720 that include viable cell count ( $\geq 5 \times 10^{10}$  CFU/g), and limits for other microorganisms, including non-lactic cell count ( $< 5,000$  CFU/g), yeast and mold ( $< 100$  CFU/g), *Enterococcus* spp. ( $< 100$  CFU/g), coliforms (negative by test ( $< 10$  most probable number (MPN)/g)), *Escherichia coli* (negative by test ( $< 0.3$  MPN/g)), coagulase-positive *Staphylococcus* spp. (negative by test ( $< 10$  CFU/g)), *Listeria* spp. (absent in 25 g), *Cronobacter sakazakii* (absent in 25 g), and *Salmonella* serovars (absent in 40 g), and heavy metals, including lead ( $< 0.5$  mg/kg). Danisco provides the results from the analyses of four<sup>3</sup> non-consecutive batches to demonstrate that the ingredient can be manufactured to conform with the provided specifications.

Danisco estimates dietary exposure to *B. longum* ATCC SD 6720 for infants ( $< 12$  months of age) and toddlers by assuming use levels up to  $10^8$  CFU/g of powdered formula, addition of 13.5 g powder per 100 mL prepared formula, published estimates of intake of infant formula, and estimates of intake of infant and toddler formula reported in an earlier submission (GRN 000952)<sup>4</sup> based on 2015-2016 National Health and Nutrition Examination Survey data. Using estimated mean and 90<sup>th</sup> percentile daily formula intakes of 800 mL and 1240 mL, respectively, for infants 0-6 months of age, the highest consumers of infant formula, Danisco estimates dietary exposure would be approximately  $10^9$ - $10^{10}$  CFU/d at the mean and up to  $1.7 \times 10^{10}$  CFU/d at the 90<sup>th</sup> percentile.

Danisco explains that bifidobacteria are found in human food and are common colonizers of the human body. Danisco states that *B. longum* ATCC SD 6720 does not produce antibiotics. Danisco further states that *in vitro* data showed no significant findings for safety-related issues associated with the strain (i.e., antibiotic resistance, bacterial virulence, biogenic amine production, and D-lactic acid production). Danisco summarizes and discusses an acute animal study in which no toxicologically relevant findings associated with *B. longum* ATCC SD 6720 were reported. Danisco discusses the long history of safe use of *B. longum* in human foods. Danisco cites publications that support the safe consumption of *B. longum* and *B. longum* subsp. *infantis*, including peer-reviewed scientific journals and governmental reviews. Additionally, Danisco

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<sup>3</sup> Danisco provides the results from three additional batch analyses, including analysis of *C. sakazakii*, in the July 8, 2021 amendment to the notice.

<sup>4</sup> GRN 000952 was for the use of *Bifidobacterium animalis* species in infant formula and in some conventional foods. We evaluated this notice and responded in a letter dated March 17, 2021, stating that we had no questions at the time regarding the notifier's GRAS conclusion.

performed a literature search through June 2021 and summarizes published clinical studies in which infants, children, and adults were fed *B. longum* subsp. *infantis*. Danisco notes that bacteremia was reported in some preterm infants with extremely low birth weight or major gastrointestinal or immunocompromising disorders. However, aside from these cases in at-risk populations, the clinical studies reported no treatment-related adverse effects, and Danisco states that infections associated with bifidobacteria are rare.

Danisco includes the report of a panel of individuals (Danisco's GRAS panel). Based on its review, Danisco's GRAS panel concluded that *B. longum* ATCC SD 6720 is safe under the conditions of its intended use.

Based on the totality of evidence, Danisco concludes that *B. longum* ATCC SD 6720 is GRAS for its intended use.

### **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 *B. longum* ATCC SD 6720 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 *B. longum* ATCC SD 6720 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 *B. longum* ATCC SD 6720 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* ATCC SD 6720. Accordingly, our response should not be construed to be a statement that foods containing *B. longum* ATCC SD 6720, 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 *B. longum* ATCC SD 6720 is GRAS under its intended conditions of use. This letter is not an affirmation that *B. longum* ATCC SD 6720 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 000985 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).

Sincerely,

Susan J.

Carlson -S

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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