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

Re: GRAS Notice No. GRN 001107

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001107. We received the notice that you submitted on behalf of Nestlé Nutrition (Nestlé) on September 7, 2022 and filed it on March 2, 2023.[1] Nestlé submitted amendments to the notice on June 29, 2023 and September 25, 2023 that provided revised specifications and clarification on the processing aids used during manufacturing, intended uses, and estimates of dietary exposure.

The subject of the notice is *Bifidobacterium longum* subsp. *infantis* LMG 11588 for use as an ingredient in cow milk-, goat milk-, soy-, and partially hydrolyzed whey protein-based non-exempt[2] powdered infant formula for term infants and powdered formula-type drinks for young children (1-3 years of age) at a level up to 1.2 x 10^8 colony forming units (CFU)/g of powder. The notice informs us of Nestlé's view that these uses of *B. longum* subsp. *infantis* LMG 11588 are GRAS through scientific procedures.

Nestlé discusses the identity and characterization of *B. longum* subsp. *infantis* LMG 11588 and describes it as a creamy beige powder. Nestlé states that *B. longum* subsp. *infantis* LMG 11588 is a Gram-positive, irregular rod-shaped, strictly anaerobic, heterofermentative, non-motile, and non-sporulating bacterium that is non-toxigenic and non-pathogenic. Nestlé discusses the initial isolation of *B. longum* subsp. *infantis* LMG 11588 from a two-month-old, breast-fed infant. Nestlé states that *B. longum* subsp. *infantis* LMG 11588 is deposited in the Belgian Coordinated Collection of Microorganisms (BCCM/LMG).[3] Nestlé states that 16S rDNA sequencing, Matrix Assisted Laser Desorption Ionization-Time of Flight (MALDI-TOF) mass spectrometry profiling, and whole genome sequencing was conducted to confirm the identity of *B. longum* subsp. *infantis* LMG 11588.

Nestlé describes the manufacturing process for *B. longum* subsp. *infantis* LMG 11588, stating that it is produced by fermentation under controlled conditions. Nestlé explains that after fermentation, the bacterial biomass is separated from the fermentation

[1] Nestlé clarified the intended use in non-exempt infant formula in an email dated February 22, 2023.
[2] FDA notes that non-exempt infant formula is intended for use by healthy, term infants; https://www.fda.gov/media/87996/download.
[3] Nestlé notes that *B. longum* subsp. *infantis* LMG 11588 is also deposited in other collections, including the American Type Culture Collection (ATCC) under ATCC 17930.

medium via centrifugation. Nestlé states that safe and suitable formulating agents are added, and the biomass is then spray-dried. The powder is standardized with corn maltodextrin. Nestlé states that all processing aids used in the manufacture of *B. longum* subsp. *infantis* LMG 11588 are used in accordance with applicable U.S. regulations or are GRAS for their intended uses.

Nestlé provides specifications for *B. longum* subsp. *infantis* LMG 11588 that include a minimum level of *B. longum* subsp. *infantis* LMG 11588 (>4.0 x 10^{10} CFU/g); and limits for heavy metals, including lead (<0.01 mg/kg); and microorganisms, including yeast and molds (< 1000 CFU/g), *Salmonella* serovars (negative in 10 g), *Listeria monocytogenes* (negative in 25 g), and *Cronobacter* spp. (negative in 10 g). Nestlé provides the results from the analyses of three non-consecutive batches to demonstrate that *B. longum* subsp. *infantis* LMG 11588 can be manufactured to meet these specifications. Nestlé states that *B. longum* subsp. *infantis* LMG 11588 is stable for up to one year when stored at 12 °C.

Nestlé provides an estimate of dietary exposure to *B. longum* subsp. *infantis* LMG 11588 in infant formula and formula-type drinks for young children based on the maximum intended use level of 1.2 x 10^8 CFU/g powder, published estimates of energy intake for infants,[4] and unpublished estimates of milk consumption for young children.[5] Nestlé estimates the maximum dietary exposure to *B. longum* subsp. *infantis* LMG 11588 for infants 0-12 months of age to be 3.6 x 10^9 CFU/kg body weight (bw)/d, based on an infant population (14-27 days of age) with the highest reported energy intakes per kg of body weight (141.3 and 138.9 kcal/kg bw/d for males and females, respectively) from consumption of infant formula, and assuming a level of addition of 14.7 g powder/100 mL prepared term infant formula and a caloric density of 67.6 kcal/100 mL for term infant formula. Nestlé estimates the maximum dietary exposure to *B. longum* subsp. *infantis* LMG 11588 from formula-type drinks to be 9.8 x 10^9 CFU/p/d, based on estimates of daily milk consumption (up to 552 g/p/day or 18.1 ounces/p/day for children ages 1-3 years), the assumption that formula-type drinks for young children will be consumed as substitutes for fluid milk, and a level of addition of 36 g powder per 8 ounces water to prepare formula-type drinks for young children. Nestlé notes that, for a one-year-old child weighing 8.1 kg, the corresponding estimate of dietary exposure is 1.2 x 10^9 CFU/kg bw/d.

Nestlé discusses data and information used to support the safety of *B. longum* subsp. *infantis* LMG 11588. Nestlé cites published clinical studies in which infants and children ingested closely related strains of *B. longum* subsp. *infantis* and states that no serious adverse events were reported. Nestlé also cites a published clinical study in which infants ingested *B. longum* subsp. *infantis* LMG 11588 and states that it was well tolerated. Nestlé discusses the results of *in vitro* analyses, stating that *B. longum* subsp. *infantis* LMG 11588 is sensitive to antibiotics of human and veterinary importance. Nestlé discusses data showing that *B. longum* subsp. *infantis* LMG 11588 does not produce biogenic amines or D-lactate.

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[4] Fomon, SJ (1993) Energy intake by normal infants. In: Nutrition of Normal Infants. Mosby, St. Louis, MO: pp. 104-111.

[5] Nestlé's Feeding Infants and Toddlers Study (FITS), 2016 (unpublished).

Based on the totality of the data and information, Nestlé concludes that *B. longum* subsp. *infantis* LMG 11588 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* subsp. *infantis* LMG 11588 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 Nestlé's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. longum* subsp. *infantis* LMG 11588 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 Nestlé's notice concluding that *B. longum* subsp. *infantis* LMG 11588 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* subsp. *infantis* LMG 11588. Accordingly, our response should not be construed to be a statement that foods containing *B. longum* subsp. *infantis* LMG 11588, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Nestlé provided, as well as other information available to FDA, we have no questions at this time regarding Nestlé's conclusion that *B. longum* subsp. *infantis* LMG 11588 is GRAS under its intended conditions of use. This letter is

not an affirmation that *B. longum* subsp. *infantis* LMG 11588 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 001107 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.11.15 18:00:48 -05'00'

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