Claire L. Kruger, Ph.D.
Spherix Consulting Group, Inc.
11821 Parklawn Drive
Suite 310
Rockville, MD 20852

Re: GRAS Notice No. GRN 000877

Dear Dr. Kruger:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000877. We received the notice that you submitted on behalf of Morinaga Milk Industry Co., Ltd. (Morinaga) on July 25, 2019, and filed it on August 26, 2019. Morinaga submitted amendments to the notice on October 28, 2019, November 8, 2019, and November 13, 2019, providing additional manufacturing specifications and clarification on the intended use.

The subject of the notice is *Bifidobacterium longum* strain BB536 (*B. longum* BB536) for use as an ingredient in non-exempt milk, soy, or whey-based powdered infant formula for term infants at a level of 1×10^8 colony forming units (CFU) per gram of infant formula powder. The notice informs us of Morinaga's view that this use of *B. longum* BB536 is GRAS through scientific procedures.

Morinaga describes *B. longum* BB536 as a white to slightly brown powder. Morinaga states that *B. longum* BB536[1] is a Gram-positive, non-motile, non-spore forming, rod or Y-shaped bacterium, which is deposited in the strain collection of the American Type Culture Collection and is designated as BAA-999. Morinaga states that *B. longum* BB536 is non-pathogenic and non-toxigenic. Morinaga discusses the results of phenotypic and genotypic characterization used to confirm the strain's identity. Bifidobacteria occur naturally in food and in the digestive tract of humans.

Morinaga describes the manufacture of *B. longum* BB536 by fermentation of a pure culture under controlled conditions. After fermentation, the medium is concentrated by centrifugation, washed, re-concentrated, lyophilized and milled to a powder. The resulting powder is mixed with cornstarch as a carrier to yield the final product. Morinaga states that *B. longum* BB536 is manufactured with food-grade materials that comply with FDA regulations for such use under current good manufacturing practices.

[1] 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 metabolic end-product of carbohydrate metabolism and other physiological traits.

Morinaga provides specifications for *B. longum* BB536, including appearance (white to slightly brown powder), moisture (< 6 g/100 g), casein (< 10 mg/kg), β-lactoglobulin (< 10 mg/kg), cell count as *B. longum* BB536 (> 8.0 x 10^{10} CFU/g), total aerobic bacteria (< 300 CFU/g), yeast and mold (< 30 CFU/g each), *Enterobacteriaceae* (absent in 10 g)[2], *Staphylococcus aureus* (absent in 0.01 g), *Salmonella* serovars (absent in 25 g), *Cronobacter sakazakii* (absent in 25 g) and lead (< 0.5 mg/kg), arsenic (< 1 mg/kg), cadmium (< 0.5 mg/kg), and mercury (< 0.1 mg/kg). Morinaga provides the results of batch analyses for six non-consecutive lots to demonstrate that the product can be manufactured to conform with the provided specifications.

Morinaga intends to use *B. longum* BB536 as an ingredient in non-exempt milk, soy, or whey-based powdered infant formula for term infants at a level that results in a daily dietary exposure of 10^9 to 10^{10} CFU/day (d). Morinaga estimates dietary exposure for infants by assuming that the average caloric requirements of one-month old infants and six-month old infants are 472 kilocalories per day (kcal/d) and 645 kcal/d, respectively, and that infant formulas provide a caloric density of 0.67 kcal/mL of infant formula. Morinaga then assumes that the powdered infant formula is reconstituted at a rate of 14.1 g/100 mL and states that the addition of 1 x 10^8 CFU *B. longum* BB536 per gram of powdered infant formula will result in daily exposures of 9.9 x 10^9 CFU/d for a one-month old infant and 1.35 x 10^{10} CFU/d for a six-month old infant.

Morinaga discusses the long history of safe use of LAB in foods and how *Bifidobacterium* genera have been safely used in fermented foods. Morinaga states that the literature and information supporting safety of *B. longum* BB536 has been previously evaluated in GRN 000268[3] and is incorporated into GRN 000877. Morinaga conducted a literature search through February 2019 and discusses additional, published clinical studies in infants and toddlers (12 studies) and in children and adults (3 studies), as well as one animal study conducted with *B. longum* BB536. Morinaga concludes that these data and information support the safety of *B. longum* BB536 for the intended use.

Based on the totality of evidence, Morinaga concludes that *B. longum* BB536 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* BB536 bear any nutrient content or health claims on the label or in labeling,

[2] In the October 28, 2019, amendment to the notice, the notifier states that the microbiological specifications for *Enterobacteriaceae* (absent in 10 g) is inclusive of *Escherichia coli*.

[3] We evaluated GRN 000268 and responded in a letter dated July 8, 2009, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

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 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* BB536 may require labeling under the FD&C Act because it may contain protein derived from milk (in GRN 000268, which was incorporated into this notice, Morinaga states that the original isolate of *B. longum* BB536 was resuspended in 10% reconstituted skim milk). Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in the Office of Food Additive Safety. Questions related to food labeling in general should be directed to the Office of Nutrition and Food Labeling in the Center for Food Safety and Applied Nutrition.

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 Morinaga's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. longum* BB536 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 Morinaga's notice concluding that *B. longum* BB536 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* BB536. Accordingly, our response should not be construed to be a statement that foods containing *B. longum* BB536, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Morinaga provided, as well as other information available to FDA, we have no questions at this time regarding Morinaga's conclusion that *B. longum* BB536 is GRAS under its intended conditions of use. This letter is not an affirmation that *B. longum* BB536 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 000877 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2019.12.26 10:37:14 -05'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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