Claire L. Kruger, PhD, DABT
Spherix Consulting Group
751 Rockville Pike, Unit 30-B
Rockville, MD 20852

Re: GRAS Notice No. GRN 001003

Dear Dr. Kruger:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001003. We received the notice that you submitted on behalf of Morinaga Milk Industry Co., Ltd. (Morinaga) on April 29, 2021, and filed it on July 15, 2021. Morinaga submitted amendments to the notice on January 14, 2022, February 28, 2022, and March 22, 2022, that provided additional information on identity, intended uses, specifications, analytical methods, and estimated dietary exposure.

The subject of the notice is *Bifidobacterium longum* subsp. *infantis* M-63 (*B. infantis* M-63) for use as an ingredient in non-exempt cow milk- and soy-based infant formula for term infants at a level up to 10^8 colony forming units (CFU)/g of powdered formula, and at a level up to 1.25×10^{10} CFU per serving in the following conventional foods: baked goods; breakfast cereals; fruit juices, nectars, and fruit-vegetable juice blends; frozen fruit and ices; milk drinks (plain and flavored), fermented milk, and milk drink powders; heavy cream and cream substitutes; coffee drinks; meal replacements; frozen dairy desserts; puddings and custards; whipped toppings; yogurt; butter and dried milk products; processed cheese and cheese spreads; soft candy, hard candy, and chewing gum; peanut and nut butters and spreads; condiments, sauces, and marinades; gelatin desserts; snack foods; and infant and toddler foods. The notice informs us of Morinaga's view that these uses of *B. infantis* M-63 are GRAS through scientific procedures.

Morinaga describes *B. infantis* M-63 as a white to light brown powder. Morinaga states that *B. infantis* M-63 is a non-pathogenic, non-toxigenic, Gram-positive, non-motile, non-spore forming, anaerobic, rod-shaped bacterium. The strain was first isolated from a healthy infant in 1963 and is deposited in the strain collection of the National Institute of Technology and Evaluation (NITE) in Japan under the designation NITE BP-02623. Morinaga discusses the results of the phenotypic and genotypic characterization used to confirm the strain's identity.

Morinaga describes the manufacture of *B. infantis* M-63 by batch fermentation of a pure culture under controlled conditions. After fermentation, the *B. infantis* M-63 cells are concentrated and washed to remove the fermentation medium. Following this, the *B. infantis* M-63 is freeze-dried, milled to a powder, and blended with a tapioca starch or

corn starch carrier; either carrier may be used for conventional foods, but only the corn starch form is intended for use in infant formula.[1] Morinaga states that the manufacturing process is monitored for contamination, and that *B. infantis* M-63 is manufactured under current good manufacturing practices using food-grade materials. Morinaga states that no components of the fermentation media are allergens or are derived from allergenic sources.

Morinaga provides specifications for *B. infantis* M-63 that include anaerobic plate count (>8 X 10^{10} CFU/g), heavy metals, including lead (< 0.5 mg/kg), and limits for other microorganisms, including *Cronobacter sakazakii* (absent in 25 g) and *Salmonella* serovars (negative in 25 g). Morinaga provides the results from the analyses of three batches for each carbohydrate carrier to demonstrate that the ingredient can be manufactured to conform with the provided specifications. Morinaga states that *B. infantis* M-63 has a shelf life of up to 36 months when stored at less than 10 °C.

Morinaga estimates dietary exposure to *B. infantis* M-63 from use in infant formula and conventional food using food consumption data from the 2015-2016 National Health and Nutrition Examination Survey. For use in infant formula, Morinaga assumes a use level for *B. infantis* M-63 that provides up to 10^8 CFU/g of powdered formula and that 141 g powder is used to prepare a liter of prepared formula. Use levels in conventional foods were converted from 1.25 x 10^{10} CFU/serving to CFUs per gram based on serving sizes defined in the Reference Amounts Customarily Consumed (21 CFR 101.12(b)) for each food category. Morinaga provides estimates of dietary exposure to *B. infantis* M-63 for infants consuming infant formula and weaning foods, including baby food and foods for very young children. The mean and 90th percentile eaters-only dietary exposures for infants 0-6 months of age are 4.42 x 10^9 CFU/d and 1.14 x 10^{10} CFU/d, respectively, while the mean and 90th percentile eaters-only dietary exposures for infants 7-12 months of age are 9.49 x 10^9 CFU/d and 1.55 x 10^{10} CFU/d, respectively. Morinaga estimates a mean and 90th percentile eaters-only dietary exposure to *B. infantis* M-63 from use as an ingredient in various food categories, including weaning foods, for the U.S. population aged 2 years and older to be 1.42 x 10^{10} CFU/d and 2.62 x 10^{10} CFU/d, respectively.

Morinaga discusses data and information used to support the safety of *B. infantis* M-63, including a history of safe use of *B. infantis* strains in food products. Morinaga conducted *in vitro* safety studies of *B. infantis* M-63 including antibiotic resistance, biogenic amine production, absence of plasmids, and genomic analyses and states that the results of these studies support the safety of *B. infantis* M-63. Morinaga also discusses published literature that supports the safety of *B. infantis* M-63, including acute and subchronic studies, with no reports of toxicity or adverse effects. Additionally, Morinaga describes published clinical studies in which infants, children, and adults were fed *B. infantis* M-63 and states that no adverse effects were noted in any of these studies that could be attributed to the microorganism.

Morinaga includes the report of a panel of individuals (Morinaga's GRAS panel). Based

[1] Morinaga denotes *B. infantis* M-63 with the corn starch carrier as M-63 type C in the notice.

on its review, Morinaga's GRAS panel concluded that *B. infantis* M-63 is safe under the conditions of its intended use.

Based on the totality of evidence, Morinaga concludes that *B. infantis* M-63 is GRAS for its intended use.

Standards of Identity

In the notice, Morinaga states its intention to use *B. infantis* M-63 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, 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. infantis* M-63 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 Morinaga's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. infantis* M-63 to make the submission required by section 412. Infant formulas are the purview of the ONFL in the Center for Food Safety and Applied Nutrition.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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. infantis* M-63 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. infantis* M-

63. Accordingly, our response should not be construed to be a statement that foods containing *B. infantis* M-63, 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. infantis* M-63 is GRAS under its intended conditions of use. This letter is not an affirmation that *B. infantis* M-63 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 001003 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2022.04.26 20:05:57 -04'00'

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