Susan S. Cho, Ph.D.
NutraSource, Inc.
6309 Morning Dew Court
Clarksville, MD 21029

Re: GRAS Notice No. GRN 000814

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000814. We received the notice that you submitted on behalf of BIFIDO Co., Ltd. (BIFIDO) on September 20, 2018 and filed it on November 27, 2018. On March 16, April 4, April 25, and June 6, 2019, we received amendments that contained additional information about the estimated dietary exposure, method of manufacture, product specifications, and the safety assessment.

The subject of the notice is *Bifidobacterium bifidum* BGN4 for use in non-exempt powdered infant formulas for term infants at levels up to 10^8 colony forming units (CFU)/g powdered formula; and in dairy products and dairy-based foods; dairy substitutes including fermented milk, flavored milk beverages mixes, dried milk powder, imitation milk, and yogurt; baby cereals and powdered baby foods; meal replacement and powdered nutritional drink mixes; and powdered sugar substitutes at levels up to 10^9 CFU/serving. The notice informs FDA of BIFIDO's view that these uses of *B. bifidum* BGN4 are GRAS, through scientific procedures.

BIFIDO describes the isolation and characterization of *B. bifidum* BGN4. The bacterium was isolated from the feces of a healthy infant, phenotypically characterized and deposited at the Korean Culture Center of Microbiology as KCCM 80046. BIFIDO describes *B. bifidum* BGN4 as an anaerobic, nonmotile, Gram-positive bacterium. BIFIDO provides the results of genotypic analysis based on 16S rDNA sequencing to confirm the identity of the bacterium.

BIFIDO describes the manufacture of *B. bifidum* BGN4, noting that it is fermented under aseptic, pH- and temperature-controlled conditions in a growth medium containing soy peptone. BIFIDO states that after fermentation, the bacterial cells are harvested by centrifugation, mixed with a cryoprotectant, freeze-dried, milled and blended with an excipient. BIFIDO states that all ingredients used are food-grade, and the production is conducted in accordance with current good manufacturing practice.

BIFIDO provides specifications for *B. bifidum* BGN4. These include cell counts (a minimum of 10^{11} CFU/g) and limits for microorganisms including, non-lactic acid bacteria cell (<100 CFU/g), yeasts and molds (<100 CFU/g), *Salmonella* (negative in 25

g), *Cronobacter* spp. (negative in 60 g), and *Listeria* (negative in 25 g). BIFIDO provides batch analyses for three non-consecutive lots to show that their product can be manufactured to meet the specifications.

BIFIDO provides estimates of the dietary exposure to *B. bifidum* BGN4 from uses in both infant formula and conventional foods. BIFIDO estimates infant dietary exposure by assuming average caloric requirements of 472 kilocalories per day (kcal/d) for one-month old infants, 645 kcal/d for six-month old infants and a caloric density of 0.67 kcal/mL of infant formula. BIFIDO then assumes that infant formula is reconstituted at a rate of 14.1 g/100 mL and states that the addition of 10^8 CFU *B. bifidum* BGN4 per gram of powdered infant formula will result in daily intakes of 9.9×10^9 CFU/d for a one-month old infant and 1.35×10^{10} CFU/d for a six-month old infant. BIFIDO estimates that for its intended use rate of 10^9 CFU/serving in select conventional foods, the estimated 90th percentile intake will result in a dietary exposure of 3×10^{10} CFU/person/day. BIFIDO states that this value is most likely to be an overestimation because it is unlikely that *B. bifidum* BGN4 will be used at maximum levels in all intended food categories.

BIFIDO discusses the safety of *B. bifidum* BGN4 by citing published studies that show that *B. bifidum* BGN4 is non-pathogenic, non-toxigenic, and is unable to produce biogenic amines. BIFIDO also reports that *B. bifidum* BGN4 is susceptible to antimicrobial agents tested and thus would not pose a risk of transferring antibiotic resistance to other microorganisms. BIFIDO also cites published data that shows that the bacterium does not have any observable hemolytic or mucolytic activity. In a review of published studies covering the period up through June 2018, BIFIDO notes that no animal or human clinical studies have reported any adverse effects from the intake of *B. bifidum* BGN4 at levels comparable to those described in this notice. BIFIDO notes that *Bifidobacterium* spp. are recognized by the European Food Safety Authority with a Qualified Presumption of Safety.

BIFIDO notes that humans are exposed to bifidobacteria through the consumption of fermented foods such cheese and yogurt. BIFIDO also cites several examples of bifidobacteria currently used in foods including[1]: *B. lactis* Bb-12 for use in milk-based infant formula for infants four months and older, *B. longum* BB536 for use in select foods including milk-based powdered infant formula for term infants nine months and older, *B. animalis* ssp. *lactis* Bf-6 for use in conventional foods, and *B. breve* M-16V for use in exempt powdered amino acid-based formulas for term infants.

Based on the totality of the data and information described above, BIFIDO concludes that *B. bifidum* BGN4 is GRAS for its intended use in non-exempt infant formulas for term infants and select conventional foods.

[1] GRNs 000049, 000268, 000377, and 000455 describe the use of specific bifidobacteria in various food categories. FDA evaluated these notices and responded in letters dated March 19, 2002, July 8, 2009, September 29, 2011, and September 30, 2013, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

Standards of Identity

In the notice, BIFIDO states its intention to use *B. bifidum* BGN4 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 Labelling Issues

Under section 403(a) of the Federal Food, Drug, and 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). The notice raises a potential issue under these labeling provisions. In the notice, BIFIDO cites studies that describe *B. bifidum* BGN4 as having certain health benefits. If products containing *B. bifidum* BGN4 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.

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. bifidum* BGN4 may require labeling under the FD&C Act because it may contain soy-derived protein. 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 ONFL 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 BIFIDO's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. bifidum* BGN4 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 BIFIDO's notice concluding that *B. bifidum* BGN4 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. bifidum* BGN4. Accordingly, our response should not be construed to be a statement that foods containing *B. bifidum* BGN4, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that BIFIDO provided, as well as other information available to FDA, we have no questions at this time regarding BIFIDO's conclusion that *B. bifidum* BGN4 is GRAS under its intended conditions of use. This letter is not an affirmation that *B. bifidum* BGN4 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 000814 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2019.06.25 16:04:11 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
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