



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

Re: GRAS Notice No. GRN 000813

Dear Dr. Cho:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000813. We received the GRAS notice that you submitted on behalf of BIFIDO Co., Ltd (BIFIDO) on October 2, 2018, and filed it on November 27, 2018. BIFIDO submitted amendments to the notice on February 21, 2019, May 20, 2019, and June 6, 2019 to state soy allergens were below detection limits in the final product, to explain the threshold settings for virulence factor search, the use of a processing step to remove magnetic particles and to clarify the sample sizes for bacteria testing.

The subject of the notice is *Bifidobacterium longum* BORI (*B. longum* BORI) for use as an ingredient in non-exempt infant formulas (soy-, milk-, and whey-based) for term infants at up to 10^8 colony forming units (CFU)/g powdered formula, and in selected conventional food products (dairy products/dairy-based foods and dairy substitutes, including fermented milks, flavored milk beverage mixes, dried milk powder, imitation milk and yogurt; powdered baby cereals and foods; meal replacement and nutrition drink mix powders; and powdered sugar substitutes) for the general population at up to 10^9 CFU/serving. The notice informs us of BIFIDO's view that these uses of *B. longum* BORI are GRAS through scientific procedures.

BIFIDO describes *B. longum* BORI as a non-spore forming, homofermentative, Gram-positive, facultative anaerobe. BIFIDO states that *B. longum* BORI is a member of the lactic acid bacteria (LAB), a group characterized by the production of lactic acid as the major metabolic end-product of carbohydrate metabolism and other physiological traits. Additionally, *Bifidobacterium* occurs naturally in food and in the digestive tracts of humans and other animals. BIFIDO notes that *B. longum* BORI is non-pathogenic and non-toxic.

BIFIDO states that *B. longum* BORI is produced in a batch-type fermentation process with medium composed of sucrose, soy peptone, yeast extract, sodium acetate, sodium phosphate, L-cysteine HCl, and taurine. The medium is sterilized and then inoculated with the production strain, which is grown under defined fermentation conditions (pH, temperature). After growth, the bacteria are pelleted, mixed with cryoprotectants, freeze-dried, then milled and sieved. Corn starch is added to the concentrate to standardize the blends. BIFIDO states that *B. longum* BORI is manufactured in

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compliance with current good manufacturing practice, and the final preparation contains no major food allergens.

BIFIDO states that DNA from the strain has been sequenced. The strain bears no plasmids capable of transferring antibiotic resistances. The *B. longum* BORI genome lacks known antibiotic resistance genes and virulence factors; 16S sequencing shows that *B. longum* BORI shares a 99.4% homology with *B. longum* BB536.¹

BIFIDO provides specifications for *B. longum* BORI, including color (yellow-grey powder), viable cell count ($\geq 5 \times 10^{10}$ CFU/g as *B. longum* BORI), water activity ($\leq 6.0\%$), heavy metals, non-lactic acid bacteria ($\leq 10^2$ CFU/g), *Escherichia coli* (negative in 200 g), *Cronobacter sakazakii* (negative in 60 g), Salmonella (negative in 25 g), Listeria (negative in 25 g), molds and yeasts (≤ 100 CFU/g). BIFIDO provides data from three non-consecutive lots to demonstrate that the ingredient can be manufactured to meet the specifications. Additionally, BIFIDO provides stability data that indicate *B. longum* BORI cells are stable for up to two years under recommended storage conditions (5°C) and 12 months under accelerated conditions (25°C).

BIFIDO states that the estimated dietary exposures to *B. longum* BORI for term infants are the same as those described for *B. breve* M-16V in GRN 454.² BIFIDO estimates that daily exposure for *B. longum* BORI is 10^{10} CFU for both one-month and six-month infants; powdered term infant formulas will contain 10^8 CFU *B. longum* BORI/g. The estimated mean exposure for all users is 10^9 CFU/person/day, with the intended use level of 10^9 CFU *B. longum* BORI/serving in the selected food categories.

BIFIDO discusses the long, safe historical use of LAB in foods and that *Bifidobacterium*, generally, and *B. longum* BORI, specifically, have been safely used in fermented foods. BIFIDO cites publications that support the safe consumption of LAB, including *B. longum* BORI. Additionally, BIFIDO provides corroborative data from several placebo-controlled studies in which infants, children, and adults were fed a variety of bacteria, including different strains of *B. longum*; none of the studies reported any adverse effects.

Based on the totality of the data and information provided, BIFIDO concludes that the intended uses of *B. longum* BORI are GRAS.

Standards of Identity

In the notice, BIFIDO states its intention to use *B. longum* BORI in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. 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.

¹ *B. longum* BB536 is the strain notified in GRN 000268; FDA evaluated this notice and responded in a letter dated July 8, 2009, that we had no questions at that time regarding the notifier's GRAS conclusion.

² FDA evaluated GRN 000454 describing uses of *B. breve* strain M-16V and responded in a letter dated September 27, 2013, that we had no questions at that time regarding the notifier's GRAS conclusion.

Potential Labeling Issues

In describing the intended use of *B. longum* BORI and in describing the information that BIFIDO relies on to conclude that *B. longum* BORI is GRAS under the conditions of its intended use, BIFIDO raises a potential issue under the labeling provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Under section 403(a) of the FD&C Act, a food is misbranded if its labeling is false or misleading in any particular way. Section 403(r) of the FD&C Act lays out the statutory framework for the use of labeling claims that characterize the level of a nutrient in a food or that characterize the relationship of a nutrient to a disease or health-related condition. If products that contain *B. longum* BORI bear any claims on the label or in labeling, such claims are 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 neither consulted with ONFL on this labeling issue nor evaluated the information in your notice to determine whether it would support any claims made about *B. longum* BORI on the label or in labeling.

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* BORI may require labeling under the FD&C Act because soy peptone is used in the manufacturing process. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in OFAS. Questions related to food labeling in general should be directed to ONFL.

Intended Use in Infant Formula

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. BIFIDO should be aware that FDA’s response to BIFIDO’s GRAS notice does not alleviate the responsibility of any infant formula manufacturer who intends to market an infant formula that contains *B. longum* BORI to make the submission required by section 412.

Section 301(II) of the FD&C Act

Section 301(II) 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(II) (1)-(4) applies. In our evaluation of BIFIDO’s notice concluding that *B. longum* BORI is GRAS under its intended conditions of use, we did not consider

whether section 301(l) or any of its exemptions apply to foods containing *B. longum* BORI. Accordingly, our response should not be construed to be a statement that foods containing *B. longum* BORI, if introduced or delivered for introduction into interstate commerce, would not violate section 301(l).

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. longum* BORI is GRAS under its intended conditions of use. This letter is not an affirmation that *B. longum* BORI 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 000813 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

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Director
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