Myeong Soo Park, Ph.D.
BIFIDO Co., Ltd.
23-16, Nonggongdanji-gil, Hongcheon-eup,
Hongcheon-gun, Gangwon-do, 25117
REPUBLIC of KOREA

Re: GRAS Notice No. GRN 000952

Dear Dr. Park:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000952. We received the notice that Dr. Susan Cho of AceOne RS[1] submitted on behalf of BIFIDO, Co., Ltd. (BIFIDO) on June 2, 2020, and filed it on September 21, 2020. BIFIDO submitted an amendment to the notice on December 7, 2020, providing clarification on the intended use.

The subject of the notice is *Bifidobacterium animalis* subsp. *lactis* strain AD011 (*B. lactis* AD011) for use as an ingredient in non-exempt infant formula (milk- and soy-based) for term infants at levels up to 10^8 colony forming units (CFU)/g of powdered formula; and, in fermented milk, including buttermilk and kefir, flavored milk beverage mixes, dried milk powder, imitation milk, yogurt, powdered baby cereals and foods, meal replacement and nutritional drink mix powders, and powdered sugar substitutes at levels up to 10^{10} CFU *B. lactis* AD011/serving. The notice informs us of BIFIDO's view that these uses of *B. lactis* AD011 are GRAS through scientific procedures.

BIFIDO states that *B. lactis* AD011 was isolated from infant stool and is deposited in GenBank under accession number CP001213. *B. lactis* AD011 is a Gram-positive, non-spore forming, rod-shaped bacterium. BIFIDO discusses the phenotypic and genotypic characteristics used to confirm the strain's identity and states that the strain is non-pathogenic and non-toxigenic.

BIFIDO describes the manufacture of *B. lactis* AD011 as a batch-type fermentation process, noting that the strain is grown under controlled conditions in a medium that includes soy peptone. After fermentation, the bacterial cells are harvested by centrifugation, washed, diluted with maltodextrin (a cryopreservative agent), freeze-dried, milled and blended with corn starch (an excipient) to yield a yellow white powder. BIFIDO states that all ingredients used are food-grade, and the production is conducted in accordance with current good manufacturing practice.

[1] An update on April 19, 2020, states that effective May 1, 2020, the company named NutraSource, Inc. is changing its name to AceOne RS.

BIFIDO provides specifications for *B. lactis* AD011 that include viable cell counts (more than 10^{11} CFU/g) and limits for microorganisms, including *Escherichia coli* (absent in 25 g), *Salmonella* serovars (absent in 25 g), *Listeria* (absent in 25 g), and *Chronobacter sakazakii* (absent in 10 g), and heavy metals, including lead (≤ 0.3 mg/kg). BIFIDO provides the analyses of three non-consecutive lots to demonstrate that the ingredient can be manufactured to conform with the provided specifications. BIFIDO provides stability data that indicate *B. lactis* AD011 cells are stable for up to 18 months at 5°C and 25°C.

BIFIDO intends *B. lactis* AD011 to be used in non-exempt infant formula (milk- and soy-based) for term infants at levels up to 10^8 CFU/g of powdered formula; and, in certain conventional foods at levels up to 10^{10} CFU *B. lactis* AD011/serving. Based on food consumption data from the 2015-2016 National Health and Nutrition Examination Survey, BIFIDO estimates the eaters-only dietary exposure for *B. lactis* AD011 to be 10^{10} CFU/day for infants, and the 90th percentile eaters-only dietary exposure to be 2.7 x 10^{10} CFU/day for the US population.

BIFIDO discusses published and publicly available information to support safety of *B. lactis* AD011. BIFIDO states that *B. lactis* AD011 genome does not contain regions with significant homology to known toxigenic or pathogenic genes. Further, BIFIDO discusses published studies that provide evidence that *B. lactis* AD011 exhibits antibiotic susceptibility, does not contain plasmid capable of transmitting antibiotic resistance genes, does not show hemolytic and mucolytic activities, and does not produce clinically significant levels of biogenic amines and ammonia. BIFIDO states that the fate and the safety profile of orally consumed *B. lactis* AD011 is not expected to be significantly different from what are observed after consumption of other *Bifidobacterium* species. Moreover, BIFIDO describes supportive published clinical studies in which infants, children, or adults consumed *B. lactis* AD011 (or other *Bifidobacterium* or *Lactobacillus* strains) and states that no adverse effects were reported.

BIFIDO includes the statement of a panel of individuals (BIFIDO's GRAS panel). Based on its review, BIFIDO's GRAS panel concluded that *B. lactis* AD011 is safe under the conditions of its intended use.

Based on the totality of the data and information, BIFIDO concludes that *B. lactis* AD011 is GRAS under its intended conditions of use.

Standards of Identity

In the notice, BIFIDO states its intention to use *B. lactis* AD011 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.

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. lactis* AD011 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. lactis* AD011 may require labeling under the FD&C Act because it may contain protein derived from soybeans. 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 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 BIFIDO's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. lactis* AD011 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. lactis* AD011 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. lactis* AD011. Accordingly, our response should not be construed to be a statement that foods

containing *B. lactis* AD011, 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. lactis* AD011 is GRAS under its intended conditions of use. This letter is not an affirmation that *B. lactis* AD011 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 000952 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.03.17 16:36:26 -04'00'

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