Yoshitaka Nakamura, Ph.D.
Meiji Co., Ltd.
R&D Division
Food Microbiology and Function Research Laboratories
1-29-1 Nanakuni, Hachiouji
Tokyo 192-0919
JAPAN

Re: GRAS Notice No. GRN 001090

Dear Dr. Nakamura:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001090. We received Meiji Co., Ltd. (Meiji)'s notice on March 8, 2022, and filed it on November 30, 2022. Meiji submitted an amendment to the notice on February 22, 2023, that clarified the intended use, manufacturing, and specifications.

The subject of the notice is *Bifidobacterium bifidum* strain NITE BP-31 for use as an ingredient in reconstituted or ready-to-drink, cow milk-based, non-exempt infant formula for term infants at a level of 2.28 x 10^6 colony forming units (CFU)/mL of reconstituted formula. The notice informs us of Meiji's view that this use of *B. bifidum* strain NITE BP-31 is GRAS through scientific procedures.

Meiji discusses the identity of *B. bifidum* NITE BP-31 and describes it as a milky white powder. Meiji states that *B. bifidum* NITE BP-31 is an anaerobic, Gram-positive, rod-shaped bacterium. Meiji discusses the isolation and characterization of *B. bifidum* NITE BP-31, noting that the strain was isolated from the feces of a healthy human infant and whole genome sequencing was conducted to confirm the strain's identity. Meiji states that *B. bifidum* NITE BP-31 is deposited in the National Institute of Technology and Evaluation Patent Microorganism Depository. Meiji states that *B. bifidum* NITE BP-31 is not genetically modified.

Meiji describes the manufacturing process for *B. bifidum* NITE BP-31, stating that it is produced using culture fermentation in a contained, sterile environment. Meiji explains that after fermentation, the bacterial cells are concentrated by centrifugation, mixed with a cryoprotectant,[1] freeze-dried, and milled. Meiji states that all additives, processing aids, and food contact substances are food-grade, permitted for their

[1] In the February 22, 2023, amendment, Meiji states that sucrose is the only cryoprotectant that will be used in the manufacturing process.

respective uses by a federal regulation, previously concluded to be GRAS for their respective uses, or have been the subject of an effective food contact notification.

Meiji provides specifications for *B. bifidum* NITE BP-31 that include limits for *B. bifidum* NITE BP-31 (>1.25 x 10^{11} CFU/g); heavy metals, including lead (<0.05 mg/kg); and other microorganisms, including yeast (negative/0.1 g), mold (negative/0.1 g), *Salmonella* spp. (negative/25 g), and *Cronobacter sakazakii* (negative/5 g).[2] Meiji provides the results of four non-consecutive batch analyses to demonstrate that *B. bifidum* NITE BP-31 can be manufactured to meet these specifications.

Meiji provides estimates of dietary exposure to *B. bifidum* NITE BP-31 based on the intended use and food consumption data from the 2015-2016 National Health and Nutrition Examination Survey. The mean and 90th percentile dietary exposures are reported to be 1.73 × 10^9 and 2.60 x 10^9 CFU/person(p)/d, respectively, for infants up to 6 months of age and 1.70 x 10^9 and 2.76 × 10^9 CFU/p/d, respectively, for infants 7-12 months of age.

Meiji discusses data and information used to support the safety of *B. bifidum* NITE BP-31, including a history of safe use of *B. bifidum* in dairy and fermented foods worldwide. Meiji cites published studies showing that *B. bifidum* NITE BP-31 is non-pathogenic and non-toxigenic and is susceptible to most antibiotics. Meiji notes that *B. bifidum* NITE BP-31 is resistant to aminoglycosides, but this resistance is a structural characteristic of the *Bifidobacterium* genus, as members of this genus lack the membrane transport system needed to transport the aminoglycoside into the bacterium. Meiji states that *B. bifidum* NITE BP-31 is not capable of DNA transfer to other microorganisms. Meiji discusses data showing that *B. bifidum* NITE BP-31 does not have hemolytic activity and does not produce secondary bile acids or D-lactic acid. Meiji describes published clinical studies with infants consuming *B. bifidum* NITE BP-31 (or other *Bifidobacterium* spp.) and states that no adverse effects were reported.

Based on the totality of the data and information, Meiji concludes that *B. bifidum* strain NITE BP-31 is GRAS for its intended use.

Potential Labeling Issues

Under section 403(a) of the Federal Food, Drug, & 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). If products containing *B. bifidum* strain NITE BP-31 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 (OFAS) did not consult with ONFL on this issue or evaluate any information in terms of labeling claims.

[2] Meiji states that the method used for the *C. sakazakii* test is validated for this sample size.

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 nine foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans, and sesame) or a food ingredient that contains protein derived from one of those foods. *B. bifidum* strain NITE BP-31 requires labeling under the FD&C Act because it contains protein derived from milk.

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 Meiji's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. bifidum* strain NITE BP-31 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 Meiji's notice concluding that *B. bifidum* strain NITE BP-31 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* strain NITE BP-31. Accordingly, our response should not be construed to be a statement that foods containing *B. bifidum* strain NITE BP-31, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Meiji provided, as well as other information available to FDA, we have no questions at this time regarding Meiji's conclusion that *B. bifidum* strain NITE BP-31 is GRAS under its intended conditions of use. This letter is not an affirmation that *B. bifidum* strain NITE BP-31 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 001090 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.04.05 11:54:31 -04'00'

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