Winnig Ng, Ph.D., DABT
Chr. Hansen A/S
Boege Alie 10-12
2970 Hoersholm
DENMARK

Re: GRAS Notice No. GRN 001114

Dear Dr. Ng:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001114. We received Chr. Hansen A/S (Chr. Hansen)'s notice on August 10, 2022, and filed it on March 21, 2023. Chr. Hansen submitted an amendment to the notice on May 26, 2023, that clarified the manufacturing, specifications, and dietary exposure.

The subject of the notice is *Bifidobacterium breve* DSM 33444 for use as an ingredient in non-exempt infant formula for term infants[1] at a level up to 1.0 x $10^8$ colony forming units (CFU)/g of powdered formula, as well as in conventional foods at levels up to 5.0 x $10^9$ CFU/serving.[2] The notice informs us of Chr. Hansen's view that this use of *B. breve* DSM 33444 is GRAS through scientific procedures.

Chr. Hansen discusses the identity of *B. breve* DSM 33444 and describes it as a white to light-beige powder. Chr. Hansen states that *B. breve* DSM 33444 is a Gram-positive, rod-shaped, anaerobic bacterium. Chr. Hansen discusses the isolation and characterization of *B. breve* DSM 33444, stating that the strain was originally isolated from the intestinal flora of a healthy infant. Chr. Hansen states that *B. breve* DSM 33444 is deposited in the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM). Chr. Hansen states that 16S rDNA sequencing was conducted to confirm *B. breve* DSM 33444's identity.

Chr. Hansen describes the manufacturing process for *B. breve* DSM 33444, stating that it is produced by industrial batch fermentation in a controlled, sterile environment. Chr. Hansen explains that after fermentation, the bacterial cells are concentrated by centrifugation, mixed with cryoprotectants, freeze-dried, and ground into a powder. Chr. Hansen states that all raw materials and processing aids used in the manufacture of

[1] Chr. Hansen states that the use of *B. breve* DSM 33444 in infant formula is not restricted to any specific protein base (e.g., cow milk-based, soy-based, etc.).
[2] Chr. Hansen states that *B. breve* DSM 33444 is not intended for use in products under the U.S. Department of Agriculture's jurisdiction.

*B. breve* DSM 33444 are safe and suitable under the intended conditions of use and are used in accordance with applicable U.S. regulations or are GRAS for their intended uses.

Chr. Hansen provides specifications for *B. breve* DSM 33444 that include limits for *B. breve* DSM 33444 (>4.8 x $10^{11}$ CFU/g); heavy metals, including lead (0.05 mg/kg); and other microorganisms, including yeast (<10 CFU/g), mold (<10 CFU/g), *Salmonella* spp. (not detected in 25 g), *Listeria* spp. (not detected in 25 g), and *Cronobacter* spp. (not detected in 10 g). Chr. Hansen provides the results of three non-consecutive batch analyses to demonstrate that *B. breve* DSM 33444 can be manufactured to meet these specifications.

Chr. Hansen provides an estimate of dietary exposure to *B. breve* DSM 33444 in conventional foods based on the assumption that a healthy individual consumes ~20 servings/d of *B. breve* DSM 33444-containing foods. Therefore, Chr. Hansen states that the maximum dietary exposure attributed to use in conventional foods is 1 x $10^{11}$ CFU/person (p)/d. As Chr. Hansen expects that *B. breve* DSM 33444 will be substitutional for other *B. breve* spp. that were the subjects of prior GRNs, they do not expect an increase in overall dietary exposure to *B. breve* spp. Chr. Hansen also provides estimates of dietary exposure to *B. breve* DSM 33444 from consuming infant formula based on the maximum intended use level of 1.0 x $10^{8}$ CFU/g of powdered formula, published estimates of caloric requirements for infants, and a reconstitution rate of 14.1 g/100 mL for infant formula with a caloric density of 0.67 kcal/mL. Chr. Hansen reports the maximum dietary exposures to be 1.8 x $10^{10}$ CFU/p/d for male infants and 1.6 x $10^{10}$ CFU/p/d for female infants.

Chr. Hansen discusses data and information used to support the safety of *B. breve* DSM 33444, including a history of safe use of *Bifidobacterium* spp. in fermented foods and dairy products. Chr. Hansen cites published clinical studies in which infants, children, and adults ingested other strains of *B. breve* and states that the species was well tolerated. Chr. Hansen also discusses the results of *in silico* and *in vitro* analyses, stating that *B. breve* DSM 33444 is non-toxigenic and non-pathogenic and is susceptible to most antibiotics. Chr. Hansen notes that *B. breve* DSM 33444 is resistant to kanamycin but explains that this resistance is intrinsic to the *Bifidobacterium* genus. Chr. Hansen discusses data showing that *B. breve* DSM 33444 does not have hemolytic activity, is non-cytotoxic, and does not produce biogenic amines.

Based on the totality of the data and information, Chr. Hansen concludes that *B. breve* DSM 33444 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. breve* DSM 33444 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. 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. breve* DSM 33444 may require labeling under the FD&C Act because it may contain protein derived from milk from the fermentation 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.

**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. Our response to Chr. Hansen's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. breve* DSM 33444 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 Chr. Hansen's notice concluding that *B. breve* DSM 33444 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. breve* DSM 33444. Accordingly, our response should not be construed to be a statement that foods containing *B. breve* DSM 33444, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

**Conclusions**

Based on the information that Chr. Hansen provided, as well as other information available to FDA, we have no questions at this time regarding Chr. Hansen's conclusion that *B. breve* DSM 33444 is GRAS under its intended conditions of use. This letter is not

an affirmation that *B. breve* DSM 33444 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 001114 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2023.07.10 17:05:53 -04'00'

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