DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
College Park, MD 20740-3835

Timothy S. Murbach, N.D.
AIBMR Life Sciences, Inc.
2800 East Madison Street
Suite 202
Seattle, WA 98112

Re: GRAS Notice No. GRN 000660

Dear Dr. Murbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000660. We received the notice, dated July 11, 2016, that you submitted on behalf of Ganeden Biotech, Inc. (Ganeden), in accordance with the agency's proposed regulation, proposed 21 Code of Federal Regulations (CFR) 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal) on July 12, 2016, and filed it on August 16, 2016. We received an amendment containing additional safety information on October 26, 2016.

FDA published the GRAS final rule on August 17, 2016 (81 FR 54960), with an effective date of October 17, 2016. As GRN 000660 was pending on the effective date of the GRAS final rule, we requested additional information consistent with the format and requirements of the final rule. We received an amendment responding to this request on October 31, 2016.

The subject of the notice is a preparation of *Bacillus coagulans* GBI-30, 6086 spores (*B. coagulans* spore preparation). The notice informs us of Ganeden's view that *B. coagulans* spore preparation is GRAS, through scientific procedures, for use as an ingredient in non-exempt powdered and liquid infant formulas for term infants (infant formula) at levels up to 2×10^8 colony forming units (CFU) per 100 milliliters (mL) infant formula as consumed.

Ganeden discusses the identity of *B. coagulans* spore preparation. *B. coagulans* strain GBI-30, 6086 is a Gram-positive, spore-forming, L(+) lactic acid-producing bacterium. Ganeden states that *B. coagulans* spore preparation is a beige to light gray powder.

Ganeden describes the manufacture of *B. coagulans* spore preparation. All ingredients, fermentation tanks, and culture media are heat-sterilized prior to inoculation.[1] The strain is fermented under pH- and temperature-controlled aseptic conditions. After fermentation, the spores are separated from the culture media by centrifugation and are then freeze- or spray-dried before packaging. The dried spores are blended with diluents or bulking agents such as maltodextrin, microcrystalline cellulose, sodium bicarbonate, inulin, or milk powder. Ganeden states that all materials used in the manufacturing process are food-grade and *B. coagulans* spore preparation is produced in accordance with current good manufacturing practices.

Ganeden provides specifications for *B. coagulans* spore preparation that include a minimum of 1.5×10^{10} CFU/gram (g) and limits for moisture (≤ 6 %), arsenic (≤ 1 milligram per kilogram (mg/kg)), cadmium (≤

[1] The culture media may contain soy- and milk-derived ingredients. Ganeden states that a version of *B. coagulans* spore preparation is also manufactured on allergen-free culture media.

1 mg/kg), lead (≤ 1 mg/kg), mercury (≤ 1 mg/kg), *Cronobacter sakazakii* (absent in 100 g), and *Salmonella* (none detected). Ganeden provides the results of five non-consecutive batch analyses to demonstrate compliance with these specifications.

Ganeden states that *B. coagulans* spore preparation is intended for use at a maximum level of 2×10^8 CFU/100 mL infant formula as consumed. Ganeden estimates the intake of infant formula at 213.4 mL/kg body weight (bw)/day at the 90th percentile based on an assumption that term infant formulas contain 67 kilocalories (kcal)/100 mL and that the highest reported energy consumption is 143 kcal/kg bw/day. Therefore, Ganeden estimates the dietary exposure to *B. coagulans* spore preparation to be 4.3×10^8 CFU/kg bw/day. Ganeden notes that energy intake from infant formula declines with age and any increase in consumption of conventional foods containing *B. coagulans* spore preparation would be substitutional.[2]

Ganeden incorporates into the notice all published information from GRN 000399, including acute, subchronic, chronic, and reproductive toxicity studies and mutagenicity and genotoxicity studies for its safety assessment and states that an updated literature search was conducted through June 29, 2016. Ganeden states that *B. coagulans* is non-pathogenic and non-toxigenic. Ganeden discusses new published information not described in GRN 000399 involving whole-genome sequencing and bioinformatic analyses showing that *B. coagulans* strain GBI-30, 6086 does not encode any putative virulence factors that are considered harmful, lacks genes related to the production of or does not produce detectable levels of biogenic amines, and lacks genes involved in the biosynthesis of harmful lipopeptides, enterotoxins, and hemolysins. Ganeden discusses the data from a study described in GRN 000399 that was since published, showing that *B. coagulans* strain GBI-30, 6086 is sensitive to many clinically-used antibiotics with no evidence suggesting that the strain transmits antibiotic resistance to other bacterial species. Ganeden states that published results of clinical trials with its *B. coagulans* spore preparation in adults showed no adverse events. Ganeden cites four published, randomized, blinded, placebo-controlled clinical trials in which infants were administered *B. coagulans* at levels up to 3.5×10^8 CFU/day for up to one year with no treatment-related adverse events.[3]

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

Based on the totality of information discussed above, Ganeden concludes that *B. coagulans* spore preparation is GRAS for its intended use.

Potential Labeling 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

[2] GRN 000399 describes the use of *B. coagulans* spore preparation as an ingredient in baked goods and baking mixes; beverages and beverage bases; breakfast cereals; chewing gum; coffee and tea; condiments and relishes; confections and frostings; dairy product analogs; fruit juices; frozen dairy desserts and mixes; fruit and water ices; gelatins, puddings, and fillings; grain products and pastas; hard candy; herbs, seeds, spices, seasonings, blends, extracts, and flavorings; jams and jellies; milk; milk products; nuts and nut products; plant protein products; processed fruits; processed vegetables and vegetable juices; snack foods; soft candy; soups and soup mixes; sugar; and sweet sauces, toppings, and syrups at a maximum level of approximately 2×10^9 CFU/serving. We evaluated this notice and responded in a letter on July 31, 2012 stating that we had no questions at that time regarding Ganeden's GRAS determination.

[3] Ganeden states that three of the four studies mentioned do not specify if spore preparations were used. However, Ganeden states that it is highly unlikely for *B. coagulans* to be administered in the vegetative cell form in such studies and assumes that *B. coagulans* spore preparations were used in the infant clinical trials.

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, Ganeden cites studies that describe *B. coagulans* spore preparation as having certain health benefits. If products containing *B. coagulans* spore preparation bear any nutrient content or health claims on the label or in labeling, such claims are the 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 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. coagulans* spore preparation may require labeling under the FD&C Act because the culture media may contain soy and milk-derived protein. Importantly, any *B. coagulans* spore preparation blended with milk powder requires labeling under the FD&C Act because milk powder contains milk-derived protein. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Biotechnology and GRAS Notice Review in OFAS. 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 Ganeden's GRAS notice does not alleviate the responsibility of any infant formula manufacturer that intends to market an infant formula containing *B. coagulans* spore preparation 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 Ganeden's notice concluding that *B. coagulans* spore preparation 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. coagulans* spore preparation. Accordingly, our response should not be construed to be a statement that foods containing *B. coagulans* spore preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Ganeden provided, as well as other information available to FDA, we have no questions at this time regarding Ganeden's conclusion that *B. coagulans* spore preparation is GRAS under its intended conditions of use. This letter is not an affirmation that *B. coagulans* spore preparation 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 000660 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300042713, cn=Michael A. Adams -S
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