Timothy Murbach, ND, DABT
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Re: GRAS Notice No. GRN 000725

Dear Dr. Murbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000725. We received the notice you submitted on behalf of Ganeden Biotech, Inc. (Ganeden) on August 15, 2017, and filed it on August 31, 2017. We received an amendment to the notice on November 29, 2017. In the amendment, Ganeden clarifies the intended use.

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

Ganeden provides information about the identity and composition of inactivated *B. coagulans*. Ganeden describes inactivated *B. coagulans* as a light tan to beige powder. Ganeden notes that *B. coagulans* GBI-30, 6086 was identified to the genus, species, and strain levels, and is the same strain that was the subject of GRNs 000399,[1] 000660,[2] and 000670.[3]

[1] GRN 000399 describes uses of *B. coagulans* spore preparation as an ingredient in conventional food at a maximum level of approximately 2 x 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 conclusion.
[2] GRN 000660 describes uses of *B. coagulans* spore preparation as an ingredient in non-exempt powdered and liquid infant formulas for term infants at levels up to 2 x 10^8 CFU/100 ml infant formula as consumed. We evaluated this notice and responded in a letter on January 13, 2017, stating that we had no questions at that time regarding Ganeden's GRAS conclusion.
[3] GRN 000670 describes the use of inactivated *B. coagulans* as an ingredient in conventional food at a maximum level of approximately 2 x 10^9 inactivated CFU/serving. We evaluated this notice and responded in a letter on March 15, 2017, stating that we had no questions at that time regarding Ganeden's GRAS conclusion.

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Ganeden describes the manufacture of inactivated *B. coagulans*. The strain is fermented under pH- and temperature-controlled aseptic conditions.[4] After fermentation, the cells are inactivated by pH, temperature, or pressure changes. The inactivated cells are collected by centrifugation and are freeze- or spray-dried. The final powder is blended with diluents and bulking agents, including maltodextrin, microcrystalline cellulose, inulin, and/or milk powder to obtain a desired final concentration of inactivated *B. coagulans* before packaging. Ganeden states that all materials used in the manufacturing process are food-grade and meet appropriate regulations.

Ganeden provides specifications for inactivated *B. coagulans* that include a minimum of 1.5×10^{10} inactivated CFU/g and limits for microbes including *Cronobacter sakazakii* (absent in 100 g) and *Salmonella* serovars (none detected). Ganeden provides results from five non-consecutive batch analyses to confirm that inactivated *B. coagulans* meets the intended specifications. Ganeden states that inactivated *B. coagulans* has a three-year shelf life based on the shelf-life of dried live *B. coagulans*.

Ganeden estimates the dietary exposure to inactivated *B. coagulans*. Ganeden estimates infant formula intake to be 213 ml/kg body weight (bw)/d at the 90th percentile. Therefore, Ganeden estimates the dietary exposure to inactivated *B. coagulans* to be 4.3×10^8 CFU/kg bw/d. Ganeden states that inactivated *B. coagulans* would be substitutional for *B. coagulans* spore preparation in infant formulas. Additionally, as energy intake from infant formula declines with age, Ganeden considers that any increase in consumption of conventional foods containing inactivated *B. coagulans* or *B. coagulans* spore preparation would be substitutional and not result in increased exposure to *B. coagulans*.

Ganeden incorporates into the notice all published information from GRN 000399 and GRN 000660 for its safety assessment. Ganeden discusses that these incorporated published studies show no evidence of genotoxic potential or toxicity of *B. coagulans* strain GBI-30 6086 in acute, subchronic, chronic, and reproductive toxicity studies. Additionally, Ganeden states that the incorporated clinical trials in which *B. coagulans* was administered to infants did not show any treatment-related adverse events. Ganeden states that an updated literature search was conducted through July 2017 and did not identify any additional published studies relevant to safety. Additionally, Ganeden states that FDA, Health Canada, and the European Food Safety Authority (EFSA) recognize *B. coagulans* as a non-pathogenic, non-toxigenic organism. Ganeden further notes EFSA conferred Qualified Presumption of Safety status to *B. coagulans* in 2007 and has maintained its status through the current 2016 publication.

Based on the data and information described above, Ganeden concludes that inactivated *B. coagulans* is GRAS for its intended use in food.

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

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 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 inactivated *B. coagulans* as having certain health benefits. If products containing inactivated *B. coagulans* 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. Inactivated *B. coagulans* may require labeling under the FD&C Act because the fermentation media may contain soy and milk-derived proteins. Importantly, inactivated *B. coagulans* 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 inactivated *B. coagulans* 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 inactivated *B. coagulans* 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 inactivated *B. coagulans*. Accordingly, our response should not be construed to be a statement that foods containing inactivated *B. coagulans*, 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 inactivated *B. coagulans* is GRAS under its intended conditions of use. This letter is not an affirmation that inactivated *B. coagulans* 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 000725 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Michael A. Adams -S

Digitally signed by Michael A. Adams -S
Date: 2018.02.12 16:29:35 -05'00'

Dennis M. Keefe, Ph.D.
Director
Office of Food Additive Safety
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