



John R. Endres, ND  
AIBMR Life Sciences, Inc.  
2800 E. Madison St.  
Suite 202  
Seattle, WA 98112

Re: GRAS Notice No. GRN 000670

Dear Dr. Endres:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000670. We received the notice, dated September 16, 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 September 20, 2016, and filed it on October 7, 2016. We received amendments containing additional safety information on December 13, 2016, January 17, 2017, and March 13, 2017.

FDA published the GRAS final rule on August 17, 2016 (81 FR 54960), with an effective date of October 17, 2016. As GRN 000670 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 inactivated *Bacillus coagulans* GBI-30, 6086 (inactivated *B. coagulans*). The notice informs us of the view of Ganeden that inactivated *B. coagulans* is GRAS, through scientific procedures, for use as an ingredient at a maximum level of approximately  $2 \times 10^9$  inactivated colony forming units (CFU) per serving 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 and milk products; nuts and nut products; plant protein products; processed fruits; processed vegetables and vegetable juices; snack foods; soft candy; and soups and soup mixes.<sup>1</sup>

Ganeden discusses the identity of inactivated *B. coagulans* as the thermally-killed vegetative cells of the same strain (*B. coagulans* GBI-30, 6086) that was the subject of GRN 000399.<sup>2</sup> Ganeden describes inactivated *B. coagulans* as a light tan to beige powder.

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<sup>1</sup> Ganeden states that inactivated *B. coagulans* is not intended for use in foods for infants and toddlers, or any meat and poultry products that are under the jurisdiction of the United States Department of Agriculture.

<sup>2</sup> GRN 000399 describes the use of *B. coagulans* spore preparation as an ingredient in several foods at a maximum level of approximately  $2 \times 10^9$  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.

Ganeden describes the manufacture of inactivated *B. coagulans*. All ingredients, fermentation tanks, and fermentation media are heat-sterilized prior to inoculation.<sup>3</sup> The strain is fermented under pH- and temperature-controlled aseptic conditions. 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 mixed as needed with maltodextrin, microcrystalline cellulose, or sodium bicarbonate, as well as milk powder and inulin to obtain the desired final concentration of inactivated *B. coagulans*. Ganeden states that all processing aids, fermentation media, and diluents are either GRAS substances or approved food additives. Inactivated *B. coagulans* is produced in accordance with current good manufacturing practices.

Ganeden provides specifications for inactivated *B. coagulans*, including appearance and limits for microbiological contaminants: yeast and mold (NMT 100 CFU/g); total coliforms (NMT 10 CFU/g); *Escherichia coli*, Staphylococci, and *Listeria* (none detected in 10 g); *Salmonella* and *Pseudomonas aeruginosa* (none detected in 25 g). Ganeden provided three non-consecutive batch analyses to establish that their production can meet the specifications.

Ganeden discusses the dietary exposure to inactivated *B. coagulans*. Ganeden states that inactivated *B. coagulans* is intended for use in conventional foods at a maximum level of approximately  $2 \times 10^9$  CFU/serving. Ganeden states that the dietary exposure to inactivated *B. coagulans* is comparable to that described for live bacteria in GRN 000399. Ganeden explains that inactivated *B. coagulans* will be used in the same food categories and at the same use level as in GRN 000399. Ganeden notes that while exposure to the cell components would be the same when consuming live or inactivated *B. coagulans*, the inactivated cells would not increase in number following consumption.

Ganeden incorporates into the notice all published information on *B. coagulans* strain GBI-30, 6086 from GRN 000399 for its safety assessment and states that an updated literature search was conducted through June 2016. Ganeden concludes that these incorporated published studies showed no evidence of genotoxic potential or toxicity in acute, subchronic, chronic, and reproductive toxicity studies. Ganeden states that *B. coagulans* GBI-30, 6086 is non-toxicogenic and non-pathogenic. Ganeden discusses new published information not described in GRN 000399 involving whole-genome sequencing results showing that *B. coagulans* GBI-30, 6086 does not encode enterotoxins or hemolysins. Ganeden states that no reports of allergic reactions to *B. coagulans* were found in searches of the scientific literature and government databases.

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

Based on the totality of information discussed above, Ganeden concludes that inactivated *B. coagulans* is GRAS under the conditions of its intended use.

### **Standards of Identity**

In the notice, Ganeden states its intention to use inactivated *B. coagulans* in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR.

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<sup>3</sup> The culture media may contain soy- or milk-derived ingredients. Ganeden states that a version of inactivated *B. coagulans* is also manufactured using allergen-free culture media.

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). The notice raises a potential issue under these labeling provisions. In the notice, Ganeden cites studies that describe *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 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. Inactivated *B. coagulans* may require labeling under the FD&C Act because the culture media may contain soy and milk-derived protein. Inactivated *B. coagulans* blended with milk powder requires labeling under the FD&C Act because milk powder contains milk-derived protein.

### **Section 301(II) of the FD&C Act**

Section 301(II) 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(II)(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(II) 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(II).

### **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 000670 is accessible to the public at [www.fda.gov/grasnoticeinventory](http://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,  
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