Madhu G. Soni, Ph.D.
Soni and Associates Inc.
749 46th Square
Vero Beach, FL 32968

Re: GRAS Notice No. GRN 001177

Dear Dr. Soni:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 001177. We received the notice you submitted on behalf of Unique Biotech Limited, India (Unique Biotech) on January 22, 2024, and filed it on April 4, 2024. Unique Biotech submitted an amendment to the notice on June 11, 2024, that clarified the manufacturing and specifications.

The subject of the notice is *Bacillus coagulans* Unique IS-2 spore preparation (*B. coagulans* spore preparation) for use as an ingredient in powder, liquid concentrate, and ready-to-feed, soy- and milk-based, non-exempt infant formula for term infants at a maximum level of 2 x 10^8 colony forming units (CFU)/100 mL infant formula as consumed. The notice informs us of Unique Biotech's view that this use of *B. coagulans* spore preparation is GRAS through scientific procedures.

Unique Biotech describes *B. coagulans* spore preparation as a white to greyish-white colored powder, and states that it is a Gram-positive, non-pathogenic, non-toxigenic, catalase-positive, spore-forming, rod-shaped bacterium. The strain was isolated from healthy human feces and is deposited in the ATCC under the designation PTA-11748. The strain is also deposited with the Microbial Type Culture Collection and Gene Bank (MTCC) with an accession number of *B. coagulans* Unique IS-2 (MTCC 5260). Further, Unique Biotech discusses the results of the phenotypic and genotypic characterization used to confirm the strain's identity.

Unique Biotech describes the manufacture of *B. coagulans* spore preparation, which occurs through fermentation of a pure culture under controlled conditions.[1] The bacterial culture is then centrifuged to separate the spores from the soluble media components and water and then is spray dried. The final dried spore preparation is then standardized using approved food-grade stabilizers, such as maltodextrin, microcrystalline cellulose powder, or fructooligosaccharides. Unique Biotech states that

[1] Unique Biotech states that the manufacturing method is the same as that described in GRN 000526. A preparation of *B. coagulans* strain Unique IS2 spores was the subject of GRN 000526. We evaluated this notice and responded in a letter dated March 23, 2015, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

the manufacturing process is monitored for contamination, and that *B. coagulans* spore preparation is manufactured under current good manufacturing practices using food-grade materials. Unique Biotech states that none of the raw materials used in the manufacture of the spore preparation is derived from the nine major allergens.

Unique Biotech provides specifications for *B. coagulans* spore preparation that include total viable spore count (≥1.5 x 10^{10} CFU/g); moisture (≤5.0%); heavy metals, including lead (≤0.2 mg/kg); and limits for microorganisms, including yeast and mold (≤50 CFU/g), coliforms (≤10 CFU/g), *Escherichia coli* (absent in 10 g), *Salmonella* serovars (absent in 25 g), *Cronobacter* spp. (absent in 25 g), and *Listeria monocytogenes* (absent in 25 g). Unique Biotech provides the results of three non-consecutive batch analyses to demonstrate that *B. coagulans* spore preparation can be manufactured to meet these specifications.

Unique Biotech estimates the dietary exposure to *B. coagulans* spore preparation to be 4.27 x 10^{8} CFU/kg body weight (bw)/d based on the highest 90th percentile infant formula consumption of 213.4 mL/kg bw/d; the highest reported energy consumption of 143 kcal/kg bw/d; and an assumption that infant formula contains 67 kcal/100 mL. Unique Biotech states that the intended uses of *B. coagulans* spore preparation are substitutional for those described in GRNs 000660 and 000864.[2]

Unique Biotech discusses data and information used to support the safety of *B. coagulans* spore preparation, including a history of safe use of *B. coagulans* in fermented foods, such as dairy and meat products. Unique Biotech performed a literature search on the safety and toxicity of *B. coagulans,* including *B. coagulans* Unique IS-2 and other strains, through October 2023. Unique Biotech cites published pre-clinical toxicity studies in animals, as well as human clinical studies with infants, children, and adults in which *B. coagulans* spore preparation and other strains of *B. coagulans* were ingested, showing *B. coagulans* spore preparation is safe and well-tolerated. Unique Biotech also cites published studies noting they did not reveal any pathogenic or opportunistic illness in healthy individuals following administration of *B. coagulans*.

Based on the totality of the data and information, Unique Biotech concludes that *B. coagulans* spore preparation 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.*

[2] A preparation of *B. coagulans* GBI-30, 6086 spores was the subject of GRN 000660. *B. coagulans* SNZ 1969 spore preparation was the subject of GRN 000864. We evaluated these notices and responded in letters dated January 13, 2017, and February 6, 2020, stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

coagulans spore preparation 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.

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 Unique Biotech'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 Unique Biotech'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 Unique Biotech provided, as well as other information available to FDA, we have no questions at this time regarding Unique Biotech'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 001177 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2024.07.05 14:06:19 -04'00'

Susan J. Carlson, Ph.D.
Director
Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition