William J. Rowe
GRAS Associates, LLC
11810 Grand Park Ave.
Suite 500
North Bethesda, MD 20852

Re: GRAS Notice No. GRN 000955

Dear Mr. Rowe:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000955. We received the notice that you submitted on behalf of BIO-CAT Microbials, LLC (BIO-CAT) on June 11, 2020 and filed it on November 10, 2020. BIO-CAT submitted amendments to the notice on January 19, 2021, and February 8, 2021, providing information about the microorganism, clarifications on specifications and intended use, and an updated literature search.

The subject of the notice is *Bacillus subtilis* strain BS-MB40 PTA-122264 (*B. subtilis* BS-MB40 PTA-122264) spore preparation for use as an ingredient in baked goods and baking mixes; beverage and beverage bases, nonalcoholic; breakfast cereals; cheeses; chewing gum; coffee and tea; condiments and relishes; confections and frostings; dairy product analogs; fats and oils; fruit juices; frozen dairy desserts and mixes; fruit and water ices; gelatins, puddings, and fillings; grain products and pasta; hard candy and soft candy; herbs, seeds, spices, seasonings, blends, extracts, and flavorings; jams and jellies; milk and milk products; nut and nut products; plant protein products; processed fruits and fruit juices; processed vegetables and vegetables juices; snack foods; soups and soup mixes; sugar and sugar substitutes; and sweet sauces, toppings, and syrups at a maximum level of $2 \times 10^9$ colony forming units (CFU)/serving.[1] The notice informs us of BIO-CAT's view that these uses of *B. subtilis* BS-MB40 PTA-122264 spore preparation are GRAS through scientific procedures.

BIO-CAT describes *B. subtilis* BS-MB40 PTA-122264 spore preparation as a light tan to tan-colored powder. BIO-CAT states that *B. subtilis* BS-MB40 PTA-122264 is a non-pathogenic, non-toxigenic, spore-forming, Gram-positive, rod-shaped bacterium. The strain was isolated from the soil and is deposited in the strain collection of the American Type Culture Collection (ATCC) in Manassas, Virginia. BIO-CAT discusses the results of the phenotypic and genotypic characterization used to confirm the strain's identity.

BIO-CAT describes the manufacture of *B. subtilis* BS-MB40 PTA-122264 spore

[1] BIO-CAT states that *B. subtilis* BS-MB40 PTA-122264 spore preparation is not intended for use in infant formula or in any products under the jurisdiction of the United States Department of Agriculture (USDA).

preparation by fermentation of a pure culture. Following fermentation, acid is added to the bacterial culture to decrease the pH to 4.5[2]; the stabilized culture is concentrated by centrifugation, followed by addition of maltodextrin so that the total solids is up to 10%, and then spray dried. BIO-CAT states that the resulting product is blended with additional maltodextrin (or other food-grade diluents, such as sodium chloride, calcium carbonate, and sodium bicarbonate), resulting in the final spore preparation. BIO-CAT states that no components of the fermentation medium are allergens or are derived from allergenic sources.[3] BIO-CAT states that the *B. subtilis* BS-MB40 PTA-122264 spore preparation is manufactured under current good manufacturing practices using food-grade raw materials.

BIO-CAT provides specifications for *B. subtilis* BS-MB40 PTA-122264 spore preparation that include total viable spore count (not less than $10^{11}$ CFU/g); moisture (< 10%); heavy metals, including lead (< 0.5 mg/kg); yeast and mold (≤ 300 CFU/g); coliforms (≤ 30 CFU/g); *Escherichia coli* (negative/25 g); *Salmonella* serovars (negative/25 g); *Staphylococcus aureus* (not detected)[4]; and *Listeria* spp. (negative/25 g). BIO-CAT provides the results from the analyses of five non-consecutive lots to demonstrate that the ingredient can be manufactured to conform with the provided specifications. BIO-CAT states that results of stability testing indicate that *B. subtilis* BS-MB40 PTA-122264 spore preparation is stable for up to 30 months at room temperature (21±2 °C).

BIO-CAT states that according to a publication from the USDA Center for Nutrition Policy and Promotion, males aged 51 years and older consume the highest number of servings of food at 18.2 servings per day. Using this estimate, and assuming that *B. subtilis* BS-MB40 PTA-122264 spore preparation is added at the maximum use level of $2 \times 10^9$ CFU/serving, BIO-CAT estimates the maximum dietary exposure to *B. subtilis* BS-MB40 PTA-122264 spore preparation to be $3.64 \times 10^{10}$ CFU/d from the intended uses.

BIO-CAT describes the history of safe use of *B. subtilis* in human food, specifically in fermented food products, and explains that *B. subtilis* has been isolated from water, soil, air, and decomposing plant matter. BIO-CAT performed a literature search through January 2021 and summarizes published literature and governmental reviews that support the safety of consumption of *B. subtilis* BS-MB40 PTA-122264 spore preparation, including a published 14-day oral toxicity study and two published clinical studies, with no reports of toxicity or treatment-related effects noted. BIO-CAT explains that infection linked to *B. subtilis* is rare and the species is generally regarded as non-

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[2] BIO-CAT states that spores will survive at pH 4.5 while vegetative cells will not. Furthermore, BIO-CAT explains that the vegetative cells will not survive the spray drying process. As such, BIO-CAT states that *B. subtilis* BS-MB40 PTA-122264 spore preparation is as close to 100% spores as can be measured.

[3] BIO-CAT states that *B. subtilis* BS-MB40 PTA-122264 spore preparation is produced on an allergen-free medium. However, BIO-CAT manufactures other *Bacillus* products that contain soy and milk in the fermentation medium, and therefore states that the product may contain traces of soy and milk.

[4] BIO-CAT states that the limit of detection for *S. aureus* is 10 CFU/g; however, BIO-CAT explains that any detectable growth of *S. aureus* in the final product is considered a failed test, resulting in destruction of the final product.

pathogenic and non-toxigenic.

BIO-CAT includes the report of a panel of individuals (BIO-CAT's GRAS panel). Based on its review, BIO-CAT's GRAS panel concluded that *B. subtilis* BS-MB40 PTA-122264 spore preparation is safe under the conditions of its intended use.

Based on the totality of evidence, BIO-CAT concludes that *B. subtilis* BS-MB40 PTA-122264 spore preparation is GRAS for its intended use.

**Standards of Identity**

In the notice, BIO-CAT states its intention to use *B. subtilis* BS-MB40 PTA-122264 spore preparation in several food categories, including foods for which standards of identity exist, located in Title 21 of the CFR. 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). If products containing *B. subtilis* BS-MB40 PTA-122264 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 (CFSAN). 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. subtilis* BS-MB40 PTA-122264 spore preparation may require labeling under the FD&C Act because it may contain protein derived from soy and milk. 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 in CFSAN.

**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 BIO-CAT's notice concluding that *B. subtilis* BS-MB40 PTA-122264 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. subtilis* BS-MB40 PTA-122264 spore preparation. Accordingly, our response should not be construed to be a statement that foods containing *B. subtilis* BS-MB40 PTA-122264 spore preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

**Conclusions**

Based on the information that BIO-CAT provided, as well as other information available to FDA, we have no questions at this time regarding BIO-CAT's conclusion that *B. subtilis* BS-MB40 PTA-122264 spore preparation is GRAS under its intended conditions of use. This letter is not an affirmation that *B. subtilis* BS-MB40 PTA-122264 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 000955 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.03.26 17:18:55 -04'00'

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