James Heimbach, Ph.D.
JHeimbach LLC
923 Water Street
#66
Port Royal, VA 22535

Re: GRAS Notice No. GRN 000905

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000905. We received the notice that you submitted on behalf of SporeGen Ltd. (SporeGen) on January 28, 2020 and filed it on March 5, 2020. SporeGen submitted amendments to the notice on April 7, 2020, April 8, 2020, and April 13, 2020, providing additional manufacturing specifications, safety information, and clarification on the intended use.

The subject of the notice is *Bacillus subtilis* strain DSM 32444 (*B. subtilis* DSM 32444) spore preparation for use as an ingredient in conventional foods (excluding infant formula and foods under the jurisdiction of the United States Department of Agriculture) at a level of 10^9 colony forming units (CFU)/serving.[1] The notice informs us of SporeGen's view that this use of *B. subtilis* DSM 32444 spore preparation is GRAS through scientific procedures.

SporeGen describes *B. subtilis* DSM 32444 spore preparation as an opal powder. SporeGen states that *B. subtilis* DSM 32444 is a Gram-positive, motile, spore-forming, rod-shaped bacterium. The strain was isolated from the feces of a healthy human and is deposited in the strain collection of the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ) in Braunschweig, Germany. SporeGen discusses the results of phenotypic and genotypic characterization used to confirm the strain's identity. SporeGen describes the manufacture of *B. subtilis* DSM 32444 spore preparation by fermentation of a pure culture under controlled conditions. After 48 hours, the culture is comprised of approximately 90% spores. The bacterial culture is then concentrated by centrifugation. The final spore suspension is then heat-treated at 68°C for 1 hour[2], brought to room temperature and freeze-dried. The freeze-dried powder is milled to reduce aggregates. SporeGen states that the freeze-dried powder is formulated with food grade excipients, such as maltodextrin, and that no components of the fermentation media are allergens or are derived from allergenic sources. The manufacturing process

[1] SporeGen states that over 99% of the CFUs in this preparation are in the form of spores.

[2] SporeGen states that heat treatment at 68°C for 1 hour kills any residual vegetative cells, and each batch is checked for conformance.

is monitored for contamination at all stages, including the starting culture, fermentation, centrifugation, and spray drying. SporeGen states that *B. subtilis* DSM 32444 spore preparation is manufactured under current good manufacturing practices using food-grade materials.

SporeGen provides specifications for *B. subtilis* DSM 32444 spore preparation that include spore density (≥ 10^{11} CFU/g), water content (≤ 10%), ash (≤ 2%) and limits for other microorganisms, including fungal spores (≤ 10 CFU/1 g), coliforms (≤ 10 CFU/1 g), *Escherichia coli* (absent in 1 g), *Salmonella* serovars (absent in 25 g), *Staphylococcus aureus* (≤ 5 CFU/1 g), *Clostridium perfringens* (≤ 10 CFU/1 g), *Bacillus cereus* (≤ 10 CFU/1 g) and heavy metals, including lead (≤ 0.5 mg/kg). SporeGen provides the results from batch analyses of five non-consecutive lots to demonstrate that the ingredient can be manufactured to conform with the provided specifications.

SporeGen intends to use *B. subtilis* DSM 32444 spore preparation as an ingredient in conventional foods at a level of 10^9 CFU/serving. SporeGen states that in an extreme case, an individual might consume as many as five servings of food containing *B. subtilis* DSM 32444 spore preparation in a day. This would result in consumption of up to 5 x 10^9 viable spores in a day.

SporeGen states that members of the genera *Bacillus* are commensals within the digestive tract of humans and animals. SporeGen describes the history of safe use of *B. subtilis* in fermented foods. SporeGen relies on published literature that supports the safety of consumption of *B. subtilis* DSM 32444 spore preparation. SporeGen states that numerous strains of *B. subtilis* with close homology to *B. subtilis* DSM 32444 are non-pathogenic and non-toxigenic. Additionally, SporeGen describes published human tolerance studies in which adults were fed *B. subtilis* and states that no significant adverse effects were noted in any of these studies.

SporeGen includes the statement of a panel of individuals (SporeGen's GRAS panel). Based on its review, SporeGen's GRAS panel concluded that *B. subtilis* DSM 32444 spore preparation is safe under the conditions of its intended use.

Based on the totality of evidence, SporeGen concludes that *B. subtilis* DSM 32444 spore preparation is GRAS for its intended use.

Standards of Identity

In the notice, SporeGen states its intention to use *B. subtilis* DSM 32444 spore preparation in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations. 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* DSM 32444 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 (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.

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 SporeGen's notice concluding that *B. subtilis* DSM 32444 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* DSM 32444 spore preparation. Accordingly, our response should not be construed to be a statement that foods containing *B. subtilis* DSM 32444 spore preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that SporeGen provided, as well as other information available to FDA, we have no questions at this time regarding SporeGen's conclusion that *B. subtilis* DSM 32444 spore preparation is GRAS under its intended conditions of use. This letter is not an affirmation that *B. subtilis* DSM 32444 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 000905 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2020.06.08 11:57:20 -04'00'

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