



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

Re: GRAS Notice No. GRN 000949

Dear Dr. Heimbach:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000949. We received the notice that you submitted on behalf of Advanced Enzymes Technologies Ltd. (Advanced Enzymes) on June 3, 2020 and filed it on October 7, 2020. Advanced Enzymes submitted an amendment to the notice on December 1, 2020, providing information about the microorganism, additional manufacturing specifications, and results from analysis of three non-consecutive batches.

The subject of the notice is *Bacillus coagulans* strain DSM 17654 (*B. coagulans* DSM 17654) spore preparation for use at a maximum level of 2×10^9 colony forming units (CFU)/serving as an ingredient in baked goods and baking mixes; breakfast cereals; beverages and beverage bases; coffee and tea; milk and milk products; dairy product analogs; fruit juices; condiments and relishes; confections and frostings; frozen dairy desserts and mixes; fruit and water ices; jams and jellies; gelatins, puddings and fillings; grain products and pastas; hard and soft candy; chewing gum; extracts, flavorings, herbs, seeds, spices, seasonings and blends; nuts and nut products; plant protein products; processed fruits; processed vegetables and vegetable juices; snack foods; soups and soup mixes; sugar; and sweet sauces, toppings and syrups.¹ The notice informs us of Advanced Enzymes' view that these uses of *B. coagulans* DSM 17654 spore preparation are GRAS through scientific procedures.

Advanced Enzymes describes *B. coagulans* DSM 17654 spore preparation as a light brown to brown-colored powder. Advanced Enzymes states that *B. coagulans* DSM 17654 is a Gram-positive, non-pathogenic, non-toxicogenic, motile, spore-forming, rod-shaped bacterium. The strain was isolated from the soil and is deposited in the strain collection of the Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ) in Braunschweig, Germany. Advanced Enzymes discusses the results of the phenotypic and genotypic characterization used to confirm the strain's identity.

¹ Advanced Enzymes states that *B. coagulans* DSM 17654 spore preparation is not intended for use in infant formula, foods formulated for infants, or any products under the jurisdiction of the United States Department of Agriculture.

U.S. Food and Drug Administration
Center for Food Safety & Applied Nutrition
5001 Campus Drive
College Park, MD 20740
www.fda.gov

Advanced Enzymes describes the manufacture of *B. coagulans* DSM 17654 spore preparation by fermentation of a pure culture under controlled conditions. When the desired spore count is reached, the fermentation is complete. The bacterial culture is then heat-treated at 75 °C for 30 minutes², centrifuged to separate the spores from the soluble media components and water, and the spores are then washed and spray dried in the presence of approved food-grade stabilizers, such as maltodextrin. Advanced Enzymes states that no components of the fermentation media are allergens or are derived from allergenic sources. Advanced Enzymes states that the manufacturing process is monitored for contamination, and that *B. coagulans* DSM 17654 spore preparation is manufactured under current good manufacturing practices using food-grade materials.

Advanced Enzymes provides specifications for *B. coagulans* DSM 17654 spore preparation that include total viable spore count (not less than 1.5×10^{11} CFU/g); moisture (not more than 7.0%); heavy metals, including lead (not more than 0.5 mg/kg); and limits for other microorganisms, including total bacterial counts (not more than 2×10^5 CFU/g), yeast and mold (not more than 100 CFU/g), coliforms (not more than 100 CFU/g), *Escherichia coli* (absent in 10 g), *Salmonella* serovars (absent in 10 g), *Pseudomonas aeruginosa* (absent in 1 g), *Staphylococcus* spp. (absent in 1 g), and *Listeria monocytogenes* (absent in 25 g). Advanced Enzymes provides the results from the analyses of three non-consecutive lots to demonstrate that the ingredient can be manufactured to conform with the provided specifications. Advanced Enzymes states that stability testing was performed on *B. coagulans* DSM 17654 spore preparation and that the results indicate that the shelf life is at least 3 years under real-time storage conditions (25 °C, 60% relative humidity).

Advanced Enzymes indicates that the intended uses for *B. coagulans* DSM 17654 spore preparation are the same as those in GRNs 000399, 000526, 000597, and 000691.³ Advanced Enzymes states that because their intended use is the same as for already existing uses for other strains of *B. coagulans*, there will be no increase in consumer exposure to *B. coagulans* as this is just an alternative strain. Advance Enzyme states that the exposure would be the same as that in GRN 000399 of 36.4×10^9 CFU/d.

Advanced Enzymes describes the history of safe use of *B. coagulans* in human food and explains that *B. coagulans* has been isolated from several fermented foods. Advanced Enzymes relies on published literature and governmental reviews that support the safety of consumption of *B. coagulans* DSM 17654 spore preparation, including acute, subacute, subchronic and chronic studies, with no reports of toxicity or significant adverse effects. Advanced Enzymes states that no evidence of pathogenicity of *B.*

² Advanced Enzymes states that heat-treatment at 75 °C for 30 minutes assures that any vegetative cells are killed, and the only viable organisms in the final product are spores.

³ The subjects of GRNs 000399, 000526, 000597, and 000691 are *B. coagulans* strain “GBI-30, 6086” spore preparation, *B. coagulans* strain “Unique IS2” spore preparation, *B. coagulans* strain “SNZ1969” spore preparation, and *B. coagulans* strain “SANK 70258” spore preparation, respectively. We evaluated these notices and responded in letters dated July 31, 2012, March 23, 2015, February 29, 2016, and August 28, 2017, respectively, stating that we had no questions at that time regarding the notifiers’ GRAS conclusions.

coagulans DSM 17654 has been reported, and the species is generally regarded as non-pathogenic and non-toxicogenic. Additionally, Advanced Enzymes describes published human tolerance studies in which children and adults were fed *B. coagulans* and states that no significant adverse effects were noted in any of these studies.

Advanced Enzymes includes the report of a panel of individuals (Advanced Enzymes' GRAS panel). Based on its review, Advanced Enzymes' GRAS panel concluded that *B. coagulans* DSM 17654 spore preparation is safe under the conditions of its intended use.

Based on the totality of evidence, Advanced Enzymes concludes that *B. coagulans* DSM 17654 spore preparation is GRAS for its intended use.

Standards of Identity

In the notice, Advanced Enzymes states its intention to use *B. coagulans* DSM 17654 spore preparation in several food categories, including foods for which standards of identity exist, located in Title 21 of the Code of Federal Regulations (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. coagulans* DSM 17654 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.

Potential Requirement for a Color Additive Petition

There is no GRAS provision for color additives. In the notice, Advanced Enzymes describes *B. coagulans* DSM 17654 spore preparation as a light brown to brown-colored powder. As such, the use of *B. coagulans* DSM 17654 spore preparation in food products may constitute a color additive use under section 201(t)(1) of the FD&C Act and FDA's implementing regulations in 21 CFR Part 70. Under section 201(t)(1) and 21 CFR 70.3(f), a color additive is a material that is a dye, pigment, or other substance made by a synthetic process or similar artifice, or is extracted, isolated, or otherwise derived from a vegetable, animal, mineral, or other source. Under 21 CFR 70.3(g), a material that otherwise meets the definition of a color additive can be exempt from that definition if it is used (or is intended to be used) solely for a purpose or purposes other than coloring.

Our response to GRN 000949 is not an approval for use as a color additive nor is it a finding of the Secretary of the Department of Health and Human Services within the meaning of section 721(b)(4) of the FD&C Act. Questions about color additives should be directed to the Division of Food Ingredients in OFAS.

Section 301(ll) of the Federal Food, Drug, and Cosmetic Act (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 Advanced Enzymes' notice concluding that *B. coagulans* DSM 17654 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* DSM 17654 spore preparation. Accordingly, our response should not be construed to be a statement that foods containing *B. coagulans* DSM 17654 spore preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Advanced Enzymes provided, as well as other information available to FDA, we have no questions at this time regarding Advanced Enzymes' conclusion that *B. coagulans* DSM 17654 spore preparation is GRAS under its intended conditions of use. This letter is not an affirmation that *B. coagulans* DSM 17654 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 000949 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

Digitally signed by
Susan J. Carlson -S
Date: 2021.01.07
17:52:00 -05'00'

Susan Carlson, Ph.D.

Director

Division of Food Ingredients
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition