



Madhu G. Soni, PhD, FACN, FATS
Soni & Associates, Inc.
749 46th Square
Vero Beach, FL 32968

Re: GRAS Notice No. GRN 000864

Dear Dr. Soni:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000864. We received the notice that you submitted on behalf of Sanzyme Biologics Pvt. Ltd (Sanzyme) on May 28, 2019, and filed it on July 10, 2019. Sanzyme submitted amendments to the notice on October 2, 2019, that clarified the intended use in infant formulas and the source of maltodextrin used in the spore preparation, and on December 19, 2019, and January 17, 2020, that clarified the analytical methods used to demonstrate conformance with the stated specifications.

The subject of the notice is *Bacillus coagulans* SNZ 1969 spore preparation (*B. coagulans* spore preparation) for use as an ingredient in non-exempt infant formulas for term infants, at levels up to 2×10^8 colony forming units (CFU) per 100 mL infant formula, as consumed. The notice informs us of Sanzyme's view that this use of *B. coagulans* spore preparation is GRAS through scientific procedures.

Sanzyme states that *B. coagulans* is a Gram-positive, spore-forming, rod-shaped bacterium, which was isolated from green malt in 1949. The SNZ 1969 strain is deposited in the Microbial Type Culture Collection as MTCC 5724 and in the Belgian Coordinated Collections of Microorganism as LMG S - 27484. Sanzyme discusses the results of phenotypic and genotypic characterization used to confirm the strain's identity.

Sanzyme describes the manufacture of *B. coagulans* spore preparation as a pure culture fermentation under controlled conditions. Sanzyme states that the manufacturing process is identical to that used to produce the *B. coagulans* spore preparation that was the subject of GRN 000597.¹ After fermentation, the bacterial spores are concentrated by centrifugation, spray-dried to a powder and mixed with maltodextrin or milk-derived lactose to obtain the desired final concentration of the spores. Sanzyme states that *B. coagulans* spore preparation is manufactured under current good manufacturing

¹ GRN 000597 describes uses of *B. coagulans* SNZ 1969 spore preparation as an ingredient in conventional food categories at levels up to 2×10^9 CFU/serving. We evaluated this notice and responded in a letter on February 29, 2016, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

practices with processing aids, fermentation media, and diluents that are either approved as food additives or are GRAS for their intended use.

Sanzyme provides specifications for *B. coagulans* spore preparation that include a viable spore count of 5×10^{10} spores/g, and limits for microorganisms, including total bacteria ($\leq 1 \times 10^5$ CFU/g), yeast and molds (≤ 10 CFU/g), *Escherichia coli* (absent in 10 g), *Salmonella* serovars (absent in 10 g) and *Cronobacter sakazakii* (absent in 100 g). Sanzyme provides the results of batch analyses for five non-consecutive lots to show that the product can be manufactured to comply with the stated specifications. Sanzyme states that the analytical methods were validated for these analyses.

Sanzyme intends to use *B. coagulans* spore preparation as an ingredient in non-exempt infant formulas for term infants, at levels up to 2×10^8 CFU/100 mL infant formula, as consumed. Sanzyme notes that this is the same use level as the subject of GRN 000660,² which describes the use of *B. coagulans* GBI-30, 6086 spore preparation in non-exempt infant formulas for term infants. Sanzyme estimates dietary exposure to *B. coagulans* spore preparation to be 4.27×10^8 CFU/kg bodyweight/day. Sanzyme states that the intended use is not expected to affect the current dietary exposure to *B. coagulans* spores provided in GRN 000660. Additionally, Sanzyme states that the dietary exposure to *B. coagulans* spore preparation for infants consuming conventional foods would be substitutional to that from infant formulas.

Sanzyme discusses the data used to support the safety of consumption of *B. coagulans* spore preparation. Sanzyme describes the results of published animal studies, which demonstrate that consumption of *B. coagulans* strains did not induce acute, subchronic, or chronic toxicity. Sanzyme discusses the results of clinical studies where *B. coagulans* was consumed by children (including infants) and adults and reports that no relevant adverse reactions were observed. Sanzyme also describes the results of unpublished studies demonstrating that *B. coagulans* is susceptible to antibiotics, and based on whole genome sequence analyses, does not possess antibiotic resistance or virulence factor genes.

Sanzyme notes that in 21 CFR 184.1372, *B. coagulans* is described as a non-pathogenic and non-toxicogenic production organism for insoluble glucose isomerase enzyme preparation. Sanzyme also cites GRAS notices that describe food uses of *B. coagulans* cultures, *B. coagulans* spore preparations, and inactivated *B. coagulans*.³ Sanzyme notes that the European Food Safety Authority concluded that *B. coagulans* met Qualified Presumption of Safety criteria in 2008 and has maintained this status. Sanzyme discusses the regulatory status and uses of *B. coagulans* in Canada, India, and Japan. Sanzyme states that *B. coagulans* is classified as a Biosafety Level 1 organism not

² GRN 000660 describes uses of *B. coagulans* GBI-30, 6086 spore preparation as an ingredient in non-exempt powdered and liquid infant formulas for term infants at levels up to 2×10^8 CFU/100 mL infant formula as consumed. We evaluated this notice and responded in a letter on January 13, 2017, stating that we had no questions at that time regarding the notifier's GRAS conclusion.

³ Between 2008 and 2018, FDA evaluated GRNs 000240, 000378, 000399, 000526, 000597, 000601, 000660, 000670, 000691, and 000725 and issued letters stating that we had no questions at that time regarding the notifiers' GRAS conclusions.

known to cause disease in healthy humans. Sanzyme states that a comprehensive literature search for safety and toxicity information on *B. coagulans* SNZ 1969 and other strains was conducted through March 2019.

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

Based on the totality of the available data and information, Sanzyme concludes that *B. coagulans* spore preparation is GRAS under the conditions of its intended use.

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* 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.

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. coagulans* spore preparation that has been formulated with lactose requires labeling under the FD&C Act.

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 Sanzyme'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 in the Center for Food Safety and Applied Nutrition.

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 Sanzyme’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 Sanzyme provided, as well as other information available to FDA, we have no questions at this time regarding Sanzyme’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 000864 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J.
Carlson -S

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