



Mary M. Murphy
Exponent, Inc.
1150 Connecticut Ave., NW
Suite 1100
Washington, DC 20036

Re: GRAS Notice No. GRN 000691

Dear Ms. Murphy:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000691. We received the notice that you submitted on behalf of Mitsubishi-Chemical Foods Corporation (MFC) on February 6, 2017 and filed it on March 2, 2017. We received an amendment to the notice on May 16, 2017. The amendment contained additional information on the manufacturing process, product identity, formulation and intended uses. In an amendment dated June 13, 2017, MFC designated some of the information contained in the May 16, 2017 amendment as confidential.¹

The subject of the notice is *Bacillus coagulans* SANK 70258 spore preparation (*B. coagulans* spore preparation) for use as an ingredient at a maximum level of 2×10^9 colony forming units (CFU)/serving in baked goods and baking mixes; beverages and beverage bases; breakfast cereals; chewing gum; coffee and tea; condiments and relishes; confections and frostings; dairy product analogs; fruit juices; frozen dairy desserts and mixes; fruit and water ices; gelatins, puddings and fillings; grain products and pastas; hard candy; herbs, seeds, spices, seasonings, blends, extracts, and flavorings; jams and jellies; milk and milk products; nuts and nut products; plant protein products; processed fruits; processed vegetables and vegetable juices; snack foods; soft candy; soups, and soup mixes; sugar; and sweet sauces, toppings, and syrups.² The notice informs us of the view of MFC that this use of *B. coagulans* spore preparation is GRAS through scientific procedures.

MFC describes the identity and composition of *B. coagulans* spore preparation. *B. coagulans* SANK 70258 is a Gram-positive, spore-forming, lactic acid bacterium, which was isolated from green malt in 1949. MFC states that *B. coagulans* spore preparation is a white to yellow powder.

¹ An amendment to GRN 000691 was received on May 16, 2017. It included information about the manufacturing process among other topics. On June 13, 2017, MFC designated some of the information about the manufacturing process as confidential.

² MFC states that *B. coagulans* SANK 70258 spore preparation is not intended for use in any products that are under the jurisdiction of the United States Department of Agriculture.

MFC describes the manufacture of *B. coagulans* spore preparation. The strain is fermented under pH- and temperature-controlled conditions. After fermentation, the spores are separated from the fermentation medium by centrifugation, are dried, and blended with the diluent milk-derived lactose. MFC states that all materials used in manufacturing are food grade and are used in accordance with current good manufacturing practices.

MFC provides specifications for *B. coagulans* spore preparation that include a minimum of 5×10^9 CFU/g and limits for heavy metals (0.5 mg/kg) and microbial limits including total bacteria (1,000 CFU/g), fungi (500 CFU/g), and coliforms (absent in 1 g sample). MFC provides the results of six non-consecutive batch analyses to demonstrate compliance with these specifications.

MFC estimates the dietary exposure to *B. coagulans* spore preparation. MFC intends to use *B. coagulans* spore preparation in the same food categories and at the same use level (2×10^9 cfu/serving) described in GRN 000399,³ where the exposure was calculated to be 36.4×10^9 CFU/day. MFC expects that the uses of *B. coagulans* spore preparation that is the subject of GRN 000691 would be substitutional for other sources of *B. coagulans* spore preparations and therefore the intended use of this ingredient would not increase exposure.

MFC discusses published and unpublished data and information to support the safety of *B. coagulans* spore preparation and *B. coagulans* SANK 70258. MFC incorporates into this notice, the safety information provided in previous GRAS notices describing the intended uses of other *B. coagulans* spore preparations (GRNs 000399,² 000526,⁴ and 000597⁵) in conventional foods, noting that we had no questions in response to the GRAS conclusions at the time of each evaluation. MFC notes that its literature search on the safety of *B. coagulans* spore preparation includes information gathered through June 8, 2016. MFC discusses published studies conducted in rats demonstrating that *B. coagulans* spore preparations do not induce acute, subchronic, chronic, or reproductive toxicity following consumption. The *in vitro* studies incorporated show that *B. coagulans* spore preparation is not mutagenic or genotoxic. MFC cites published human studies conducted to investigate effects of ingesting *B. coagulans*, including a randomized, controlled clinical trial in which adults were orally administered with *B. coagulans* SANK 70258 spores at levels up to 4×10^8 CFU/day for eight weeks with no treatment-related adverse events. MFC states that *B. coagulans* SANK 70258 is non-

³ GRN 000399 describes the use of a preparation of *B. coagulans* strain GBI-30, 6086 spores. We evaluated this notice and responded with a letter on July 31, 2012, stating that we had no questions at that time regarding Ganeden Biotech, Inc.'s GRAS conclusion.

⁴ GRN 000526 describes the intended use of a preparation of *B. coagulans* strain Unique IS2 spores. We evaluated this notice and responded with a letter on March 23, 2015, stating that we had no questions at that time regarding Unique Biotech's GRAS conclusion.

⁵ GRN 000597 describes the intended use of a preparation of *B. coagulans* strain SNZ1969 spores. We evaluated this notice and responded with a letter on February 29, 2016, stating that we had no questions at that time regarding Sanzyme's GRAS conclusion. MFC describes *B. coagulans* SNZ1969 as closely related to *B. coagulans* SANK 70258.

pathogenic and non-toxigenic. MFC discusses the results of published and unpublished studies that demonstrate *B. coagulans* SANK 70258 is susceptible to antibiotics and that there is no evidence suggesting that the strain transmits antibiotic resistance genes. MFC discusses the results of an unpublished *in vitro* test demonstrating that *B. coagulans* SANK 70258 is negative for enterotoxin and hemolysin.

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

Based on the totality of information discussed above, MFC concludes that *B. coagulans* spore preparation is GRAS for its intended use.

Standards of Identity

In the notice, MFC states its intention to use *B. coagulans* 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 (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). The notice raises a potential issue under these labeling provisions. In the notice, MFC cites studies that describe *B. coagulans* spore preparation as having certain health benefits. 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 (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. MFC's *B. coagulans* spore preparation may require labeling under the FD&C Act because the spore preparation is blended with milk-derived lactose which may contain milk-derived protein. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Biotechnology and GRAS

Notice Review in OFAS. Questions related to food labeling in general 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 MFC'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 MFC provided, as well as other information available to FDA, we have no questions at this time regarding MFC's conclusion that *Bacillus coagulans* SANK 70258 spore preparation is GRAS under its intended conditions of use. This letter is not an affirmation that *B. coagulans* SANK 70258 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 000691 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Dennis M. Keefe

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Dennis M. Keefe, Ph.D.

Director

Office of Food Additive Safety

Center for Food Safety

and Applied Nutrition

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