Marco Marcucci
Taixing Dongsheng Bio-Tech Co., Ltd.
No.1 Tonglian Rd., Huangqiao Town
Taixing City, Jiangsu Province
People's Republic of China
225411

Re: GRAS Notice No. GRN 001021

Dear Mr. Marcucci,

The Food and Drug Administration (FDA, we) completed our evaluation of Taixing Dongsheng Bio-Tech Co., Ltd. (TDS Biotech)'s supplement to GRN 001021. We received the supplement on October 23, 2023. The supplement addresses additional uses for a transglutaminase enzyme preparation produced by *Streptomyces mobaraensis* strain M2020197 (transglutaminase enzyme preparation), as well as a change in the manufacturing process. TDS Biotech submitted additional information on March 20, 2024, to clarify intended uses and provide additional information on batch analysis data and enzyme activity.

We previously responded to GRN 001021 on November 3, 2022. We stated that we had no questions at that time regarding TDS Biotech's conclusion that transglutaminase enzyme preparation is GRAS for use as an enzyme at a maximum level of 97.6 mg Total Organic Solids (TOS) per kg food in fish products (including restructured fish and shellfish, excluding Siluriformes fish products), dairy products, meat analogs, baked goods (including pastries and breads), pasta and noodles, grain mixtures, and ready-to-eat cereals, and for use as a binder at a maximum level of 65 mg TOS per kg in meat and poultry products.

In the supplement received October 23, 2023, TDS Biotech informed us of its view that transglutaminase enzyme preparation is GRAS for use as an enzyme at a maximum level of 71.4 mg TOS per kg food in fish products (including restructured fish and shellfish, excluding Siluriformes fish products), dairy products, dairy analogs, meat analogs, fish analogs, baked goods (including pastries and breads), pasta and noodles, grain mixtures, and ready-to-eat cereals and for use as a binder at a maximum use level of 47.6 mg TOS per kg food in meat and poultry products.

In GRN 001021, TDS Biotech described the manufacturing process for transglutaminase enzyme preparation with submerged fermentation of a pure culture of the *S. mobarensis* M2020197 production strain under controlled conditions. TDS Biotech stated that the fermentation media contained fish protein concentrate. In this

supplement, TDS Biotech states that in the fermentation media, fish protein concentrate was replaced with yeast peptone. Further, the supplement describes modified downstream filtration steps, in which multiple passages in the ultra-filtration stage further concentrate the transglutaminase enzyme. TDS Biotech states that the rest of the manufacturing process is the same as described in GRN 001021.

TDS Biotech states that the transglutaminase enzyme preparation conforms to specifications established in the Food Chemicals Codex (FCC 13, 2023) and to the General Specifications and Considerations for Enzyme Preparations Used in Food Processing established by the FAO/ WHO Joint Expert Committee on Food Additives (JECFA, 2006). TDS Biotech updates food grade specifications for lead (≤0.2 mg/kg) and arsenic (≤0.2 mg/kg) and states that the rest of the specifications remain the same as in GRN 001021. TDS Biotech provides the results of six non-consecutive batch analyses to demonstrate that transglutaminase enzyme preparation produced through the updated manufacturing process can be manufactured to meet the stated specifications.

TDS Biotech notes that the additional filtration steps lead to a higher enzymatic activity in the transglutaminase enzyme preparation. TDS Biotech states that the maximum use levels have been reduced from those of the original GRN 001021 to account for the increased enzymatic activity.

TDS Biotech estimates a maximum dietary exposure to transglutaminase enzyme preparation to be 0.89 mg TOS/kg body weight per day (mg TOS/kg bw/d) from the proposed uses, and the assumption that the transglutaminase enzyme preparation will be active and remain in the final food.[1]

TDS Biotech states that the change to the fermentation medium does not impact the composition of the transglutaminase enzyme preparation significantly. Since the transglutaminase preparation produced as described in this supplement to GRN 001021 is compositionally similar to the transglutaminase preparation previously described in GRN 001021, TDS Biotech states that data and information used to reach a GRAS conclusion in GRN 001021 can be used to support their GRAS conclusion for the change in manufacturing and additional uses. TDS Biotech states that higher enzymatic activity from the change in manufacturing is not a safety concern, and that in fact, the exposure from the intended uses is lowered than what was estimated in the original notice to account for this activity.

Based on the totality of the data and information available, TDS Biotech concludes that transglutaminase enzyme preparation is GRAS for its intended uses.

[1] TDS Biotech uses the Budget Method to estimate dietary exposure to transglutaminase enzyme preparation based on consumption of a maximum of 0.0125 kg of solid foods per kg bw/d containing transglutaminase enzyme preparation.

Standards of Identity

In the supplement, TDS Biotech states its intention to use transglutaminase enzyme 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.

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 nine foods or food groups (i.e., milk, eggs, fish, Crustacean shellfish, tree nuts, peanuts, wheat, soybeans, and sesame) or a food ingredient that contains protein derived from one of those foods. Transglutaminase enzyme standardized with lactose may require labeling under the FD&C Act because it may contain protein derived from milk. Questions about petitions or notifications for exemptions from the food allergen labeling requirements should be directed to the Division of Food Ingredients in the Office of Food Additive Safety. Questions related to food labeling in general should be directed to the Office of Nutrition and Food Labeling in the Center for Food Safety and Applied Nutrition.

Use in Products under USDA Jurisdiction

As provided under 21 CFR 170.270, during our evaluation of the supplement to GRN 001021, we coordinated with the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture. Under the Federal Meat Inspection Act, the Poultry Products Inspection Act, and the Egg Products Inspection Act, FSIS determines the efficacy and suitability of ingredients used in meat, poultry, and egg products, and prescribes safe conditions of use. Suitability relates to the ingredient's effectiveness in performing its intended technical effect and the assurance that the ingredient's use will not result in products that are adulterated or misleading for consumers.

FSIS has completed its review and has no objection to the use of transglutaminase enzyme preparation described in the supplement to GRN 001021. Regarding labeling, meat or poultry products (excluding Siluriformes fish products) containing transglutaminase enzyme are required to be labeled in the ingredients statement of the products in which it is used.

FSIS requested that we advise you to seek regulatory guidance from its Risk Management and Innovations Staff (RMIS) about the use of transglutaminase enzyme preparation in meat, poultry, and egg products. You should direct such an inquiry to Dr. Stephanie Hretz, Director, RMIS, Office of Policy and Program Development, FSIS by email at stephanie.hretz@usda.gov.

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 TDS Biotech's supplement concluding that transglutaminase enzyme 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 transglutaminase enzyme preparation. Accordingly, our response should not be construed to be a statement that foods containing transglutaminase enzyme preparation, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that TDS Biotech provided, as well as other information available to FDA, we have no questions at this time regarding TDS Biotech's conclusion that transglutaminase enzyme preparation is GRAS under its intended conditions of use. This letter is not an affirmation that transglutaminase enzyme 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 the supplement to GRN 001021 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S Digitally signed by Susan J. Carlson -S
Date: 2024.07.22 17:50:53 -04'00'

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

cc: Stephanie Hretz, M.P.H.
Director
USDA/FSIS/OPPD/RMIS
1400 Independence Ave. SW
Washington, DC 20250-3700