Dr. Andrey Nikiforov
Toxicology Regulatory Services, Inc.
154 Hansen Road
Suite 201
Charlottesville, VA 22911

Re: GRAS Notice No. GRN 000977

Dear Dr. Nikiforov:

The Food and Drug Administration (FDA, we) completed our evaluation of GRN 000977. We received the notice that you submitted on behalf of Bonumose, LLC (Bonumose) on October 26, 2020 and filed it on January 27, 2021. Bonumose submitted an amendment to the notice on February 01, 2021, March 17, 2021, and September 13, 2021 clarifying that the uses will not be in food categories under USDA jurisdiction, clarifying information about the source organism for one of the enzymes used in the manufacturing process, and clarifying information about the drying step of the manufacturing process.

The subject of the notice is D-tagatose for use as a nutritive sweetener, flavor enhancer, humectant, texturizer, and stabilizer in food categories as described in Table 1. The notice informs us of Bonumose's view that these uses of D-tagatose are GRAS through scientific procedures.

Table 1
Intended food categories and maximum use levels for D-tagatose

Food Category	Maximum Intended Level of Use (Percent (%))
Tabletop sweetener	100
Ready-to-eat breakfast cereals	33
Diet soft drinks	2
Non-diet soft drinks	3
Confectionery	30
Meal replacement drinks	3
Meal replacement drink mix (powder)	33
Cake, pie	10
Cake mix	15
Frostings	15
Ice cream and frozen yogurt	7.5
Yogurt	7.5

Chewing gum	60
Jelly and pudding	25
Coffee mix powder	38
Biscuits	10
Cookies	10
Cereal bars	25
Ready-to-drink teas	1
Low fat, reduced fat, diet, energy or nutrient fortified bars	10
Regular and dietetic hard candies	15
Dietetic soft candies	10

Bonumose provides information on the identity and composition of D-tagatose (CAS registry number 87-81-0). Bonumose describes D-tagatose as a white crystal or powder containing ≥ 98% D-tagatose on dry matter basis. D-tagatose is a ketohexose, an epimer of D-fructose isomerized at position 4 chiral carbon. Bonumose notes that D-tagatose has approximately 90% of the sweetness of sucrose.

Bonumose describes the use of a production strain expressing six microbially-produced enzymes (4-alpha-glucanotransferase, alpha-glucan phosphorylase, phosphoglucomutase, phosphoglucoisomerase, fructo-6-phosphate-epimerase, tagatose-6-phosphate phosphatase) in a multi-stage manufacturing process for D-tagatose. Bonumose states that the production organism is the non-pathogenic and non-toxigenic *Escherichia coli* BL21 (DE3).[1] Bonumose also states that a seventh enzyme, microbially produced pullulanase used in D-tagatose production, is obtained from a commercially available non-pathogenic and non-toxigenic source.

Bonumose describes the manufacturing process of D-tagatose from food-grade maltodextrin via an enzymatic cascade, followed by purification and drying steps. Bonumose first describes the fermentation of the production strain expressing six of the seven enzymes under controlled conditions, followed by cell homogenization, heating, centrifugation, diafiltration, and lyophilization. Bonumose notes that the seven enzymes are immobilized on a column. An aqueous solution of maltodextrin is passed through the column containing the immobilized enzymes to produce D-tagatose syrup. Bonumose states that the D-tagatose syrup is filtered, passed through an ion-exchange resin, and evaporated stepwise to 60°Bx and 75°Bx with a purification step to remove residual sugars. Solids are separated and dried to white crystals or powder. Bonumose states that the enzymes are not expected to be present in the final D-tagatose. Bonumose states that the D-tagatose is manufactured in accordance with current good manufacturing practices. Bonumose states that the processing and filtering aids, components of the fermentation medium, and the resin utilized for immobilizing the

[1] Bonumose states that the non-pathogenic and non-toxigenic nature of *E. coli* BL21 (DE3) is summarized in GRN 000485. The subject of GRN 000485 is beta-galactosidase enzyme preparation. We evaluated this notice and responded in a letter dated April 15, 2014, stating that we had no questions at the time regarding the notifier's GRAS conclusion.

enzymes are used in accordance with U.S. regulations.

Bonumose provides specifications for D-tagatose that include D-tagatose (≥ 98%), limits for lead (≤ 0.1 mg/kg), arsenic (≤ 0.1 mg/kg), cadmium (≤ 0.1 mg/kg), mercury (≤ 0.1 mg/kg), melting temperature range (133 – 137 °C), specific optical rotation (between -4° and -5.6°), and loss on drying (< 0.5%). Bonumose also notes that additional quality control specifications include aerobic plate count, total coliforms, *E. coli*, *Salmonella* serovars, *S. aureus*, endotoxin, kanamycin activity, *kan* gene, and sulfites. Bonumose provides the results of three non-consecutive batch analyses to demonstrate that D-tagatose can be manufactured to meet the specifications. Bonumose demonstrates that D-tagatose is stable for at least one year at 20 °C, 30 °C, and 40 °C.

Bonumose estimates the dietary exposure to D-tagatose from the intended uses based on food consumption data from the 2011-2012 National Health and Nutrition Examination Survey (NHANES)) dataset. Bonumose first estimates dietary exposure to added sugar[2] to be 58 g/person (p)/day (d) at the middle quintile (41-60%) and 155 g/p/d at the highest quintile (81-100%). Bonumose estimates that an average 30% of added sugars will be replaced with D-tagatose in all foods and beverages, resulting in an estimated dietary exposure to D-tagatose of 17 g/p/d at the middle quintile (aged 2 years and older), 47 g/p/d at the highest quintile (aged 2-18 years), and 53 g/p/d at the highest quintile (aged 19 years and older).[3] Bonumose notes that D-tagatose will be substitutional for the added sugars in the food categories presented in Table 1.

Bonumose references the safety and toxicity data described in previous GRAS notices[4] to corroborate the safety of their D-tagatose. Bonumose discusses findings from published short-term and long-term studies in rats up to a duration of 24 months as well as developmental and reproductive toxicity studies. In a 24-month rat study in which Wistar rats were administered D-tagatose in the diet at 0, 2.5, 5 and 10%, Bonumose concludes that there were no adverse effects up to 10% D-tagatose in the diet. Bonumose also summarizes studies in mice with a duration of up to 168 days in which groups of mice were administered 30% D-tagatose in the diet or in water. In addition, Bonumose summarizes studies in pigs with a duration of up to 33 days at levels up to 20% D-tagatose in the diet. Bonumose concludes that there were no adverse effects associated with D-tagatose in these animal toxicity studies. Bonumose notes that an updated search of the literature through October 2018 did not identify any information that raises safety concerns.

Bonumose describes several published human studies in which healthy adults, adults with non-insulin dependent diabetes mellitus, and/or hyperglycemic adults were given a single dose of D-tagatose up to 75 g or repeated doses of D-tagatose up to 45 g/d for up

[2] The definition of "added sugars" is included in 21 CFR 101.9(c)(6)(iii).

[3] Based on the 2015-2016 NHANES food consumption surveys, FDA estimates the dietary exposure to D-tagatose to be 15.9 g/p/day at the mean and 39.8 g/p/day at the 90th percentile for the U.S. population aged 2 years and older.

[4] We evaluated GRN 000078 and GRN 000352 (D-tagatose), and we responded in letters dated October 24, 2001 and February 1, 2011, respectively, that we had no questions at that time regarding the notifiers' GRAS conclusions.

to 365 days. Bonumose notes that overall D-tagatose was well tolerated in these human studies, with mild and transient gastrointestinal symptoms such as diarrhea, flatulence and bloating observed in some subjects.

Based on the totality of the data and information, Bonumose concludes that its D-tagatose is GRAS under the intended conditions of use.

Standards of Identity

In the notice, Bonumose states its intention to use D-tagatose 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 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 D-tagatose bear any nutrient content or health claims on the label or labeling, such claims are subject to the applicable requirements and are under the purview of 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.

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 Bonumose's notice concluding that D-tagatose 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 D-tagatose. Accordingly, our response should not be construed to be a statement that foods containing D-tagatose, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll).

Conclusions

Based on the information that Bonumose provided, as well as other information available to FDA, we have no questions at this time regarding Bonumose's conclusion that D-tagatose is GRAS under its intended conditions of use. This letter is not an affirmation that D-tagatose 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 170.257(b)(2), the text of this letter responding to GRN 000977 is accessible to the public at www.fda.gov/grasnoticeinventory.

Sincerely,

Susan J. Carlson -S

Digitally signed by Susan J. Carlson -S
Date: 2021.10.21 18:01:38 -04'00'

Susan Carlson, Ph.D.
Director
Division of Food Ingredients
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