U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY & APPLIED NUTRITION

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RE: Petition for a Qualified Health Claim for D-Tagatose and Reduced Risk of Type 2 Diabetes (Docket No. FDA-2022-Q-0051)

Dear Dr. Weikel and Mr. Rogers:

This letter responds to the qualified health claim petition you submitted to the Food and Drug Administration (FDA, we, or the agency). The petition was submitted on behalf of Bonumose, Inc. and is reviewed by FDA pursuant to FDA's guidance on the procedures for the submission of qualified health claim petitions and on the evidence-based review system for the scientific evaluation of health claims.[1] The petition requested that the agency review the use of a qualified health claim regarding the relationship between consumption of D-tagatose and reduced risk of type 2 diabetes.

The petition proposed the following language for a qualified health claim to be used on the labels or in the labeling of conventional foods:

> "Scientific evidence suggests but does not prove that long-term consumption of foods/drinks containing D-tagatose instead of sugar may reduce risk for type 2 diabetes."

> "Scientific evidence suggests but does not prove that consumption of foods/drinks containing

[1] FDA, "Guidance for Industry: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements. July 10, 2003. [https://www.fda.gov/food/food-labeling-nutrition/consumer-health-information-better-nutrition-initiative-task-force-final-report]; see also FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims—Final, January 2009 [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims].

D-tagatose instead of sucrose may reduce risk for type 2 diabetes."

"Scientific evidence suggests but does not prove that consumption of foods/drinks containing D-tagatose instead of sugar may reduce risk for type 2 diabetes. This product contains _____ g of D-tagatose and may help control glycemia when consumed in the context of a balanced diet."

"Scientific evidence suggests but does not prove that consumption of foods/drinks containing D-tagatose instead of sucrose may reduce risk for type 2 diabetes. This product contains _____ g of D-tagatose and may help control glycemia when consumed in the context of a balanced diet."

FDA filed the petition for comprehensive review on January 14, 2022 (Docket number FDA-2022-Q-0051) and posted it on the Regulations.gov website with a 60-day comment period, consistent with FDA's guidance for procedures on qualified health claims.[2] There were no comments submitted to the docket for this petition.

After reviewing the relevant materials, FDA is denying your petition because FDA has determined there is no credible evidence to support a qualified health claim regarding the relationship between D-tagatose and reduced risk of type 2 diabetes. This letter sets out the basis for FDA's determination and the reasons why the agency is denying this claim.

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup, is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease or health-related condition.[3] In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that are the subject of the proposed claim and the population to which the claim is targeted.[4]

FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.[5]

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[2] See FDA's 2006 Implementation of "Qualified Health Claims": Questions and Answers; Final Guidance. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-fdas-implementation-qualified-health-claims.

[3] See Whitaker v. Thompson, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA's interpretation of what constitutes a health claim), cert. denied, 125 S. Ct. 310 (2004).

[4] See FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims—Final, January 2009 [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-evidence-based-review-system-scientific-evaluation-health-claims].

[5] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of this letter except when quoting or paraphrasing a regulation that uses the longer term.

The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.[6]

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,[7] review articles,[8] and animal and *in vitro* studies. The data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements, such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[9] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship.[10] If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, which affect how humans respond to the consumption of foods and dietary supplements (Institute of Medicine, 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study (Spilker, 1991; National Research Council, 2011). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals

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[6] In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (*i.e.*, disease). Intervention studies provide the strongest evidence for an effect. See *supra,* note 4.

[7] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[8] Review articles summarize the findings of individual studies.

[9] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

[10] Certain meta-analyses may be used as part of the health claim review process. See *supra*, note 4.

diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (*e.g.*, use of a placebo control versus a non-placebo controlled group), data collection (*e.g.*, type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (*e.g.*, disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (*e.g.*, selection bias and whether important information about the study subjects – *e.g.*, age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low-quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies from which FDA cannot draw scientific conclusions (*e.g.*, low-quality studies) cannot be used to support the health claim relationship, and therefore are eliminated from further review.

Finally, FDA evaluates the results of the high-quality and moderate-quality studies. The agency then rates the strength of the total body of publicly available evidence.[11] The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of studies of each type and study sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[12] and the overall consistency[13] of the total body of evidence.[14] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance-disease relationship, and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

II. The Agency's Consideration of Bonumose's Qualified Health Claim Petition

A. Whether D-tagatose Meets the Regulatory Definition of "Substance"

[11] See *supra*, note 4.
[12] Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson, 1990).
[13] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill AB. 1965); see also Agency for Healthcare Research and Quality, "Systems to rate the scientific evidence" (March 2002) [http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf (accessed May 10, 2017)], defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."
[14] See *supra*, note 4.

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of a food, regardless of whether the food is in conventional form or a dietary supplement (21 CFR 101.14(a)(2)). The petition identified D-tagatose as the substance that is the subject of the proposed health claim.

D-tagatose is a monosaccharide, an epimer of D-fructose isomerized at C4. It occurs naturally in heated-treated milk and dairy products (*e.g.*, cheese, yogurts), where it is formed from galactose by isomerization, as well as in some fruits. Since 2001, D-tagatose has been generally recognized as safe (GRAS) for consumption in the United States.

Therefore, the agency concludes that D-tagatose, the substance identified in the petition, is a component of a food and meets the definition of a substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Whether Type 2 Diabetes Meets the Regulatory Definition of "Disease or Health-Related Condition"

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified type 2 diabetes as the disease that is the subject of the proposed claims. Diabetes is a disease that occurs when blood glucose (i.e., blood sugar) is too high, resulting in a disorder of metabolism from the body's impaired ability to use blood glucose (sugar) for energy. Over time, having too much glucose in the blood can cause health problems, such as heart disease, nerve damage, eye problems, and kidney disease.[15] In type 2 diabetes, either the pancreas does not make enough insulin, or the body is unable to use insulin effectively, and therefore blood glucose cannot enter the cells to be used for energy. The agency concludes that type 2 diabetes meets the definition of a disease under 21 CFR 101.14(a)(5) because, in persons with this condition, the glucose metabolism systems of the body have been damaged such that the body is not functioning properly.

C. Safety Review

Under 21 CFR 101.14(b)(3), if the substance that is the subject of the health claim is to be consumed at other than decreased dietary levels, the substance must, regardless of whether the food is a conventional food or a dietary supplement, contribute taste, aroma, or nutritive value, or any other technical effect listed in 21 CFR 170.3(o) to the food and must retain that attribute when consumed at levels that are necessary to justify a claim. The substance must be a food or a food ingredient or a component of a food ingredient whose use at the levels necessary to justify the claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act (the Act) (21 CFR 101.14(b)(3)(ii)).

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[15] National Institutes of Health (NIH), "Diabetes" [https://www.niddk.nih.gov/health-information/diabetes] (accessed September 24, 2022).

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act (21 CFR 101.14(b)(3)(ii)). For conventional foods, this evaluation involves considering whether the ingredient that is the source of the substance is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA (see 101.70(f)).

Because we are denying the proposed qualified health claims for lack of credible evidence, as discussed in section II of this letter, it is therefore not necessary for FDA to make a determination about the safety of D-tagatose in this letter. *Cf.* 21 C.F.R. § 101.14(b)(3)(ii).

However, the petition notes that D-tagatose is intended for use in foods as a sweetener, humectant, texturizer or stabilizer. According to the petition, D-tagatose is a monosaccharide that provides a sweet taste and can be used to replace sucrose for a variety of food applications and maintains its sweetness and nutritive value at all food use levels. The petition also states that D-tagatose is GRAS for its use in diet/sugar-free carbonated beverages, ready-to-eat cereals, sugar-less/sugar-free chewing gum, low calorie ready-to-drink tea beverages, icings or glazes used on baked goods, frozen dairy desserts, bars, hard candies, dietetic soft candies, and meal replacements as a bulk sweetener, humectant, texturizer or stabilizer at varying levels and does not have an upper limit. We note that FDA had no concerns regarding three GRAS notifications submitted to us on D-tagatose (GRN 000078, GRN 000352 and GRN 000977).

D. Assessment of the Scientific Evidence

FDA identified incidence of type 2 diabetes[16] and the following surrogate endpoints as appropriate to use in identifying type 2 diabetes risk reduction for purposes of a health claim evaluation: impaired fasting glucose, defined as fasting plasma glucose (FPG) of 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L); or impaired glucose tolerance, defined as 2-hr plasma glucose (2 hr-PG) during 75-gram oral glucose tolerance test (OGTT) of 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L); or HbA1c 5.7 to 6.4 % (39-47 mmol/mol).[17] These disease incidence and surrogate endpoints were used to evaluate the potential effects of D-tagatose intake on type 2 diabetes risk.

The petition cited 57 unduplicated publications[18] as evidence to substantiate the relationship for the proposed claims (see Docket Number FDA-2022-Q-0051). These publications consisted of

[16] A diagnosis of type 2 diabetes can be made after positive results on any one of three tests, with confirmation from a second positive test on a different day: 1) fasting is defined as no caloric intake for at least 8 hours with a fasting plasma glucose (FPG) of $\geq$126 mg/dL (7.0 mmol/L); or 2) 2-hour plasma glucose (2-hr PG) $\geq$ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT); or 3) HbA1c $\geq$6.5% (48 mmol/mol). In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose $\geq$200 mg/dL (11.1 mmol/L) are considered risk factors for type 2 diabetes (U.S. FDA Memorandum to the File, 2024).

[17] Evidence of insulin resistance when combined with any of the parameters described (*i.e.,* impaired fasting glucose, impaired glucose tolerance, or HbA1c) would strengthen risk for type 2 diabetes. (U.S. FDA Memorandum to the File, 2024).

[18] There were 58 publications cited in the citizen petition in which the article by Ensor et al. 2014 was cited twice, resulting in 57 unduplicated citations.

18 human intervention studies[19] (seven evaluating the substance-disease relationship and eleven studies evaluating other aspects, some related to D-tagatose); nine animal studies;[20] six U.S. government documents;[21] five reviews;[22] five reports including a summary table on sugars and sweeteners;[23] four articles related to the chemical analysis of D-tagatose (Christiansen, 1998; Richards & Chandrasekhara, 1960; Troyano et al., 1992; Troyano et al., 1991); three U.S. patents (Lodder & Cassis, 2011; Seri et al., 1995; Vigh, 2007); three GRAS notices (GRN 000078, GRN 000352 and GRN 000977); one article on glycemic index claims on food labels (Aziz et al., 2013); one technical report on a health risk assessment of D-tagatose from a foreign country (Food Standards Australia New Zealand, 2004); one meta-analysis on health education for glycemic control through mobile text-messaging (Saffari et al., 2014); and one position statement on nutrition therapy recommendations for the management of adults with diabetes (Evert et al., 2014). FDA did not identify any additional human studies during our literature search.

Among the eleven human intervention studies that did not evaluate the substance-disease relationship requested for FDA's review by the petitioner, one study evaluated whether incorporating D-tagatose into bakery products affected their flavors (Armstrong et al., 2009), other studies investigated the suitability of replacing sucrose with D-tagatose in cookies (Taylor et al., 2008), and the sensory characteristics and relative sweetness of D-tagatose compared to other sweeteners (Fujimaru et al., 2012). One study investigated whether partial substitution of dietary sucrose by D-tagatose for 28 days would affect the volume of the human liver (Boesch et al., 2001), other studies investigated the gastrointestinal tolerance of D-tagatose in chocolate (Lee & Storey et al., 1999), the effect of osmolarity on gastric emptying among several hexoses, including D-tagatose (Little et al., 2010), increase in acid uric production after ingestion of D-tagatose as compared to D-fructose (Buemann et al., 2000b), and the effect of acute and repeated doses of D-tagatose on uric acid in plasma of normal and diabetic individuals (Saunders et al., 1999). One study investigated the association between glycemic control and the level of knowledge and disease awareness in type 2 diabetic patients (Ozcelik et al., 2010). Another study assessed the effectiveness of Mobile Short Message Service intervention on education of basic self-care skills in patients with type 2 diabetes (Peimani et al., 2016). Seligman et al. 2012 investigated whether food insecurity was associated with poor glycemic control or emotional distress related to diabetes. None of these studies investigated the relationship between D-tagatose and reduced risk of type 2 diabetes, and therefore, they are not relevant to FDA's evaluation of this qualified health claim petition.

i. Review Articles, Meta-analysis, and Other Background Materials

[19] Armstrong et al., 2009; Boesch et al., 2001; Buemann et al., 2000; Buemann et al., 1998; Buemann et al., 2000; Donner et al., 2010; Donner et al., 1999; Ensor et al., 2014; Fujimaru et al., 2012; Kwak et al., 2013; Lee & Storey, 1999; Little et al., 2010; Ozcelik et al., 2010; Peimani et al., 2016; Saunders et al., 1999; Seligman et al., 2012; Taylor et al., 2008; Wu et al., 2012.

[20] Bapat et al., 2016; Bar et al., 1999; Bertelsen et al., 1999; Durante et al., 2021; Kruger et al., 1999; Laerke & Jensen, 1999; Livesey & Brown, 1996; Police et al., 2009; Saunders et al., 1999.

[21] U.S. Food and Drug Administration, 2001, 2011, 2013, 2014, 2016; U.S. National Institute of Diabetes and Digestive and Kidney Diseases, 2017.

[22] Ali et al., 1998; Bar, 1999; Levin, 2002; Lu et al., 2008; Muddada, 2012.

[23] American Diabetes Association, 2021; Bar, 2004; Boston University, 2017; JECFA, 2006; World Health Organization, 2001.

"Background materials" here refers to review articles, meta-analyses, reports from federal agencies and other articles that provide background information on D-tagatose and type 2 diabetes. As explained in FDA's guidance on the evidence-based review system for the scientific evaluation of health claims, although useful for background information and identifying additional studies, these materials do not contain sufficient information on the individual studies reviewed and, therefore, FDA could not draw any scientific conclusions regarding the substance-disease relationship from these sources.[24] FDA could not determine factors such as the study population characteristics or the nutrient composition of the products used (*e.g.*, whether the substance under investigation was provided to the intervention group alone or mixed with other substances; the latter case prevents measuring the independent role of the substance in reducing the risk of a disease). Similarly, the lack of detailed information on studies summarized in review articles, meta-analyses, and reports prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies (*e.g.*, whether a valid surrogate endpoint was used), and data analysis (*e.g.*, whether an appropriate statistical method was used).[25] FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it.[26] As a result, the background materials supplied by the petitioner did not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship claimed by the petitioner.

ii. Animal and *In Vitro* Studies

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. They can also be used to generate hypotheses, investigate biological plausibility of hypotheses, or to explore a mechanism of action. However, as explained in FDA's guidance on the evidence-based review system for the scientific evaluation of health claims, these types of studies cannot adequately support a relationship between the substance and disease in humans.[27] As such, the animal studies cited with the petition did not provide any supportive information about the substance-disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of type 2 diabetes. Therefore, FDA could not draw any scientific conclusions regarding D-tagatose and the reduction of risk of type 2 diabetes from the animal studies cited in this petition.

iii. Intervention Studies

FDA evaluated seven intervention studies that investigated the relationship between D-tagatose and type 2 diabetes risk.[28] As explained above, an additional eleven intervention studies did not investigate the substance-disease relationship requested for FDA's review by the petitioner, and therefore they are not relevant to FDA's evaluation of this qualified health claim petition.

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[24] See *supra*, note 4.
[25] *Id.*
[26] *Id.*
[27] *Id.*
[28] Buemann et al., 1998; Buemann et al., 2000a; Donner et al., 2010; Donner et al., 1999; Ensor et al., 2014; Kwak et al., 2013; Wu et al., 2012.

Scientific conclusions could not be drawn from any of the seven studies investigating the relationship between D-tagatose and type 2 diabetes risk for the reasons discussed below.[29] Two studies (Donner et al., 2010 and Ensor et al., 2014) were conducted on a diseased population, that is, individuals with type 2 diabetes.[30] Health claims characterize the relationship between the substance and a reduction in risk of a disease. In these studies, however, participants already had the disease (type 2 diabetes). FDA considers evidence from studies with subjects who have the disease that is the subject of the claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence demonstrates that (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations and (2) the substance affects these mechanisms in the same way in both diseased and healthy people. Because such evidence (*i.e.*, whether the mechanism of action for D-tagatose is the same for diseased populations and non-diseased populations) is not available, the agency cannot draw any scientific conclusions from studies that used subjects that have the disease that is the subject of the health claim to evaluate the substance/disease relationship. Therefore, no scientific conclusions could be drawn from these two studies for the purpose of evaluating the substance/disease relationship.

Another study (Buemann et al., 1998) evaluated the effect of D-tagatose on fasting blood glucose among subjects who were part of a metabolic study. The study was conducted in a balanced and randomized crossover design and fasting blood glucose was reported being measured at days 1, 7 and 15. The fasting blood glucose levels, either at baseline or after the treatment period, were not reported, with the publication providing only a statement that no statistically significant differences were observed on fasting blood glucose after consumption of D-tagatose as compared to consumption of sucrose. The study did not report on the subjects' health status related to type 2 diabetes other than reporting the average weight and height for females and males, separately, and that the subjects were non-smokers. For example, there was no information on exclusion criteria related to a diseased population (i.e., exclusion of subjects with type 2 diabetes), and the study only reported to screen candidates for adverse responses (nausea or diarrhea) to D-tagatose. Therefore, we cannot assume that the subjects involved in the study did not have type 2 diabetes. As explained above, the agency cannot draw any scientific conclusions from studies where subjects have the disease that is the subject of the health claim to evaluate the substance/disease relationship unless it is scientifically appropriate to extrapolate to individuals who do not have the disease, and there is no evidence available that the mechanism of action for D-tagatose is the same for diseased populations and non-diseased populations. Because we cannot assume that the subjects involved in this study did not have type 2 diabetes in the absence of reported information about the subjects' health status related to type 2 diabetes, no scientific conclusions could be drawn from this study for the purpose of this health claim evaluation.

Three studies (Donner et al., 1999; Buemann et al., 2000a; Kwak et al., 2013) evaluated the acute effect of D-tagatose on blood glucose levels. In these acute studies, a dose of D-tagatose was given to subjects, as part of an oral glucose tolerance test or a meal tolerance test, in which their

[29] This section contains a general discussion of major flaws in the reports of intervention studies from which scientific conclusions could not be drawn. Such studies may have other flaws in addition to those specifically mentioned.
[30] Donner et al., 2010; Ensor et al., 2014.

blood glucose levels were continuously measured for a short period of time, ranging from 120 to 450 minutes, after ingestion of D-tagatose. While such short-term studies (e.g., following acute exposures) may be methodologically adequate, they are designed to assess the food's immediate effect on blood glucose levels, and they cannot be used to draw any conclusion regarding D-tagatose consumption on risk reduction of type 2 diabetes.[31] For this reason, the agency could not draw scientific conclusions from these three studies for the purpose of this health claim evaluation.

In one intervention study (Wu et al., 2012), the substance evaluated was a mixture of D-tagatose and isomalt. Isomalt is a sugar alcohol, and like D-tagatose, isomalt is partially digested and metabolized in the human body. FDA has not evaluated the relationship between isomalt consumption and reduced risk of type 2 diabetes. Therefore, it is not possible for the agency to determine the independent effect of D-tagatose on reducing the risk of type 2 diabetes, and no scientific conclusions could be drawn from this study for the purpose of this health claim evaluation.

iv. Observational Studies

There were no observational studies that evaluated the association between D-tagatose and risk of type 2 diabetes.

v. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of various types of studies and sample sizes), whether the body of evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[32] and the overall consistency of the total body of evidence. [33] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship, and if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

As discussed in Section II(D)(i)-(iv), there were no references or materials from which scientific conclusions could be drawn about the relationship between intake of D-tagatose and risk of type 2 diabetes. Based on its review of the totality of publicly available scientific evidence, FDA concludes that there is no credible evidence for a relationship between D-tagatose intake and reduced risk of type 2 diabetes.

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[31] U.S. Food and Drug Administration (2024). Memorandum to the File "Criteria for the diagnosis of type 2 diabetes and valid surrogate endpoints for increased risk of type 2 diabetes".
[32] See, *supra*, note 12.
[33] See, *supra*, note 13.

E. Consideration of Disclaimers or Qualifying Language

Because FDA has determined that the scientific evidence cited by the petitioner is not credible to support a relationship between D-tagatose intake and reduced risk of type 2 diabetes, *see* Section II(D)(v), *supra*, FDA concludes that it does not intend to consider the exercise of enforcement discretion for the use of any of the proposed qualified health claims regarding the relationship between consumption of D-tagatose and reduced risk of type 2 diabetes. Specifically, with respect to the proposed claims, all of which state that "Scientific evidence suggests but does not prove that consumption (or long-term consumption) of foods/drinks containing D-tagatose instead of sugar (or sucrose) may reduce risk of type 2 diabetes," there is no credible evidence to support the substance-disease relationship described in such claims, for the reasons explained in Section II(D).

The petitioner's proposed claims are also not protected under the First Amendment. Under the *Central Hudson* framework, the threshold question is whether the speech is false or inherently or actually misleading or concerns unlawful activity – such speech may be prohibited. *Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 563–66 (1980). If the speech is truthful and not inherently or actually misleading, the government must establish that the regulation directly advances a substantial governmental interest, and the regulation is no more extensive than necessary to serve that interest. *Id*.

Here, because the petitioner's proposed claims are not supported by credible evidence, they are misleading and thus not protected under the First Amendment. *See Alliance for Natural Health v. Sebelius*, 786 F. Supp. 2d 1, 17 (D.D.C. 2011) ("Claims which are not supported by credible evidence are misleading commercial speech and may be prohibited under the threshold step of the *Central Hudson* test."); *see also Bellion Spirits, LLC v. United States*, 7 F.4th 1201, 1213 (D.C. Cir. 2021) ("[T]he proposed claims are misleading because they are not backed by credible scientific findings."). As discussed at length above, scientific conclusions could not be drawn from any of the seven intervention studies that evaluated the relationship between D-tagatose and reduced risk of type 2 diabetes. There were an additional eleven intervention studies that did not investigate the substance-disease relationship between D-tagatose and reduced risk of type 2 diabetes, and therefore they are not relevant to FDA's evaluation of this qualified health claim petition. Of the seven studies that investigated the substance-disease relationship, two studies were conducted on subjects that already had type 2 diabetes, one study did not report on the subjects' health status related to type 2 diabetes and did not provide specific data on fasting blood glucose at baseline and after the study subjects consumed D-tagatose (e.g., after the treatment period), three studies measured the acute effect of D-tagatose on blood glucose, impeding our ability to draw scientific conclusions on the long-term effect of D-tagatose on reduced risk of type 2 diabetes, and one study evaluated a substance that was a mixture of D-tagatose and isomalt. Therefore, none of the studies—individually or collectively—provide credible evidence to support the proposed claims.

However, even if the remaining prongs of the *Central Hudson* test applied, they are satisfied. The second prong of the *Central Hudson* test is satisfied because the Government clearly has a substantial interest in preventing consumer deception and confusion. *See Fleminger, Inc. v. U.S.*

Dep't of Health & Hum. Servs., 854 F. Supp. 2d 192, 209 (D. Conn. 2012) ("[T]he Court finds that the government has asserted an interest in preventing consumer confusion and protecting public health which is undeniably substantial."). The third prong is also satisfied because requiring specific health claims on labels to be adequately substantiated by scientific or medical evidence directly and materially advances such interest. *See Bellion Spirits, LLC v. United States*, 393 F. Supp. 3d 5, 25 (D.D.C. 2019), *aff'd,* 7 F.4th 1201 (D.C. Cir. 2021) ("Denying the petition is directly linked to the prevention of consumer deception.").

Denying the petition in this case also satisfies the fourth and final prong of the *Central Hudson* test because it is no more extensive than necessary to serve the substantial government interest of preventing consumer fraud and confusion. *See Central Hudson*, 447 U.S. at 566. The court in *Pearson v. Shalala* concluded that disclaimers are "constitutionally preferable to outright suppression," and therefore, "when government chooses a policy of suppression over disclosure—at least where there is no showing that disclosure would not suffice to cure misleadingness—government disregards a 'far less restrictive' means." *See* 164 F.3d 650,657–58 (D.C. Cir. 1999); *see also Bellion*, 393 F. Supp. 3d at 18 ("[M]andating a disclaimer is more likely to comply with the fourth prong [of the *Central Hudson* test] than is a blanket ban."). However, the *Pearson* court also recognized that "where evidence in support of a claim is outweighed by evidence against the claim, the FDA could deem it incurable by a disclaimer and ban it outright." Furthermore, the court "s[aw] no problem with the FDA imposing an outright ban on a claim where evidence in support of the claim is *qualitatively* weaker than evidence against the claim." *See Alliance*, 786 F. Supp. 2d at 13, citing *Pearson*, 164 F.3d 659 & 659 n.10.

As such, under *Pearson*, where credible evidence supports a health claim for a conventional food or dietary supplement, FDA must consider whether a disclaimer could cure any misleadingness. *See Alliance*, 786 F. Supp. 2d at 15. But "unsupported or very weakly supported claims may simply be banned outright." *Id.* at 14. In such cases, "the agency might reasonably determine that adding a disclaimer…would not suffice to mitigate the claim's misleadingness." *Pearson*, 164 F.3d at 659. Adding a disclaimer or incorporating qualifying language that effectively characterizes the claim as baseless is not a viable regulatory alternative because neither the disclaimer nor the qualifying language can rectify the misleadingness of the message conveyed by the unsubstantiated claim. *See, e.g., Novartis Consumer Health, Inc. v. Johnson & Johnson-Merck Consumer Pharms. Co.*, 290 F.3d 578, 598 (3d Cir. 2002) ("We do not believe that a disclaimer can rectify a product name that necessarily conveys a false message to the consumer."); *In re Warner-Lambert Co.,* 86 F.T.C. 1398, 1414 (1975), (stating that pro forma statements of no absolute prevention followed by promises of fewer colds did not cure or correct the false message that Listerine will prevent colds). In such a situation, adding a disclaimer or qualifying language does not provide additional information to help consumer understanding but merely contradicts the claim) *aff'd*, 562 F.2d 749 (D.C. Cir. 1977); *Resort Car Rental System, Inc. v. FTC*, 518 F.2d 962, 964 (9th Cir. 1975) (per curiam) (upholding FTC order to excise "Dollar a Day" trade name as deceptive because "by its nature [it] has a decisive connotation for which any qualifying language would result in contradiction in terms."), *cert denied*, 423 U.S. 827 (1975); *Continental Wax Corp. v. FTC*, 330 F.2d 475, 480 (2d Cir. 1964) (same); *Pasadena Research Labs v. United States*, 169 F.2d 375 (9th Cir. 1948) (discussing "self-contradictory labels"). In the FDA context, courts have repeatedly found such disclaimers ineffective. *See, e.g.*, *United States v. Millpax, Inc.*, 313 F.2d 152, 154 & n.1 (7th Cir. 1963) (disclaimer stating that

"no claim is made that the product cures anything, either by the writer or the manufacturer" was ineffective where testimonials in a magazine article promoted the product as a cancer cure); *United States v. Kasz Enters., Inc.*, 855 F. Supp. 534, 543 (D.R.I. 1994) ("The intent and effect of the FDCA in protecting consumers from... claims that have not been supported by competent scientific proof cannot be circumvented by linguistic game-playing."), *judgment amended on other grounds*, 862 F. Supp. 717 (1994).

In this case, FDA considered but rejected the use of a disclaimer or qualifying language to accompany the proposed claims for consumption of D-tagatose and a reduction in the risk of type 2 diabetes. The agency concluded that neither a disclaimer nor qualifying language would suffice to prevent consumer deception in this instance, where there is no credible evidence to support the claim. FDA's consideration included the qualifying language proposed by the petition, which states, "Scientific evidence suggests but does not prove that consumption (or long-term consumption) of foods/drinks containing D-tagatose instead of sugar (or sucrose) may reduce risk of type 2 diabetes." Such language does not mitigate the misleadingness of the claims because scientific conclusions could not be drawn from any of the studies purporting to evaluate the relationship between D-tagatose and reduced risk of type 2 diabetes. *See Bellion*, 393 F. Supp. 3d at 26–27 (holding that the agency reasonably chose to prohibit the claims at issue "in the absence of a disclaimer that would sufficiently qualify [them]."). For the reasons described above, denying this petition is constitutionally permissible under *Central Hudson*.

III. Conclusions

Based on FDA's consideration of the scientific evidence and other information submitted with your petition, FDA concludes that there is no credible evidence to support a qualified health claim for D-tagatose intake and reduced risk of type 2 diabetes. Thus, FDA is denying your petition for a qualified health claim.

Please note that scientific information is subject to change, as are consumer consumption patterns. In the event that new information is submitted to the agency, such as new scientific evidence or alternative claim language, FDA intends to evaluate the new information to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support the use of a qualified health claim or that will support significant scientific agreement.

Sincerely,

/S/

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