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

December 17, 2021

Melvin S. Drozen
Evangelia C. Pelonis
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1001 G Street, N.W., Suite 500 West
Washington, D.C. 20001

Re: Docket Number FDA-2020-P-2357

Dear Mr. Drozen and Ms. Pelonis:

This responds to your citizen petition dated December 28, 2020, requesting that the Food and Drug Administration (FDA or we) "amend the definition of "dietary fiber" at 21 C.F.R. § 101.9(c)(6)(i) by adding "Acacia (gum arabic)"… to the existing list of isolated or synthetic non-digestible carbohydrates determined by (FDA) to have physiological effects that are beneficial to human health."[1] See Citizen Petition from Melvin S. Drozen and Evangelia C. Pelonis, Keller and Heckman LLP, on behalf of Nexira, Alland & Robert, and Importers Service Corporation, submitted to the Division of Dockets Management, Food and Drug Administration, dated December 28, 2020 ("Petition"), at page 1.

We note that this is the second citizen petition that you have submitted requesting that FDA amend 21 CFR 101.9(c)(6)(i) to include gum acacia among the isolated or synthetic non-digestible carbohydrates that have been determined by FDA to have physiological effects that are beneficial to human health and to include gum acacia in the calculation of the amount of dietary fiber on the Nutrition Facts label. We denied your first citizen petition (see Docket No. FDA-2019-P-1911; dated April 19, 2019) ("Original Petition"), as explained in our response dated January 31, 2020.[2]

You indicate that the current petition focuses solely on the beneficial physiological effects on human heath for postprandial blood glucose attenuation and/or insulin levels, whereas the original petition included evidence that you believed supported your conclusion that gum acacia also has beneficial physiological effects on energy intake and satiety (Original Petition at page

[1] Similar to the language used in the petition, we will refer to 'Acacia (gum arabic)' as 'gum acacia' throughout this response.
[2] Citizen Petition Response from Claudine Kavanaugh, Ph.D., MPH, RD, Director, Office of Nutrition and Food Labeling, Center for Food Safety and Applied Nutrition, Food and Drug Administration, to Melvin S. Drozen and Evangelia C. Pelonis, Keller and Heckman LLP, dated January 31, 2020, available at https://www.regulations.gov/document/FDA-2019-P-1911-0008.

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2). You indicate that your petition contains a discussion of an additional study that was not cited in your original petition to support this conclusion (Petition at page 6).

In accordance with 21 CFR § 10.30(e)(3), we are granting your request and will propose to amend the list of non-digestible carbohydrates that meet the definition of dietary fiber in 21 CFR § 101.9(c)(6)(i) to include "acacia (gum arabic)." The strength of the scientific evidence shows that gum acacia has a physiological effect on postprandial blood glucose and insulin that is beneficial to human health.

In the *Federal Register* of May 27, 2016, we published a final rule titled "Food Labeling: Revision of the Nutrition and Supplement Facts Labels" (81 FR 33742). The final rule, among other things, defines dietary fiber in 21 CFR § 101.9(c)(6)(i), in part, as "non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health." In the final rule, we identified seven isolated or synthetic non-digestible carbohydrates that have a physiological effect that is beneficial to human health. We also stated that any interested person may seek to amend the listing of added fibers through the existing citizen petition process in 21 CFR § 10.30.

Your petition requests that FDA add gum acacia to the list of dietary fibers in 21 CFR § 101.9(c)(6)(i) on the grounds that gum acacia "has a physiological effect on postprandial blood glucose and insulin levels that is beneficial to human health" (Petition at page 2). Further, your petition states that "this citizen petition builds on the evidence previously submitted by including scientific evidence that was generated in a new study which adds two additional data points for insulin and glucose response" (Petition at page 3). The petition also requests that FDA use the name "acacia (gum arabic)" when amending 21 CFR § 101.9(c)(6)(i) to be consistent with the food additive/generally recognized as safe (GRAS) regulations (Petition at page 3).

In the *Federal Register* of March 2, 2018 (83 FR 8997), we announced the availability of a final guidance document entitled, "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)" ("final guidance"). This final guidance describes our views on the scientific evidence needed, and the approach for evaluating the scientific evidence, on the physiological effects of isolated or synthetic non-digestible carbohydrates added to foods that are beneficial to human health. It also provides detail on the physiological endpoints that we consider when reviewing the scientific evidence and provides detail regarding factors we consider when evaluating the strength of the evidence. We reviewed your petition under this guidance.

Your petition identifies ten publicly available studies[3,4] that evaluated the effect of gum acacia consumption on postprandial blood glucose and insulin. Scientific conclusions could not be drawn from five studies because of the following[5]: (1) no control group or an inappropriate control group was used (Nasir et al., 2016; Ross et al., 1983); (2) a mixture of non-digestible carbohydrates, including gum acacia, was used, and therefore the physiological effect of gum acacia could not be independently evaluated (Campbell et al., 1997; Pouteau et al., 2010); or (3) the study measured the glycemic index of gum acacia rather than postprandial blood glucose, and nutrient composition of the treatment and control beverages (e.g., amount of available carbohydrate and ingredients) was not provided (Torres et al., 2006).

Accordingly, the five human intervention studies from which we could draw conclusions are as follows[6]:

Sharma (1985)

Twelve healthy men participated in a randomized cross-over design study[7] in which they consumed a sugar (glucose) solution[8] with 20 grams (g) of gum acacia or without gum acacia (control). The study subjects' postprandial blood glucose and postprandial insulin were measured at several time points for 150 minutes after consumption of the glucose solutions. Consumption of the glucose solution containing gum acacia statistically significantly reduced postprandial blood glucose and postprandial insulin, as measured by area-under-the-curve

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[3] Akeo K, Kojima M, Uzuhashi Y. Physiological functions of gum Arabic. *Food Chemicals Monthly* 2002; 6:85-89; Campbell JM, Fahey GC, Demichele SJ et al. Metabolic characteristics of healthy adult males as affected by ingestion of a liquid nutritional formula containing fish oil, oligosaccharides, gum Arabic and antioxidant vitamins. *Food and Chemical Toxicology* 1997; 35:1165-1176; Larson R, Nelson C, Korczak R et al. Acacia gum is well tolerated while increasing satiety and lowering peak blood glucose response in healthy human subjects. *Nutrients* 2021; 13:618; Nasir O, Babiker S, Salim AM. Protective effect of gum Arabic supplementation for type 2 diabetes mellitus and its complications. *International Journal of Multidisciplinary and Current Research* 2016; 4:288-294; Pouteau E, Ferchaud-Roucher V, Zair Y et al. Acetogenic fibers reduce fasting glucose turnover but not peripheral insulin resistance in metabolic syndrome patients. *Clinical Nutrition* 2010; 29:801-807; Ross AH, Eastwood MA, Brydon WG et al. A study of the effects of a dietary gum arabic in humans. *American Journal of Clinical Nutrition* 1983; 37:368-375; Sharma RD. Hypoglycemic effect of gum acacia in healthy human subjects. *Nutrition Research* 1985; 5:1437-1441; Torres N, Palacios-Gonzalez B, Noriega-Lopez L et al. Glycaemic index, insulinemic index and glycaemic load of soy beverages with a low and high content of carbohydrates. *Revista de lnvestigacion Clinica [Clinical Research Journal*] 2006; 58:487-497; Uebelhack R. Study report on the effect of gum acacia on postprandial glucose and insulin levels in healthy subjects. October 2020, *unpublished*; Wolever T, Jenkins AL, Ezatagha A. Effect of dietary fiber incorporated into pudding on postprandial glucose and insulin responses. March 2019, *unpublished*.

[4] Your petition also identifies an additional 2004 unpublished Australian study that you submitted to FDA on February 13, 2017. As stated in our response to your original petition, while we reviewed this study when examining the materials you submitted as part of your original petition, we did not consider the study as part of our scientific evaluation of this petition nor addressed in this response because it is not publicly available.

[5] This section contains the studies from which scientific conclusions could not be drawn. Such studies may have other flaws in addition to those specifically mentioned.

[6] Our review of four of these studies was also included in our response to your original petition (Sharma et al. 1985; Akeo et al. 2002; Larson et al. 2019 (unpublished), which has since been published as Larson et al., 2021; Wolever et al., 2019).

[7] The article provides no description as to whether the study was double-blinded (where neither the participants nor the experimenters know who is receiving a particular treatment).

[8] The sugar solution contained 100 grams (g) of glucose dissolved in 250 mL (8.5 oz) of water.

(AUC),[9] compared to the control glucose solution ($P < 0.05$). However, there were no statistically significant differences in peak concentrations of postprandial blood glucose or insulin after consumption of a glucose solution containing gum acacia versus the control glucose solution ($P > 0.05$ for both).

Akeo et al. (2002)

Twelve healthy men participated in a cross-over design study[10] in which they consumed a sugar (sucrose) solution[11] containing either 5 g or 10 g of gum acacia or without gum acacia (control). The study subjects' postprandial blood glucose was measured at several time points for 150 minutes after consumption of the sucrose solutions. The peak concentration of postprandial blood glucose was statistically significantly lower with the consumption of sucrose solutions containing both levels of gum acacia (5 g, 10 g) compared to the control sucrose solution ($P < 0.05$ for both). No statistical analysis comparing the two doses was reported in the study. The postprandial blood glucose, as measured by AUC, was also not reported. Postprandial insulin was not measured.

Wolever et al. (2019; *unpublished*)

Forty healthy men and women participated in a randomized, double-blind, cross-over design study in which they consumed pudding containing either 13 g or 24 g of gum acacia or pudding without gum acacia (control). All pudding contained 59 g of digestible (available) carbohydrate. The study subjects' postprandial blood glucose and insulin were measured at several time points for 120 minutes after consumption of the pudding. No statistically significant differences were observed in postprandial blood glucose, as measured by either AUC or peak concentrations, between the pudding containing gum acacia (13 g or 24 g) and the control pudding ($P > 0.05$ for both doses). Consumption of the pudding containing both 13 g and 24 g of gum acacia statistically significantly lowered postprandial insulin, as measured by AUC ($P < 0.05$). The lower dose (13 g) also resulted in a statistically significantly lower peak concentration of postprandial insulin compared to the control pudding ($P < 0.05$), whereas the higher dose (24 g) did not ($P > 0.05$). Furthermore, peak concentration of postprandial insulin was statistically significantly lower following consumption of the 13 g dose of gum acacia compared to the 24 g dose of gum acacia ($P < 0.05$).

Uebelhack (2020; *unpublished*)

Thirty-five normal-weight and overweight men and women who were otherwise healthy participated in a randomized, double-blind, placebo-controlled, cross-over design study. After an overnight fast, the subjects were randomly assigned to consume an isocaloric standardized breakfast meal, containing the same amount of digestible carbohydrate, and 300 mL (10 oz) of orange juice containing either 40 g, 20 g, or 0 g (control) of gum acacia powder added.

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[9] The rise and fall of blood glucose over several hours after consuming a food, beverage, or meal is often reported as area-under-the-curve (AUC) (sometimes referred to as incremental AUC).
[10] The article provides no description as to whether the study was randomized or double-blinded (where neither the participants nor the experimenters know who is receiving a particular treatment).
[11] The sugar solution contained 100 g of sucrose dissolved in 300 mL (10 oz) of water.

Postprandial blood glucose and postprandial insulin were measured at baseline and at several time points for 180 minutes after consumption of the breakfast meal. Postprandial blood glucose, as measured by AUC and peak concentration, was statistically significantly lower after consumption of gum acacia compared to control at both doses, 20 g and 40 g ($P < 0.05$ for both doses). Postprandial insulin, as measured by AUC and peak concentration, was also statistically significantly lower after consumption of gum acacia compared to control ($P < 0.05$ for both doses). There was no dose-response effect observed between the two doses of gum acacia ($P > 0.05$).

Larson et al. (2021)

Forty-eight healthy men and women participated in a randomized, double-blind, cross-over design study in which they consumed orange juice containing either 20 g or 40 g of gum acacia or without gum acacia added (control). The orange juice (8 oz) was given to subjects as part of a breakfast meal that included a bagel and cream cheese. The breakfast meal contained approximately 76 g carbohydrate, 2 g fiber, 13 g protein, and 6 g total fat. The study subjects' postprandial blood glucose was measured at several time points for 240 minutes after consumption of the breakfast meal. There was a statistically significantly lower peak concentration of postprandial blood glucose after consumption of the orange juice containing 20 g of gum acacia compared to the control orange juice ($P < 0.05$). However, the difference in peak concentration of postprandial blood glucose after consumption of the orange juice containing 40 g of gum acacia compared to that of the control orange juice did not reach statistical significance ($P > 0.05$). No statistically significant differences were observed in the postprandial blood glucose, as measured by AUC, after consumption of the orange juice containing either 20 g or 40 g of gum acacia compared to the control orange juice ($P > 0.05$ for both). No dose-response effect was observed between the two doses of gum acacia ($P > 0.05$). Postprandial insulin was not reported in this study.

There were five publicly available studies (Akeo et al., 2002; Larson et al., 2021; Sharma, 1985; Uebelhack, 2020 *unpublished*; Wolever et al., 2019 *unpublished*) in healthy adults, with nine dose comparisons (ranging from 5 g to 40 g), from which scientific conclusions could be drawn for the effect of gum acacia consumption on postprandial blood glucose and /or insulin.

There were nine dose comparisons that evaluated the effect of gum acacia on postprandial blood glucose. Two studies (Akeo et al., 2002; Sharma, 1985), each conducted in 12 healthy men, evaluated three dose comparisons (5 g, 10 g, and 20 g) of gum acacia when added to a sugar solution beverage. At all three dose comparisons, gum acacia statistically significantly lowered postprandial blood glucose when compared to a control beverage. The three most recent studies (Larson et al., 2021; Uebelhack, 2020 *unpublished*; Wolever et al., 2019 *unpublished*), with the remaining six dose comparisons (13 g, 20 g, 24 g, and 40 g)[12], evaluated the effect of gum acacia when consumed with food. All three of these studies were conducted in both men and women and included larger sample sizes (n = 48, 35, 40, respectively) than prior studies. In one study with two dose comparisons (Uebelhack, 2020 *unpublished*), gum acacia, at 20 g and 40 g doses, statistically significantly lowered postprandial blood glucose when added to a beverage and consumed as part of a breakfast meal. In another study with two dose comparisons (Larson et

[12] Two studies evaluated 20 g and 40 g doses, and one study evaluated 13 g and 24 g doses.

al., 2021) and a similar study design (i.e., 20 g or 40 g of gum acacia added to a beverage as part of a breakfast meal), a statistically significant lowering effect on postprandial blood glucose was observed with consumption of the 20 g dose of gum acacia. No statistically significant effect was observed on postprandial blood glucose when the beverage containing 40 g of gum acacia was consumed. In these two studies (Larson et al., 2021; Uebelhack, 2020 *unpublished*), no dose-response effect was observed on postprandial blood glucose. In the third study (Wolever et al., 2019 *unpublished*), with two dose comparisons, there was no statistically significant effect of gum acacia (13 g or 24 g), consumed in pudding, on postprandial blood glucose. We also evaluated the data on the effect of gum acacia on the relationship between postprandial insulin and postprandial blood glucose from those studies that measured both postprandial glucose and postprandial insulin.

Three studies (Sharma, 1985; Uebelhack, 2020 *unpublished*; and Wolever et al., 2019 *unpublished*), which included five dose comparisons of gum acacia ranging from 13 g to 40 g, reported the effect of gum acacia consumption on both postprandial blood glucose and postprandial insulin. These three studies with five dose comparisons (13 g, 20 g, 24 g, and 40 g)[13] allowed us to draw scientific conclusions on the relationship between consumption of gum acacia and postprandial insulin and postprandial blood glucose. At all five dose comparisons, gum acacia statistically significantly lowered postprandial insulin. In these studies, the lowering of postprandial insulin was accompanied by a statistically significant lowering (Sharma, 1985 – 20 g; Uebelhack, 2020 *unpublished* – 20 g and 40 g doses), or absence of a rise (i.e., no statistically significant change) (Wolever et al., 2019 *unpublished* – 13 g and 24 g doses) in postprandial blood glucose. A lower insulin response after a meal, without a higher glycemic response among healthy subjects, is a beneficial physiological effect because less insulin is required to achieve a similar, or lower, glycemic effect. The attenuation of postprandial blood glucose and insulin responses is associated with a reduced risk of coronary heart disease.[14,15] Therefore, the strength of the available scientific evidence supports the beneficial physiological effect that gum acacia has on postprandial blood glucose and insulin.

Based on our consideration of the scientific evidence and other information submitted with the petition, and other pertinent scientific evidence and information, we conclude that the strength of the evidence shows that gum acacia has a physiological effect that is beneficial to human health.

Therefore, in accordance with 21 CFR § 10.30(e)(3), we are granting your request and will propose to amend the list of non-digestible carbohydrates that meet the definition of dietary fiber to include “acacia (gum arabic).” We intend to exercise enforcement discretion for declaring “acacia (gum arabic)” in the amount of dietary fiber declared on Nutrition and Supplement Facts

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[13] One study evaluated a 20 g dose, one study evaluated 13 g and 24 g doses, and one study evaluated 20 g and 40 g doses.

[14] Bhat SL, Abbasi FA, Blasey C, Reaven G, Kim SH. Beyond fasting plasma glucose: the association between coronary heart disease risk and post-prandial glucose, post-prandial insulin and insulin resistance in healthy, nondiabetic adults. *Metabolism Clinical and Experimental* 2013;62:1223-1226.

[15] Augustin LSA, Kendall CWC, Jenkins DJA et al. Glycemic index, glycemic load and glycemic response: An International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). *Nutrition, Metabolism and Cardiovascular Disease* 2015;25:795-815.

labels until we can complete a rulemaking to amend 21 CFR § 101.9(c)(6)(i) to include additional dietary fibers in the list of non-digestible carbohydrates that meet our definition of dietary fiber.

Sincerely,

Claudine J. Kavanaugh -S
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