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Via Electronic Submission

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Re: Citizen Petition Requesting Amendment of the Definition of Dietary Fiber at 21 C.F.R. § 101.9(c)(6)(i) to Include "Acacia (Gum Arabic)"

CITIZEN PETITION

The undersigned, Keller and Heckman LLP, on behalf of Nexira, Ingredion Incorporated and TIC Gums, Alland & Robert, and Importers Service Corporation (collectively referred to as "Petitioners"), submits this petition pursuant to 21 C.F.R. § 10.30 and Sections 403(q), 403(a), 201(n), and 701(a) of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to amend the definition of "dietary fiber" at 21 C.F.R. § 101.9(c)(6)(i) by adding "Acacia (gum arabic)" (referred to in this petition as "Gum Acacia" or "GA") to the existing list of isolated or synthetic non-digestible carbohydrates determined by the U.S. Food and Drug Administration ("FDA") to have physiological effects that are beneficial to human health.

A. Action Requested

The Petitioners respectfully request FDA to amend the regulation defining "dietary fiber" to add Gum Acacia to the list of "isolated or synthetic nondigestible carbohydrates that have been determined by FDA to have physiological effects that are beneficial to human health and, therefore, shall be included in the calculation of the amount of dietary fiber." (21 C.F.R. § 101.9(c)(6)(i)).

i. Regulatory Background

On May 27, 2016, FDA published the final rule revising the Agency's nutrition labeling regulations (referred to as the "Nutrition Labeling Rule"). For purposes of nutrition labeling, FDA defined dietary fiber as:

(1) Non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units) and lignin that are intrinsic and intact in plants;

(2) 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.[1]

The rule further stated:

> The following isolated or synthetic non-digestible carbohydrate(s) have been determined by FDA to have physiological effects that are beneficial to human health and, therefore, shall be included in the calculation of the amount of dietary fiber: [beta]-glucan soluble fiber (as described in § 101.81(c)(2)(ii)(A)), psyllium husk (as described in § 101.81(c)(2)(ii)(A)(6)), cellulose, guar gum, pectin, locust bean gum, and hydroxypropylmethylcellulose.

As demonstrated in this petition, GA has beneficial physiological effects on (1) postprandial blood glucose and insulin levels and (2) energy intake and satiety. FDA has recognized these physiological effects to be beneficial to human health in their 2018 final guidance.[2] Information to support this request to amend the regulation is set forth in this petition and demonstrated by findings contained in the scientific studies.

The strength of the scientific evidence supports the conclusion that GA is an isolated non-digestible carbohydrate that is a dietary fiber for nutrition labeling purposes under 21 C.F.R. § 101.9(c)(6)(i). Thus, the Petitioners request that FDA amend the above-quoted language from 21

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[1] 81 Fed. Reg. 33742 (May 26, 2016); 21 C.F.R. § 101.9(c)(6)(i).

[2] See "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): Guidance for Industry," February 2018, page 9; see also 81 Fed. Reg. 33744 (May 27, 2016); see also 81 Fed. Reg. 84595 (Nov. 23, 2016).

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C.F.R. § 101.9(c)(6)(i) by adding "acacia (gum arabic),"[3] such that the sentence would read as follows:

> The following isolated or synthetic non-digestible carbohydrate(s) have been determined by FDA to have physiological effects that are beneficial to human health and, therefore, shall be included in the calculation of the amount of dietary fiber: [beta]-glucan soluble fiber (as described in § 101.81(c)(2)(ii)(A)), psyllium husk (as described in § 101.81(c)(2)(ii)(A)(6)), cellulose, guar gum, pectin, locust bean gum, hydroxypropylmethylcellulose, and **acacia (gum arabic)** [emphasis added].

B. Statement of Grounds

i. Overview of Gum Acacia

GA is the dried gummy exudate from the stems and branches of *Acacia Senegal* (L.) Willdenow or *Acacia seyal* (fam. Leguminosae).[4] It is consumed without further processing or processed minimally to remove extraneous materials and create different forms for different food applications. The manufacturing process description is set forth in **Appendix I.**

Petitioners further note that Gum Acacia is recognized as dietary fiber and an approved food additive by FDA at 21 C.F.R. § 172.780 and generally recognized as safe (GRAS) at 21

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[3] We note that the ingredient is referred to as "acacia (gum arabic)" at 21 C.F.R. § 172.780 and § 184.1330 and the Food Chemicals Codex (FCC) monograph refers to "gum arabic" and "acacia". FDA's fiber documents refer to "gum acacia (gum arabic)." Thus, we are requesting that FDA use the name "acacia (gum arabic)" when amending 21 C.F.R. § 101.9(c)(6)(i) to be consistent with the food additive/GRAS regulations.

[4] See The Joint FAO/WHO Expert Committee of Food Additives (JECFA) monograph. "Definition: Gum arabic is a dried exudate obtained from the stems and branches of *Acacia senegal* (L.) and Willdenow or *Acacia seyal* (fam. Leguminosae). Gum Arabic consists mainly of high-molecular weight polysaccharides and their calcium, magnesium and potassium salts, which on hydrolysis yield arabinose, galactose, rhamnose and glucuronic acid. Items of commerce may contain extraneous materials such as sand and pieces of bark, which must be removed before use in food," available at: http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/Monograph1/Additive-219.pdf.

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C.F.R. § 184.1330. The food additive regulation recognizes that Gum Acacia functions as a "dietary fiber."

ii. Scientific Evidence of Beneficial Physiological Effects of Gum Acacia

As discussed in FDA's final guidance[5], the dietary fiber scientific evaluation process involves a series of steps to: (1) assess publicly available scientific studies and other data; (2) eliminate those studies from which scientific conclusions about the physiological effects of an added non-digestible carbohydrate cannot be drawn; and (3) evaluate the strength of the scientific evidence to determine whether the carbohydrate provides a physiological effect that is beneficial to human health. Additionally, the final guidance explains that FDA will evaluate the strength of the evidence by considering "the number of studies and sample sizes of each study, the dose response data, the types of foods tested, the relevance of the body of scientific evidence to the U.S. population or target subgroup, and the overall consistency."[6]

In evaluating the publicly available data, Petitioners referenced FDA's final guidance to ensure such studies provided information for which scientific conclusions can be drawn (e.g., critical elements of a study, such as design, data collection, and that data analysis were not flawed). Studies that were deficient in one or more critical elements was excluded from analysis.

Based on the totality of the evidence, as further discussed below, the Petitioners found GA to have beneficial physiological effects on (1) postprandial blood glucose attenuation and insulin levels and (2) energy intake levels and increased satiety.

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[5] See "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): Guidance for Industry," February 2018.

[6] See "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): Guidance for Industry," February 2018, page 14, 19.

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1. Endpoint: Postprandial Blood Glucose Attenuation and/or Insulin Levels

Attenuation of blood glucose and/or insulin levels is a physiological effect that is beneficial to human health.[7] As indicated in FDA's guidance documents and scientific reviews,[8] attenuation of blood glucose or insulin levels may be measured by assessing postprandial blood glucose and insulin levels. Some studies reviewed by FDA evaluated the area under the curve (AUC) for blood glucose or insulin; some studies reviewed by FDA evaluated peak values of blood glucose or insulin.[9] Two recent studies have been conducted to evaluate the beneficial effects of GA on various measures of postprandial blood glucose and insulin levels, as well as on energy intake and satiety. Below, we first discuss studies found in the scientific literature that evaluated potential beneficial effects of GA as a dietary fiber on the attenuation of blood glucose and/or insulin levels; we then provide summaries and conclusions for the two additional studies.

a. Sharma (1985b)

FDA summarized the Sharma (1985b) study in their November 2016 Science Review.[10] In this study, the impact of GA on blood glucose levels was studied in 12 healthy human subjects using a randomized crossover design. The addition of 20 grams (g) of GA to a 100 g load of glucose resulted in a statistically significant reduction of 16.1% of blood glucose and a reduction of serum insulin of 11.2% at 90 minutes. The incremental area (iAUC) under the plasma glucose curve was significantly reduced ($p < 0.05$) as was the iAUC for insulin ($p < 0.05$) at the same time point.

The ages for the 12 healthy male subjects ranged from 30-50 years and body weights from 50-60 kilograms (kg). All the subjects had normal weights for their heights. The subjects were on a diet containing a typical North American intake of 300 g of total carbohydrates daily for more than three days prior to each test. The subjects were divided into two groups (A and B) of six each. After an overnight fast each subject of Group A underwent a glucose tolerance test

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[7] *Id*. at page 9.

[8] See "Review of the Scientific Evidence on the Physiological Effects of Certain Non-Digestible Carbohydrates," June 2018.

[9] For example, see the discussion of High Amylose Starch (Resistant Starch 2); *Id*. at page 28-37.

[10] See "Science Review of Isolated and Synthetic Non-Digestible Carbohydrates," November 2016, page 9; Sharma RD Hypoglycemic effect of gum acacia in healthy human subjects. *Nutrition Research* 1985b; 5:1437-1441 (Sharma 1985b).

after consuming 100 g of glucose. Five milliliters (mL) of venous blood was drawn at 30, 60, 90, 120, and 150 minutes after the glucose was ingested. The same test was repeated one week later with the same amount of glucose but including 20 g of GA dissolved in the glucose solution. The same test solutions were consumed with Group B, but in reverse order. The total incremental area (iAUC) of blood glucose values and serum insulin values were calculated. Statistical analysis data from Groups A and B were pooled and evaluated using the paired t-test.

b. Akeo et al. (2002)

The Akeo et al. (2002) study was provided to FDA in comments submitted by Keller and Heckman on February 13, 2017. This study evaluated the impact of GA on blood glucose after consumption of glucose alone, or glucose plus 5 g or 10 g of the commercial GA product Fibergum P.[11] Twelve healthy adult male subjects (mean age of 35.8) were divided into three groups of four. A glucose tolerance test was conducted by dissolving 100 g of glucose with 0 g, 5 g, or 10 g of GA, fiber content 85%, in 300 mL of water for an oral intake on each day of the study. Blood samples were taken prior to oral intake and after intake between 30 minutes to 150 minutes at a 30- minute interval. For measuring blood glucose levels, a glucose oxidase assay was performed using Glutest Ace.

Glucose levels reached their peaks 30 minutes after intake for sucrose plus 0-10 g of GA. At the peak levels after intake, with 5 g of GA intake, the peak level was 153.5 ± 7.48 ($p < 0.005$, mean ±SE) and with 10 g of GA intake, the peak level was 146.00 ± 9.83 ($p < 0.005$, mean ±SE), which is a significant reduction compared with 0 g of GA intake, for which the blood glucose level was 171.1 ± 7.65, mean ±SE. At 60 minutes after ingestion, the level was 116.2 ± 7.33 ($p < 0.05$) for 5 g of GA intake, 116.8 ± 7.98 ($p < 0.05$) for 10 g of GA intake, compared with 132.6 ± 8.58 for 0 g of GA intake. At 30 minutes after ingestion, reductions in blood glucose levels showed a trend which indicated a dose-response relationship. No adverse events were observed during the study, including diarrhea, stomachache, or other abdominal symptoms.

[11] Akeo K, Kojima M, Uzuhashi Y. Physiological Functions of Gum Arabic. Food Chemical Monthly, June, 2002. This study was not included in FDA's "Science Review of Isolated and Synthetic Non-Digestible Carbohydrates" published online in November 2016. The paper was published in a Japanese journal. A translation of the original Japanese publication is included in **Appendix II**.

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c. University of Minnesota Study (2019)

This study was commissioned by Nexira and financially supported by Nexira, Ingredion Incorporated and TIC Gums, Alland & Robert, and Importers Service Corporation, and carried out in the laboratory under the guidance of Dr. Joanne Slavin at the University of Minnesota, Department of Food Science and Nutrition.[12] The full report is provided as **Appendix III**.

The objective of the study was to determine the effect of two acute doses of GA on satiety, glycemic response, and gastrointestinal tolerance in normal human subjects. Forty-eight (48) healthy human subjects consumed 0 (controls), 20, or 40 grams of GA added to orange juice concomitant with the consumption of a bagel with cream cheese in a randomized, double-blinded, treatment schedule. Each blinded treatment was separated by at least one week. Subjects recorded subjective satiety measures for the four hours following breakfast consumption and blood glucose was measured at baseline, 30, 60, 120, 180 and 240 minutes after each treatment. The subjects were then fed an *ad libitum* pizza meal and food intake was recorded. Each subject recorded food intake subsequent to the experimental treatment for 24 hours. Subjects reported less hunger and greater fullness at 15 minutes, 30 minutes, and 240 minutes after consumption of the high fiber treatment. They also reported being significantly more satisfied and more full with the high fiber treatment at 15 minutes. There were no differences in pizza calorie intake after any GA treatment compared with controls. Reported food intake after GA consumption trended lower relative to controls. Average calorie intakes were 1790 ± 749 (SD) for controls, 1625 ± 642 for low GA treatment and 1590 ± 691 calories for the high GA treatment ($p = 0.12$).

Palatability of gum acacia did not vary among the treatments and gastrointestinal (GI) tolerance to the high GA treatment was acceptable; the results for GI tolerance were all low for gum acacia treatments.

The area under the curve (AUC) for postprandial glucose did not differ for the three treatments. Peak glucose (30-minute response) was significantly less for the GA treatment relative to controls ($p = 0.011$). Peak glucose response for controls was 144.2 ± 19.1 while peak glucose response for the 20 gram GA treatment was 136.7 ± 20.0 ($p = 0.013$). Peak glucose response after the high GA treatment was 137.9 ± 17.0, which was not different from the low GA treatment ($p = 0.84$) but was smaller than the peak response for controls ($p = 0.055$). The results

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[12] To be published as: The Effects of Gum Acacia on Satiety, Glycemic Response and Gastrointestinal Tolerance. Riley Larson, RDN, Courtney Nelson, Qi Wang, MS, Renee Korczak, PhD, RDN, Joanne Slavin, PhD, RDN. Department of Food Science and Nutrition, University of Minnesota - Twin Cities, 1334 Eckles Avenue, St. Paul, MN 55108; 612-624-7234; jslavin@umn.edu.

for postprandial glucose measurements are summarized in the following table.

Table 1. Blood Glucose for Gum Acacia Treatments

	Treatment A (Control)			Treatment B (20 g GA)			Treatment C (40 g GA)			P-value (ANOVA)
Outcome	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Glucose AUC	48	419.0	31.4	48	417.9	34.0	47	418.9	36.8	0.94
Glucose at baseline	48	95.1	8.8	48	92.6	14.5	48	94.5	8.6	0.49
Glucose at 30 min	48	144.2	19.1	48	136.7	20.0	48	137.9	17.0	**ANOVA: 0.011** **A vs. B: 0.013** A vs. C: 0.055 B vs. C: 0.84
Glucose: baseline to 30 min	48	49.1	18.3	48	44.1	23.5	48	43.5	15.9	0.16
Glucose: baseline to 60 min	48	20.0	21.0	48	23.9	21.8	48	21.9	21.6	0.57
Glucose: baseline to 120 min	48	6.3	12.0	48	10.1	16.1	48	5.2	18.1	0.28
Glucose: baseline to 180 min	48	-3.7	10.3	48	-0.3	16.1	48	0.3	13.3	0.27
Glucose: baseline to 240 min	48	-7.1	10.2	48	-4.7	16.7	47	-4.8	10.3	0.56

The evidence provided by the University of Minnesota (2019) study demonstrates that GA has a beneficial effect on postprandial blood glucose levels.

d. GI Labs Study (2019)

This study was commissioned by Ingredion Incorporated and TIC Gums and financially supported by Ingredion Incorporated and TIC Gums, Nexira, Alland & Robert, and Importers Service Corporation. The objective of the study was to determine the effect of two doses of GA on the postprandial levels of glucose and insulin by measuring the individual values of each and the incremental area under the response curve (iAUC) over two hours in healthy humans. Specific endpoints included insulin iAUC, glucose and insulin netAUC, peak rises of glucose

and insulin and glucose and insulin concentrations and increments over the two-hour study period. Forty healthy subjects (28 male, 12 female, aged 36±14 y with BMI 25.1±3.3 kg/m^2; mean±SD) fasted overnight prior to consuming a pudding containing 59 g available carbohydrate, 6 g protein, 2 g fat and either 0, 13 g or 24 g GA: termed Controls, Acacia low dose (AcLow), and Acacia high dose (AcHigh), using a randomized cross-over design.

The results showed no significant difference among test-meals for plasma glucose iAUC, netAUC or peak rise. However, the GA treatments elicited a significantly slower rise of plasma glucose (AcLow and AcHigh significantly less than Control at 15 min) followed by a slower fall and significantly delayed return to baseline. Serum insulin iAUC and netAUC after AcLow and AcHigh were similar to each other and both were significantly less than after Control by 13-18%. Insulin peak rise after AcLow was significantly less than that after AcHigh, which, in turn, was significantly less than that after Control. Glucose and insulin iAUC were not significantly affected by subject sex, age or BMI, however, both glucose and insulin iAUC were significantly higher in non-Caucasians than Caucasians. Neither sex, age, BMI nor ethnicity significantly affected glucose or insulin responses compared to the controls. We note that FDA has accepted insulin reduction without a change in blood glucose response in their review of "high amylose resistant starch".[13]

The full study report is provided in **Appendix IV** and specific values for endpoints are summarized in the table below.

Table 2. Summary Results for Glucose and Insulin

	Control	AcLow	AcHigh
Glucose iAUC (mmol×min/L)	139.7±10.8	143.9±11.6	133.4±13.2
Insulin iAUC (nmol×min/L)	18.6±2.0[a]	15.3±1.4[b]	16.1±1.6[b]
Glucose netAUC (mmol×min/L)	121.5±12.3	132.5±12.0	122.2±13.6
Insulin netAUC (nmol×min/L)	18.2±2.1[a]	15.1±1.4[b]	15.9±1.6[b]
Glucose Peak Rise (mmol/L)	3.28±0.14	3.21±0.15	3.10±1.07

[13] See "Review of the Scientific Evidence on the Physiological Effects of Certain Non-Digestible Carbohydrates," June 2018, page 33, "The six studies demonstrated that RS2 reduced post-prandial insulin response in the absence of a rise on post-prandial glucose. A lower insulin response after a meal, without a higher glycemic response among healthy subjects, is a beneficial physiological effect of RS2 because less insulin is required to achieve a similar glycemic effect."

Insulin Peak Rise (pmol/L)	409±35[a]	326±24[c]	372±35[b]

[a] Control vs AcLow, p = 0.006; Control vs AcHigh, p = 0.0495
[b] Control vs AcLow, p = 0.018
[c] Control vs AcLow, p = 0.001

Results in the table are displayed as Mean ± standard error for N = 40 subjects. To convert glucose mmol/L to mg/dL multiply by 18; to convert insulin pmol/L to μU/mL divide by 6. Superscripts, abc designate significant differences with different letter superscripts differ by Tukey's test ($p<0.05$).

e. Review of the Scientific Literature

Petitioners identified ten human studies that evaluated the effect of GA consumption on postprandial blood glucose and insulin levels.[14] Scientific conclusions could not be drawn from five studies (Ross (1983), Campbell et al. (1997), Torres et al. (2006), Pouteau et al. (2010), Nasir et al. (2016))[15] for lack of acceptable study design in accordance with FDA's final guidance[16]. One study (Unpublished Australian Study) was not supportive, despite an acceptable study design. Thus, of the five acceptable studies, four studies (University of Minnesota (2019), GI Labs (2019), Sharma (1985b), Akeo (2012)) demonstrated a statistically significant effect of GA on postprandial blood glucose and/or insulin levels.

Therefore, the strength of the evidence supports the conclusion that the consumption of GA facilitates the beneficial effect of postprandial blood glucose and/or insulin levels. The evidence from which scientific conclusions could be drawn supports our request to include GA

[14] Studies identified in FDA's 2016 Science Review; February 13, 2017 Keller and Heckman LLP Comment.

[15] FDA acknowledged that scientific conclusions could not be drawn from Campbell et al. (1997) in the November 2016 "Science Review of Isolated and Synthetic Non-Digestible Carbohydrates," page 9. Torres et al. (2006), Pouteau et al. (2010), and Nasir et al. (2016) were discussed in comments to FDA submitted by Keller and Heckman on February 13, 2017.

[16] See "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): Guidance for Industry," February 2018, page 10. .

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in the definition of dietary fiber and, until completion of such a rulemaking, to consider enforcement discretion for declaring the amount of GA as dietary fiber.

i. Unpublished Australian Study

In 2004, Colloides Naturels International[17] conducted a study (not published) in conjunction with Sydney University, Australia, to assess the glycemic index and insulin index values using GA (Fibregum™) enriched crispbreads. The objective of the study was to measure the glycemic index (GI) and insulin index (II) values of the following three fiber enriched crispbreads, using pure glucose sugar as the reference food (i.e., GI and II values of glucose are fixed at 100): Bread 1 (0% Fibregum™); Bread 2 (6% Fibregum™); Bread 3 (11 % Fibregum™).

The following results were reported: the reference food's GI value was significantly greater than the average GI values of Bread 2 and 3 (both 99.9%: $p < 0.001$), and Bread 1 (99%: $p < 0.01$). There were no significant differences between the GI values for the three crispbreads. The II value for Bread 3 was significantly lower than the II value for the reference food and Bread 1 (95%: $p < 0.05$). The authors concluded that using glucose as the reference food (GI = 100), foods with a GI value less than 55 are currently considered to be low-GI foods. The three breads, containing varying amounts of Fibregum™, acacia gum, were found to produce GI values that were not significantly different. However, the results do suggest a dose-response relationship, with the highest dose of Fibregum™ producing the lowest GI value. A full summary of the Unpublished Australian Study was provided to FDA in comments submitted by Keller and Heckman on February 13, 2017.

ii. Excluded Studies

As mentioned, scientific conclusions could not be drawn from five studies (Ross (1983), Campbell et al. (1997), Torres et al. (2006), Pouteau et al. (2010), Nasir et al. (2016)), and therefore the physiological effect of GA could not be evaluated. The studies were excluded from review for a variety of reasons, including an unmatched carbohydrate (Torres et al. (2006)), lack of an adequate control or protocol (Ross (1983); Nasir et al. (2016)), and a mixture of non-digestible carbohydrates, including GA, was provided and therefore the physiological effect of

[17] Colloides Naturels International, A study to measure the glycaemic index and insulin index values of three fibre-enriched crispbreads, Sydney University's Glycaemic Index Research Service, 2004

(continued …)

GA *per se* could not be evaluated (Campbell et al. (1997); Pouteau et al. (2010)). Petitioners further discuss the reasoning to exclude Ross (1983) below.

Ross et al. (1983)

Based on discussions with the Agency, Petitioners understand FDA considers Ross et al. (1983) to be an acceptable, but not supportive study, with regards to postprandial blood glucose and insulin levels.[18] However, Petitioners believe Ross et al. (1983) has several limitations and is not an acceptable study in accordance with FDA's study design guidance.[19] Thus, Petitioners believe that scientific conclusions cannot be drawn from Ross et al. (1983).

This study evaluated the impact of GA on blood glucose, insulin, and several other metabolic parameters measured in blood samples from five (5) male subjects. This study was rejected (1) because the information obtained from five subjects is inadequate to provide an adequate statistical power for finding a beneficial effect if one exists and (2) because of an unusual protocol that measured the impact of GA on glucose tolerance and not postprandial glucose, as well as the absence of an adequate control group or period. The subjects participated in a 7 day "control" period followed by a 21-day "test" period during which the subjects consumed 25 g GA in 125 mL of a 7% dextrose solution. An oral glucose tolerance test was conducted on day 1 of the control period by administering 200 mL of water containing 50 g glucose. Additional biochemical outcomes were assessed at this study visit, but they are not discussed herein because they do not relate to post-prandial blood glucose attenuation. The same oral glucose tolerance test and biochemical outcomes were assessed on the last day (day 21) of the test period.

This study design has several limitations. The trial was not a randomized trial. All subjects completed the control period first. Additionally, the control period was not the same length as the test period, and the control period did not include administration of a placebo. The oral glucose tolerance test and biochemical measures were assessed on day 1 of the control period, which makes these measures "baseline measures" rather than control measures. The

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[18] Petitioners note that FDA did not consider Ross et al. (1983) to be acceptable in their November 2016 Science Review and stated that "scientific conclusions could not be drawn from" Ross et al. (1983) with regards to the effect of GA on blood cholesterol levels. See "Science Review of Isolated and Synthetic Non-Digestible Carbohydrates," November 2016, page 9.

[19] See "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): Guidance for Industry," February 2018.

outcomes related to blood glucose control were oral glucose tolerance tests with insulin measures. GA was not administered in these tests. The test solution was glucose in water. This study did not assess post-prandial glucose/insulin response to ingestion of GA. Rather it assessed glucose tolerance and insulin sensitivity after a 21 day test period. These are two distinct measures of blood glucose control.

No statistical difference was found for blood glucose levels for the two solutions. Thus, due to study design, scientific conclusions cannot be determined and Ross (1983) is excluded from review.

2. Endpoint: Energy Intake and Satiety

Reduced energy intake and increased satiety are also considered beneficial physiological effects.[20] As indicated in FDA's scientific evaluation, reduced energy intake may be assessed either by direct measurement of leftover food after an *ad libitum* meal or by 24-hour recalls and food diaries.[21] Satiety may be assessed using a Visual Analogue Scale that measures various endpoints, such as hunger, appetite, and feelings of fullness.[22] One recent study has been conducted to evaluate the beneficial effects of GA on reduced energy intake and satiety. Below, we first discuss studies found in the scientific literature that evaluated potential beneficial effects of GA as a dietary fiber on energy intake reduction and satiety increase, and then provide a summary and conclusion for the study commissioned by Petitioners.

a. Calame et al. (2011)

FDA reviewed Calame et al. (2011) in the November 2016 Science Review. Two separate studies were performed to investigate energy intake and satiety enhancement by GA. The objective of the first study was to determine the extent to which high doses of gums might affect energy intake and subjective scores of satiety in healthy male subjects. The objective of the second study was a minimal dose-seeking study using both males and females, again targeting separately energy intake and VAS scores for satiety. Both studies were randomized, double-blinded placebo-controlled crossover designs. Wash-out periods of at least three days were interjected between the various interventions. To lower intersubject variations, the change in VAS score per person was evaluated using the baseline value subtracted from the result at a specific interval. Baseline values per person were evaluated for difference by paired t-tests and were found to be statistically non-significant. Randomization throughout the experiments was

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[20] *Id.* at 9.

[21] *Id.* at 11.

[22] *Id.*

achieved with a Latin-square approach applying day of entry and order of consumption as determinants.

Study I

Subjects consumed 10, 20, and 40 g of EmulGold (EG) and PreVitae (PV) brands of GA dissolved in 250 mL of water. A glass of 250 mL of water served as negative control. There were 12 male subjects. Each drank every test product with a wash-out period of at least three days. On the day of the experiment subjects fasted before entering the laboratory from 8 pm the previous day. They received a standardized breakfast, which they consumed within 30 minutes. The subjects then drank a glass of water containing 0, 10, 20, or 40 g of EG or PV gum acacia. Three hours after eating subjects were given the option to consume an *ad libitum* meal consisting of large Turkish bread with a topping of egg salad. Energy intake was calculated from the difference in energy content of the food available and the food remaining. VAS analysis was performed at regular intervals after consuming the drink containing GA, by asking the following questions: (1) How high is your satiety level right now? (2) How much hunger do you experience right now? (3) How full are you feeling right now? (4) How much do you expect to be able to consume right now? Experimentation ceased at the end of the *ad libitum* meal.

Study II

The objective for the second study was to find a low dose of GA with proven efficacy in lowering energy intake. The doses consumed were 5 g and 10 g of EG with 250 mL of water as negative control; PV was not included in this study because Study I revealed the same reduction in energy intake for both GA products, except for the 40 g of PreVitae. Study II was also a randomized, double-blinded, and place-controlled crossover study using 42 female and 16 male subjects, with participants fasting from 8 pm the previous day. Subjects were given a standardized breakfast and 30 minutes later they were given 250 mL of water containing 0, 5, or 10 g of EG brand gum acacia. An *ad libitum* meal was offered 3 hours after intake of the water with or without the gum. Subjects were instructed to eat until they felt comfortably full and to remain seated for 30 minutes while they consumed their meal, after which they were offered a second drink of water containing 0, 5, or 10 g of gum acacia. Three hours later they were offered a second *ad libitum* meal. During the study they were asked about their subjective hunger ratings as described above using VAS questionnaires. Energy intake was calculated from the difference in energy content of the food available and the food remaining.

Statistical analysis

Differences in energy intake were analyzed using the paired t-test after checking for normality of the distribution. In the second study, the relationship between energy intakes at Meal-1 to that in Meal-2 was evaluated using the Wilcoxon matched-pairs signed-ranks test.

With respect to the outcome of the various VAS, scores were evaluated using multiple regression analysis with a dummy variable based on values at the start of the experiment subtracted from those per time interval per person.

We support FDA's view that the two Calame et al. (2011) studies were adequate to derive a scientific conclusion with regard to the parameters measured and maintain that the conclusion reached supports the conclusion that Gum Acacia has an effect on energy intake and satiety.

b. University of Minnesota Study (2019)

As discussed above in Section B.ii.1., this study was commissioned by Nexira and financially supported by Nexira, Ingredion Incorporated and TIC Gums, Alland & Robert, and Importers Service Corporation, and was carried out in the laboratory under the guidance of Dr. Joanne Slavin at the University of Minnesota, Department of Food Science and Nutrition.[23] The full report is provided as **Appendix III**.

The objective of the study was to determine the effect of two acute doses of GA on satiety, glycemic response, and gastrointestinal tolerance in normal human subjects. Forty-eight (48) healthy human subjects consumed 0 (controls), 20, or 40 grams of GA added to orange juice concomitant with the consumption of a bagel with cream cheese in a randomized, double-blinded, treatment schedule. Each blinded treatment was separated by at least one week. Subjects recorded subjective satiety measures for the four hours after each treatment. The subjects were then fed an *ad libitum* pizza meal and food intake was recorded. Each subject recorded food intake subsequent to the experimental treatment for 24 hours.

Visual analog scales (VAS) were utilized to assess hunger, fullness, and desire to eat periodically for four hours following the breakfast meal. Subjects were given instructions for completing the computerized VAS and completed the baseline appetite assessment after consumption. The test meal was consumed within 15 minutes. Appetite sensations were rated by VAS at 15, 30, 45, 60, 90, 120, 180, and 240 minutes after baseline. Gastrointestinal (GI) tolerance was also measured by subjective scales. GI symptom surveys were completed at baseline, 60 minutes, 120 minutes, 180 minutes, 240 minutes, 12 hours, and 24 hours post-consumption.

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[23] To be published as: The Effects of Gum Acacia on Satiety, Glycemic Response and Gastrointestinal Tolerance. Riley Larson, RDN, Courtney Nelson, Qi Wang, MS, Renee Korczak, PhD, RDN, Joanne Slavin, PhD, RDN. Department of Food Science and Nutrition, University of Minnesota - Twin Cities, 1334 Eckles Avenue, St. Paul, MN 55108; 612-624-7234; jslavin@umn.edu.

The results of this study support the conclusion that GA can be added to beverages at doses needed to meet fiber recommendations and is well tolerated. The high doses of GA improved satiety at 15 minutes, 30 minutes and 240 minutes after consumption. Neither dose of gum acacia changed food intake at pizza lunch, although 24-hour food intake after the treatment showed a dose response trend for lower self-reported food intake with increasing GA intake. GA lowered peak glucose response. This study supports the conclusion that GA can improve satiety and lower peak glucose response in healthy, human subjects.

c. Review of the Scientific Literature

Petitioners identified seven studies that evaluated the effect of GA on energy intake and satiety.[24] Scientific conclusions could not be drawn from four studies (Davidson et al. (1998), Babiker et al. (2012), Nasir et al. (2016), Babiker et al. (2017/2018))[25] for lack of an acceptable study design in accordance with FDA's final guidance.[26] The studies were excluded from review for a variety of reasons, including a lack of an adequate control (Nasir et al. (2016)), a mixture of non-digestible carbohydrates, including GA, was provided and therefore the physiological effect of GA *per se* could not be evaluated (Davidson et al. (1998)), and statistical comparisons were not conducted between the GA treatment and control groups (Babiker et al. (2012); Babiker et al. (2017/2018)). Thus, there are three acceptable studies (University of Minnesota (2019) and two Calame et al. (2011) studies), and all three demonstrated a beneficial effect of GA consumption on energy intake levels and increased satiety. None of the studies identified were found not to be supportive of the conclusion that GA has a beneficial physiological effect on energy intake and satiety.

Therefore, the strength of the evidence supports the conclusion that the consumption of GA facilitates the beneficial effect of energy intake reduction and increased satiety. The evidence from which scientific conclusions could be drawn supports our request to include GA

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[24] Studies identified in FDA's 2016 Science Review and February 13, 2017 Keller and Heckman LLP Comment.

[25] FDA acknowledged that scientific conclusions could not be drawn from Davidson et al. (1998) and Babiker et al. (2012) in the November 2016 "Science Review of Isolated and Synthetic Non-Digestible Carbohydrates," page 10. Nasir et al. (2016) was discussed in comments to FDA submitted by Keller and Heckman on February 13, 2017. Babiker et al. (2017/2018) was found to lack acceptable study design based on discussions with the FDA.

[26] See "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): Guidance for Industry," February 2018, pages 9-10.

in the definition of dietary fiber and, until completion of such a rulemaking, to consider enforcement discretion for declaring the amount of GA as dietary fiber.

3. Conclusion: Gum Acacia Should Be Considered a Dietary Fiber Under 21 C.F.R. § 101.9(c)(6)(i)

For the reasons set forth above, Petitioners believe that the strength of the scientific evidence supports the fact that Acacia (gum arabic) has beneficial physiological effects on human health for postprandial blood glucose attenuation and/or insulin levels, as well as for energy intake and increased satiety. Thus, Petitioners conclude that Acacia (gum arabic) is a non-digestible carbohydrate that is a dietary fiber for nutrition labeling purposes and respectfully request that FDA amend 21 C.F.R. § 101.9(c)(6)(i) as described in Section A.i. above.

C. Environmental Impact

This petition is categorically excluded from the requirement for an environmental assessment or environmental impact statement under 21 C.F.R. § 25.30(h). More specifically, 21 C.F.R. § 25.30(h) categorically excludes petitions requesting the "[i]ssuance, amendment, or revocation of procedural or administrative regulations and guidance documents…." To the Petitioners' knowledge, no extraordinary circumstances exist.

D. Economic Impact

In accordance with 21 C.F.R. § 10.30(b)(3), economic impact information is to be submitted only when requested by the Commissioner following review of the petition. Petitioners hereby commit to promptly provide this information, if so requested.

E. Certification

Pursuant to 21 C.F.R. § 10.30(b), the undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the Petitioners which are unfavorable to the petition.

Sincerely,

Melvin S. Drozen

Evangelia C. Pelonis