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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, 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.

I. 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 non-digestible 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)).

II. 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 a physiological effect on post-prandial blood glucose and insulin levels that is beneficial to human health. FDA has recognized this physiological effect 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). FDA has recognized another non-digestible carbohydrate, "cross-linked phosphorylated RS4", to meet the dietary fiber definition based on it having a physiological effect on post-prandial insulin that is beneficial to human health. See FDA response to MGP Ingredients Inc. Citizen Petition for Cross-Linked Phosphorylated RS4, FDA Docket No. FDA-2016-P-3620 (March 26, 2019).

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]

We note that a previous Citizen Petition (the 2019 Citizen Petition) was submitted for GA on April 19, 2019 and FDA responded on January 31, 2020.[4] 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 as discussed further below. This new study was commissioned by Nexira and carried out by Analyze & Realize GmbH (Berlin) under the direction of Prof. Ralf Uebelhack, MD and is referred to as the Uebelhack (2020) study.

III. Statement of Grounds

A. 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).[5] It is consumed without further processing or

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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 FDA Docket No. FDA-2019-P-1911.

[5] 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

(continued …)

processed minimally to remove extraneous materials and create different forms for different food applications. The manufacturing process description is set forth in Appendix I of the 2019 Citizen Petition.

Petitioners further note that GA 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 C.F.R. § 184.1330. The food additive regulation recognizes that GA functions as a "dietary fiber."

B. Scientific Evidence of Beneficial Physiological Effects of Gum Acacia

As discussed in FDA's final guidance,[6] 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."[7]

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 were excluded from analysis.

Based on the totality of the evidence, as further discussed below, the Petitioners conclude that consumption of GA has beneficial physiological effects in the attenuation of post-prandial insulin levels.

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in food," available at: http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/Monograph1/Additive-219.pdf.

[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.

[7] 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.

C. Review of the Scientific Literature

Petitioners identified a total of eleven human studies that evaluated the effect of GA consumption on post-prandial blood glucose and insulin levels.[8] As discussed below, scientific conclusions could be drawn from five studies (Sharma (1985), Akeo et al. (2002), Larson et al. (2019; unpublished), Wolever et al. (2019; unpublished), Uebelhack (2020; unpublished)), and these studies demonstrate a statistically significant effect of GA on post-prandial blood glucose and/or insulin levels.

Scientific conclusions could not be drawn[9] from six studies because of the following: (1) no control group or an inappropriate control group was used (Nasir et al., 2016; Ross et al., 1983)[10]; (2) a mixture of non-digestible carbohydrates, including GA, was used, and therefore the physiological effect of GA could not be independently evaluated (Campbell et al., 1997; Pouteau et al., 2010); or (3) the study measured the glycemic index of GA rather than post-prandial blood glucose, and nutrient composition of the treatment and control beverages (e.g.,

[8] Studies identified in FDA's 2016 Science Review; February 13, 2017 Keller and Heckman LLP Comment; Larson et al. (2019; unpublished), Wolever et al. (2019; unpublished), Uebelhack (2020; unpublished).

[9] 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.

[10] Also, as further discussed in the 2019 Citizen Petition submission, although FDA had previously concluded Ross et al. (1983) to be an acceptable, but not supportive study, with regards to post-prandial blood glucose and insulin levels, 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. 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 post-prandial glucose, as well as the absence of an adequate control group or period.

amount of available carbohydrate and ingredients) was not provided (Torres et al., 2006; Unpublished Australian Study (2004)).[11]

D. Endpoint: Post-prandial Blood Glucose and/or Insulin Level Reduction

Attenuation of blood glucose and/or insulin levels is a physiological effect that is beneficial to human health.[12] As indicated in FDA's guidance documents and scientific reviews,[13] attenuation of blood glucose and/or insulin levels may be measured by assessing post-prandial 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.[14] There was an additional study conducted to evaluate the beneficial effects of GA on various measures of post-prandial blood glucose and insulin levels since the 2019 Citizen Petition. 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 discuss the studies that were previously discussed in the 2019 Citizen Petition, followed by a discussion of the new study that has since been conducted.

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[11] 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. The Unpublished Australian Study (2004), conducted by Colloides Naturels International, was discussed in the 2019 Citizen Petition. Summary of studies for which conclusions could not be drawn are summarized in FDA's response letter dated January 31, 2020.

[12] 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.

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

[14] For example, see the "Review of the Scientific Evidence on the Physiological Effects of Certain Non-Digestible Carbohydrates," June 2018, page 28-37 (discussion of High Amylose Starch (Resistant Starch 2)).

1. Sharma (1985)

FDA summarized the Sharma (1985) study in their November 2016 Science Review.[15] In this study, the impact of GA on blood glucose levels was studied in 12 healthy human subjects using a randomized crossover design.

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 after consuming 100 g of a glucose solution. Five milliliters (mL) of venous blood was drawn at 30, 60, 90, 120, and 150 minutes after the glucose solution 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 area (AUC) 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.

The Sharma (1985) study demonstrates that the addition of 20 g of GA to a 100 g glucose solution 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 area under the curve for glucose was 4,036 mg/min/dL without gum acacia and 3,420 mg/min/dL with gum acacia. FDA stated that "[t]his reduction in blood glucose levels with gum acacia was significantly greater compared to the control ($P < 0.05$)".[16] The area (AUC) under the plasma glucose curve was significantly reduced ($p < 0.05$) as was the AUC for insulin ($p < 0.05$) at the same time point.

2. 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 a sucrose solution alone, or a sucrose solution plus 5 g or 10 g of the commercial GA product Fibergum P.[17] Twelve healthy adult male subjects (mean age of 35.8) were divided

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[15] 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 1985).

[16] *Id*. at page 9.

[17] 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

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into three groups of four. Glycemic response was measured by dissolving 100 g of glucose with 0 g (control), 5 g, or 10 g of GA, with a GA content of 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 mg/dL ($p < 0.005$, mean ±SE) and with 10 g of GA intake, the peak level was 146.00 ± 9.83 mg/dL ($p < 0.005$, 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 mg/dL, mean ±SE. At 60 minutes after ingestion, the blood glucose level was 116.2 ± 7.33 mg/dL ($p < 0.05$) for 5 g of GA intake, 116.8 ± 7.98 mg/dL ($p < 0.05$) for 10 g of GA intake, compared with 132.6 ± 8.58 mg/dL for 0 g of GA intake, which is significantly higher. 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.

3. Larson et al. (2019; unpublished)

Larson (2019) 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.[18] The full report was provided as Appendix III in the 2019 Citizen Petition.

The objective of the study was to determine the effect of two acute doses of GA on satiety, glycemic response, and gastrointestinal tolerance in healthy human subjects. Forty-eight (48) healthy human subjects consumed 0 (control), 20 (low), or 40 (high) g 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.

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 of the 2019 Citizen Petition.

[18] 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.

Palatability of GA did not vary among the treatments and gastrointestinal (GI) tolerance to the high GA treatment was acceptable; high dose recipients did report significant increases in reported GI symptoms (bloating, flatulence, etc.), however the subjective reported scores for these parameters were still relatively low.

Peak glucose (30-minute response) was significantly less for the GA groups overall relative to the control ($p = 0.011$). Peak glucose response for controls was 144.2 ± 19.1 mg/dL while peak glucose response for the 20 gram GA treatment was significantly lower at 136.7 ± 20.0 mg/dL ($p = 0.013$). Peak glucose response after the high GA treatment was 137.9 ± 17.0 mg/dL, which was not significantly different from the low GA treatment ($p = 0.84$) but was smaller than the peak response for controls ($p = 0.055$). The results for post-prandial glucose measurements show a significant difference for glucose at 30 minutes between control group and treatment B (20g GA). The area under the curve (AUC) for post-prandial glucose was not significantly different between the three treatment groups.

The evidence provided by Larson (2019) demonstrates that GA has a beneficial effect in attenuation of post-prandial blood glucose levels.

4. Wolever et al. (2019; unpublished)

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 post-prandial 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.

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. Concerning plasma glucose, 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. 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 accepted insulin reduction without a change in blood glucose response in their review of "high amylose resistant starch."[19]

The full study report was provided in Appendix IV of the 2019 Citizen Petition and specific values for endpoints are summarized in the table below.

Table 1. 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
Insulin Peak Rise (pmol/L)	409±35[a]	326±24[c]	372±35[b]
[abc] Means with different letter superscripts differ by Tukey's test ($p<0.05$).			

Results in Table 1 are displayed as mean ± standard error for 40 subjects. To convert glucose mmol/L to mg/dL multiply by 18; to convert insulin pmol/L to µU/mL divide by 6. Different superscripts designate significant differences using Tukey's test ($p<0.05$).

Table 1 reflects the Summary table provided on page 4 of Wolever et al. (2019). The results reported in the study summary table,[20] "Figure 2. Plasma glucose and serum insulin

[19] 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."

[20] See Wolever (2019), page 4.

concentrations,"[21] and "Figure 3. Plasma glucose and serum insulin increments"[22] indicate that insulin iAUC, insulin net AUC, and peak insulin for both treatment groups are indeed significantly reduced when compared to controls (Tukey's test $p<0.05$), although the 13 g dose showed a statistically greater response than the 24 g dose. In FDA's January 31, 2020 response letter to the 2019 Citizen Petition, FDA stated that peak post-prandial insulin was only significantly reduced at the 13 g dose and was not significantly reduced at the 24 g dose.[23] However, the study report indicated a significant reduction for both the 13 g and 24 g treatment groups, as shown in the Summary table on page 4, which states that "[i]nsulin peak rise after AcLow was significantly less than that after AcHigh, which, in turn, was significantly less than that after Control." Therefore, omission of the specific p-value for control *versus* AcHigh in Table 3 of the study report is an error, and not an indication that peak insulin did not exhibit a significant reduction in the 24 g group. Wolever et al. (2019) reported peak insulin levels of 409±35, 326±24, and 372±35 pmol/L for the control group, 13 g GA, and 24 g GA, respectively. Compared to the control, both GA doses are reported to significantly reduce insulin peak rise, as stated in the study summary table. "Table 3. Plasma glucose and serum insulin iAUC, net AUC and Peak Rise"[24] erroneously included only the specific p-value for the 13 g treatment in comparison to the control group ($p=0.001$) for peak insulin, and not for the specific p-value for the 24 g treatment group.

5. Uebelhack (2020; unpublished)

This study was commissioned by Nexira and carried out by Analyze & Realize GmbH (Berlin, Germany) under the direction of Prof. Ralf Uebelhack, MD. The objective of the study was to evaluate the effect of two doses of gum acacia powder (Fibregum™) versus no treatment on post-prandial glucose (PPG), and post-prandial insulin (PPI). The study design was a double blind, placebo-controlled, crossover clinical study in healthy human subjects in which thirty-six normal-weight and over-weight men and women 25-60 years old were randomized into each of the three (0 g, 20 g, and 40 g gum acacia) treatment groups. The study design included two cross-over events with 4-15 days of wash out in between so that each participant received a single dose of each level. Treatments were administered as powder in orange juice along with a standard breakfast.

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[21] See Wolever (2019), page 13.

[22] See Wolever (2019), page 14.

[23] See "Final Response Letter from FDA CFSAN to Keller and Heckman LLP," FDA Docket No. FDA-2019-P-1911 (January 31, 2020).

[24] See Wolever (2019), page 15.

There was a statistically significant, dose dependent, reduction in PPG ($iAUC_{0-120}$) for 40 g (p=0.003) and 20 g (p=0.005) as well as when considering the baseline as a covariate (40 g p=0.034 and 20 g p=0.008). Maximal glucose concentration was also significantly reduced in both treatment groups ($p < 0.001$ for both groups) without effect on time to maximal glucose concentration. Incremental PPG was reduced by an average of 40.9 and 49.2 mmol*min/L for high and low dose respectively while maximal glucose was reduced by an average of 0.85 and 0.97 mmol/L for the high and low dose. Further evidence for an effect of gum acacia was apparent for total PPG (AUC) at the 40 g dose at the 15, 30, 45, and 60 minute time points ($p < 0.05$), with a strong statistical trend ($p = 0.054$) at 90 minutes. A similar trend was seen for the 20 g dose with a statistically significant total PPG (AUC) seen at the 15, 30, 45, 60, 90, and 120 minute timepoints.

For insulin, total PPI (AUC_{0-120}), incremental PPI ($iAUC_{0-120}$), and PPI when baseline is considered as a covariate were significantly reduced for both treatment groups ($p < 0.001$ for all groups). Total insulin exhibited an average reduction of 1,318 and 1,103 mU*min/L for 40 g and 20 g doses respectively, while incremental insulin was reduced by 1,332 and 1,136 mU*min/L. Maximal PPI, but not time to maximum, was significantly reduced as well for both treatment groups with an average reduction of 22.3 and 18.0 mU/L for high and low dose gum acacia. Glucose and insulin results are summarized in **Table 2**.

Table 2: Summary of Results for Glucose and Insulin. Values for glucose are given as mmol*min/L (AUC) and mmol/L (Max) and insulin as mU*min/L (AUC) and mU/L (Max)

		0 g		20 g		40 g	
Outcome	**Time**	**Value**	**p-value**	**Value**	**p-value**	**Value**	**p-value**
Incremental Glucose (iAUC)	0-120	133.07	N/A	79.42	0.005	87.22	0.003
Incremental Glucose (baseline as covariate)	0-120	N/A	N/A	53.7	0.008	45.9	0.034
Glucose Max	N/A	8.35	N/A	7.37	<0.001	7.50	<0.001
Total Insulin (AUC)	0-120	4,519	N/A	3,416	<0.001	3,200	<0.001
Incremental Insulin (iAUC)	0-120	3,951	N/A	2,815	<0.001	2,619	<0.001
Insulin iAUC (baseline as covariate)	0-120	N/A	N/A	1,136	<0.001	1,332	<0.001
Insulin Max	N/A	69.3	N/A	51.3	<0.001	47.0	<0.001

This study provides robust evidence that GA has significant beneficial effects on multiple post-prandial glucose and insulin endpoints, including incremental glucose (iAUC), max glucose, total insulin (AUC), max insulin, and incremental insulin (iAUC). The full Uebelhack study report is available in Appendix I to this Citizen Petition**.**

E. Strength of the Evidence for GA and Post-prandial Glucose and Post-prandial Insulin Levels

Table 3 summarizes the findings from five studies that evaluated the relationship between GA intake and post-prandial glucose and/or insulin levels.

Table 3. Summary of Five Studies Supporting Beneficial Physiological Effects of GA on Post-prandial Glucose and Post-prandial Insulin Levels

Study	Subjects	Design	GA Dose	Findings
Sharma (1985)	n=12 Healthy men	crossover	20 g Glucose solution	20 g PPG AUC + **20 g PPI AUC +** 20 g PPPG ⊘ **20 g PPPI ⊘**
Akeo (2002)	n=12 Healthy men	crossover	5g & 10g Sucrose solution	5 g PPPG + 10 g PPPG +
Larson (2019)	n=48 Healthy men & women	crossover	20 g & 40 g Orange juice + breakfast	20 g PPPG + 40 g PPPG ⊘ 20 g PPG AUC ⊘ 40 g PPG AUC ⊘
Wolever (2019)	n=40 Healthy men & women	crossover	13g & 24 g Pudding	13 g PPPG ⊘ **13 g PPPI +** 24 g PPPG ⊘ **24 g PPPI +** 13 g PPG AUC ⊘ **13 g PPI AUC +** 24 g PPG AUC ⊘ **24 g PPI AUC +**
Uebelhack (2020)	n=36	crossover	20 g & 40 g	20 g PPG AUC + **20 g PPI AUC +**

	Healthy men & women		Orange juice + breakfast	40 g PPG AUC + **40 g PPI AUC +** 20 g PPPG (30 min) + **20 g PPPI (45 min) +** 40 g PPPG (30 min) + **40 g PPPI (45 min) +**
PPG AUC = Post-prandial glucose area-under-curve; PPI AUC = Post-prandial insulin area-under-curve; PPPG = Peak post-prandial glucose; PPPI = Peak post-prandial insulin + = statistically significant attenuation compared to control ⦰ = no statistically significant change compared to control				

Sharma (20 g), Wolever (13 g and 24 g), and Uebelhack (20 g and 40 g) collectively provided five comparisons, representing 4 different doses, on the relationship between GA consumption and post-prandial insulin. These three studies provided healthy individuals GA in a glucose solution, pudding, or orange juice along with a breakfast. For all five comparisons, GA significantly lowered post-prandial insulin levels, as measured by AUC. For PPPI, 4 of the 5 comparisons showed a significant reduction (Sharma (1985), Wolever (2019), and Uebelhack (2020); all comparisons showed a significant reduction in those studies where GA was added to a food (Wolever (2019) and Uebelhack (2020)).

FDA's response to the 2019 Citizen Petition regarding post-prandial insulin concluded that there is "limited data" to base a decision on essentially two studies (Sharma (1985) and Wolever (2019)) where one study (Sharma (1985)) added GA to a sugar solution beverage and where there were only three doses to compare. The Uebelhack (2020) study provides two additional comparisons at 20 g and 40 g. Thus, we believe that the issues identified in the 2019 Citizen Petition have been addressed by the inclusion of an additional study in which both doses of GA resulted in a significant attenuation of post-prandial insulin.

In the above three studies that measured post-prandial insulin levels, when insulin was attenuated, post-prandial glucose was either statistically unchanged or attenuated. There was not a situation in which post-prandial glucose levels were elevated as a result of attenuated post-prandial insulin levels. As FDA has stated, 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.[25] This means that less

[25] See discussion of Resistant Starch 2 (RS2) in FDA's Review of the Scientific Evidence on the Physiological Effects of Certain Non-Digestible Carbohydrates. June, 2018.; see also
(continued …)

insulin is required to process glucose which is indicative of increased insulin sensitivity which can help reduce the risk of type 2 diabetes. Attenuation of post-prandial insulin response is also associated with a reduced risk of coronary heart disease.[26] Further, it should be noted that FDA recognized another non-digestible carbohydrate, "cross-linked phosphorylated RS4," to meet the dietary fiber definition based on it having a physiological effect on post-prandial insulin that is beneficial to human health.[27]

In the 2020 FDA response letter, when discussing the strength of the evidence for post-prandial blood glucose and/or insulin, FDA stated that "in the one study that measured a dose response effect of GA on postprandial insulin, the lower dose of gum acacia showed a statistically significantly higher reduction in peak concentration compared to the higher dose."[28] As noted by FDA, "[o]bserved dose-response data within a study can increase the strength of the scientific evidence. Demonstration of a dose-response relationship would depend on the levels provided. For example, a dose-response relationship would not be expected if the dose(s) provided exceed a range of intake for which a linear relationship occurs."[29] This footnote suggests that while a dose-response relationship can support a relationship between the non-digestible carbohydrate and physiological endpoint, the lack of a dose-response relationship should not necessarily affect the strength of the evidence. It was unclear if FDA had determined a range of GA intake for which a dose-response relationship would be expected for post-prandial insulin.

Based on the above, the strength of the evidence supports that GA consumption has a beneficial physiological effect on human health by attenuation of post-prandial insulin levels. As such, the available evidence from which scientific conclusions could be drawn supports

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FDA Response to Cross-Linked Phosphorylated RS4, FDA Docket No. FDA-2016-P-3620 (March 26, 2019).

[26] Bhat SL, Abbasi FA, Blasey C, Reaven G, Kim SR 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.

[27] See FDA response to MGP Ingredients Inc. Citizen Petition for Cross-Linked Phosphorylated RS4, FDA Docket No. FDA-2016-P-3620 (March 26, 2019).

[28] See "Final Response Letter from FDA CFSAN to Keller and Heckman LLP," FDA Docket No. FDA-2019-P-1911 (January 31, 2020), page 8.

[29] "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, footnote 16.

including GA in the list of non-digestible carbohydrates that meet the definition of dietary fiber.

IV. Conclusion

For the reasons set forth above GA should be considered a dietary fiber under 21 C.F.R. § 101.9(c)(6)(i). Petitioners believe that the strength of the scientific evidence supports the fact that Acacia (gum arabic) has beneficial physiological effects on human health for post-prandial insulin levels. Thus, Petitioners conclude that Acacia (gum arabic) meets the definition of 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 II above.

V. 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.

VI. 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.

VII. 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