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

April 25, 2022

Ricardo Carvajal
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700 13th Street NW, Ste 1200
Washington, D.C. 20005-5929

Re: Docket Number FDA-2019-P-6045

Dear Mr. Carvajal,

This responds to your citizen petition dated December 17, 2019, requesting that the Food and Drug Administration (FDA or we) "amend 21 C.F.R. § 101.9(c)(6)(i) to include alpha-cyclodextrin in the definition of dietary fiber set forth in that regulation." See Citizen Petition from Ricardo Carvajal, Hyman, Phelps & McNamara, P.C., on behalf of Wacker Chemical Corporation, submitted to the Division of Dockets Management, Food and Drug Administration, dated December 17, 2019 ("Petition"), at page 1.

In the *Federal Register* of May 27, 2016, we published a final rule entitled, "Food Labeling: Revision of the Nutrition and Supplement Facts Labels" (81 FR 33742). The final rule, among other things, defines dietary fiber 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" (see 21 CFR 101.9(c)(6)(i)). 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.[1]

In accordance with 21 CFR 10.30(e)(3), we are denying your petition. This letter sets out the basis for our determination that the strength of the scientific evidence does not show that the consumption of alpha-cyclodextrin has a physiological effect that is beneficial to human health.

[1] For up-to-date information on the additional non-digestible carbohydrates that FDA has determined may be added to the definition of dietary fiber, see "Questions and Answers on Dietary Fiber," available at http://www.fda.gov/food/food-labeling-nutrition/questions-and-answers-dietary-fiber#synthetic_fibers.

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I. FDA's Consideration of the Scientific Evidence

Your petition requests that FDA add alpha-cyclodextrin to the list of dietary fibers in 21 CFR 101.9(c)(6)(i) on the grounds that alpha-cyclodextrin "attenuates the postprandial blood glucose levels of a starch-based, high-glycemic meal" (Petition at page 1).

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 scientific evidence. We reviewed your petition using the factors identified in the final guidance.

The petition identifies seven publications[2] that reported on five human intervention studies that evaluated the effect of alpha-cyclodextrin on postprandial blood glucose and/or postprandial insulin. We did not identify additional human intervention studies on the effect of alpha-cyclodextrin on postprandial blood glucose and/or postprandial insulin from our review of the scientific literature.

The five human intervention studies from which we did draw conclusions are as follows.

Buckley et al. (2006)

Ten healthy adults (5 females and 5 males) participated in a randomized, double-blind, cross-over design study in which they consumed boiled rice (64 grams (g); 50 g digestible carbohydrate), with added alpha-cyclodextrin (5 g or 10 g) or without alpha-cyclodextrin (0 g; control), and a 250 milliliter (mL) glass of water. After the three randomly assigned

[2] Bär A, Diamantis I, Venetz WP. Alpha-cyclodextrin attenuates the glycemic and insulinemic impact of white bread in healthy male volunteers. *Foods* 2020; 9:62; Buckley JD, Thorp AA, Murphy KJ et al. Dose-dependent inhibition of the post-prandial glycaemic response to a standard carbohydrate meal following incorporation of alpha-cyclodextrin. *Annals of Nutrition and Metabolism* 2006; 50:108-114; Diamantis I, Venetz WP, Bär A. Alpha-cyclodextrin attenuates the glycemic and insulinemic impact of white bread in healthy male volunteers. *Foods* approved for publication, Preprints 2019 (doi: 0.20944/preprints201912.0011.v1); Fletcher EN. The effect of alpha-cyclodextrin on acute blood lipid and glycemic responses to a fat containing meal. *Wayne State University Theses* 2013. Paper 231; Gentilcore D, Vanis L, Teng JC et al. The oligosaccharide alpha-cyclodextrin has modest effects to slow gastric emptying and modify the glycaemic response to sucrose in healthy older adults. *British Journal of Nutrition* 2011; 106:583-587; Jarosz PA, Fletcher E, Elserafy E et al. The effect of alpha-cyclodextrin on postprandial lipid and glycemic responses to a fat-containing meal. *Metabolism* 2013; 62:1443-1447; Sugahara M, Inoue Y, Murata I et al. Effect of cyclodextrin on postprandial blood glucose and triglycerides. *International Journal of Pharmacy* 2016; 6:13-19.

intervention periods, all participants received boiled rice with 2 g of alpha-cyclodextrin in the last intervention period of the study. Following an overnight fast, postprandial blood glucose and insulin were measured before and at several time points for 120 minutes (at 0, 15, 30, 45, 60, 90, and 120 minutes) after consumption of the test meal. Each test day was separated by a 48-hour wash-out period. Compared to the control, consumption of the boiled rice containing 5 g and 10 g of alpha-cyclodextrin led to statistically significant reductions in postprandial blood glucose, as measured by area-under-the-curve (AUC)[3] ($P < 0.05$ for both). There was no statistically significant difference in postprandial blood glucose following consumption of the 2 g dose of alpha-cyclodextrin compared to control ($P > 0.05$). For postprandial insulin, as measured by AUC, there were no statistically significant differences after consumption of the 2 g, 5 g, and 10 g doses of alpha-cyclodextrin compared to control ($P > 0.05$ for all).

Gentilcore et al. (2011)

Ten healthy adults (3 females and 7 males) participated in a randomized, double-blind, cross-over design study in which they consumed a drink containing 100 g of sucrose dissolved in water (total volume 300 mL), with 10 g of alpha-cyclodextrin or without alpha-cyclodextrin (control). There was a seven-day wash-out period between test periods. Following an overnight fast, postprandial blood glucose and insulin were measured before and at 15-minute intervals for 300 minutes after consumption of the sucrose solution with or without alpha-cyclodextrin. Postprandial blood glucose, as measured by AUC, was not statistically significantly different between the alpha-cyclodextrin and control sucrose solutions ($P > 0.05$). Peak concentrations of postprandial blood glucose were also not statistically significantly different between alpha-cyclodextrin and control ($P > 0.05$). Postprandial insulin, as measured by AUC or peak concentration, was not statistically significantly different between alpha-cyclodextrin and control ($P > 0.05$ for both).

Jarosz et al. (2013); Fletcher (2013)[4]

Thirty-four healthy adults (28 females and 6 males) participated in a randomized, placebo-controlled, double-blind, cross-over design study in which they consumed a high-fat mixed meal (egg sausage biscuit; 32 g carbohydrate, 26 g fat, 20 g protein) with 2 g of alpha-cyclodextrin or 2 g placebo (cellulose; control). The test meals were consumed with an 8-ounce bottle of water. There was a two-day wash-out period between test periods. Following an overnight fast, postprandial blood glucose was measured before and for three hours (at 0, 1, 2, 3 hours) after consumption of the test meal. Postprandial blood glucose, as measured by AUC, was not

[3] 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). In this study, peak concentrations of postprandial blood glucose and insulin could not be evaluated because statistical comparisons were not reported between the alpha-cyclodextrin doses (2 g, 5 g, and 10 g) and control for this measure.

[4] Fletcher, 2013 was a thesis publication that reported on the same study as the Jarosz et al., 2013 publication.

statistically significantly different between the alpha-cyclodextrin test meal and the control test meal ($P > 0.05$).[5] Postprandial insulin was not measured in this study.

Sugahara et al. (2016)

Ten healthy adults (5 females and 5 males) participated in a randomized, cross-over design study[6] in which they consumed curry (200 g; 18 g carbohydrate, 14 g fat, 7 g protein) and rice (200 g; 68 g carbohydrate, 0 g fat, 4 g protein), with either 5 g of alpha-cyclodextrin or without (control), and up to 200 mL of mineral water. Following a fasted period,[7] postprandial blood glucose and insulin were measured before and at several time points for 180 minutes (at 0, 15, 30, 45, 60, 90, 120, and 180 minutes) after consumption of the test meals.[8] Postprandial blood glucose, as measured by AUC, was not statistically significantly different between the alpha-cyclodextrin and control test meals ($P > 0.05$). In addition, there was no statistically significant difference in peak concentration of postprandial blood glucose, as measured as change from baseline level before the test meal ($P > 0.05$). For postprandial insulin, there was no statistically significant difference between the alpha-cyclodextrin and control test meals, as measured by AUC or change in peak concentration (measured as change from baseline level before the test meal) ($P > 0.05$ for both).

Bar et al. (2020); Diamantis et al. (2019)[9]

Twelve healthy males participated in a sequential (non-randomized),[10] single-blind[11] study where they consumed white bread (100 g; 50 g starch) and 250 mL of water with either 10 g of alpha-cyclodextrin dissolved in the water or without alpha-cyclodextrin (control). There was a minimum of two days between test periods. Following an overnight fast, postprandial blood glucose and insulin were measured before and at several time points for 180 minutes (at 0, 15, 30, 45, 60, 75, 90, 120, 150, and 180 minutes) after consumption of the test meals. Postprandial blood glucose, as measured by AUC, was significantly lower after consumption of the alpha-

[5] Peak concentrations of postprandial blood glucose could not be evaluated in this study since postprandial blood glucose was measured at 0, 1, 2, and 3 hours and was not measured at typical time points for peak postprandial blood glucose concentrations (e.g., 30 minutes).
[6] The study did not provide a description as to whether participants or study personnel were blinded to the treatment allocation (e.g., whether participants, investigators, and/or outcome assessors were aware of who was receiving the treatment during a particular intervention period).
[7] The study did not report the duration of the fasted period.
[8] The study did not report the length of time in between test periods.
[9] Diamantis et al., 2019 was a preprint publication that was later published as the Bar et al., 2020 publication. These two publications are the same reports of the same study. Therefore, this study will subsequently be referred to as Bar et al., 2020.
[10] All participants first received the control test meal followed by the alpha-cyclodextrin test meal.
[11] Participants were not aware of which test meal contained the alpha-cyclodextrin or that the study was a sequential design.

cyclodextrin versus control test meals.[12] Postprandial insulin, as measured by AUC, was also significantly lower after consumption of the alpha-cyclodextrin versus control test meals.[13]

II. Strength of the Scientific Evidence

We evaluate the strength of the scientific evidence by considering various factors, such as the number of studies and sample sizes of each study, dose response data if available, 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 of the total body of evidence. Based on this evidence, we evaluated whether the findings presented in the relevant clinical studies demonstrated that there is a beneficial physiological effect of alpha-cyclodextrin consumption to human health, and therefore, whether to propose to include alpha-cyclodextrin as a dietary fiber in the dietary fiber definition.

There were seven publicly available publications of five studies in healthy adults (Bar et al., 2020; Buckley et al., 2006; Diamantis et al., 2019; Fletcher, 2013; Gentilcore et al., 2011; Jarosz et al., 2013; Sugahara et al., 2016), with seven dose comparisons (ranging from 2 to 10 g), from which scientific conclusions could be drawn on the effect of alpha-cyclodextrin on postprandial blood glucose and/or postprandial insulin. Among these seven dose comparisons, there were two studies that evaluated the effect of 2 g of alpha-cyclodextrin (i.e., two dose comparisons) on postprandial blood glucose (Buckley et al., 2006; Fletcher, 2013; Jarosz et al., 2013). One study (n = 10) demonstrated that there was no statistically significant effect of 2 g of alpha-cyclodextrin when consumed with boiled rice (Buckley et al., 2006), and in the largest study (n = 34), there also was no statistically significant effect of 2 g of alpha-cyclodextrin on postprandial blood glucose when consumed as part of a mixed meal (breakfast sandwich) (Fletcher, 2013; Jarosz et al., 2013). Two studies evaluated the effects of 5 g of alpha-cyclodextrin (i.e., two dose comparisons) on postprandial blood glucose (Buckley et al., 2006; Sugahara et al., 2016). The results of these studies were mixed, with one study (n = 10) demonstrating a statistically significant lowering of postprandial blood glucose with 5 g of alpha-cyclodextrin when consumed with boiled rice (Buckley et al., 2006), and one study (n = 10) showing no statistically significant effect of 5 g of alpha-cyclodextrin when consumed with curry and rice (Sugahara et al., 2016). The results of the three studies that evaluated 10 g of alpha-cyclodextrin (i.e., three dose comparisons) were also mixed (Bar et al., 2020; Buckley et al., 2006; Gentilcore et al., 2011). Two of these studies demonstrated a statistically significant lowering of postprandial blood glucose when 10 g of alpha-cyclodextrin was consumed with boiled rice (n = 10; Buckley et al., 2006) or white bread (n = 12 males; Bar et al., 2020), while one study showed no

[12] The study authors report that postprandial blood glucose was significantly lower with consumption of alpha-cyclodextrin. P-values were not reported for postprandial blood glucose. However, in the methods section of the paper they state that a significance level of $P < 0.05$ was used for comparisons between the alpha-cyclodextrin and control test meals.

[13] The study authors report that postprandial insulin was significantly lower with consumption of alpha-cyclodextrin. P-values were not reported for postprandial insulin. However, in the methods section of the paper they state that a significance level of $P < 0.05$ was used for comparisons between the alpha-cyclodextrin and control test meals.

statistically significant effect of 10 g of alpha-cyclodextrin when consumed with a sucrose solution (n = 10; Gentilcore et al., 2011).

We considered several factors as part of our evaluation of the strength of the evidence, such as those described above, to determine whether there were plausible explanations for the inconsistencies in the results from the studies. Among other factors, we considered whether the form of food in which alpha-cyclodextrin was provided or dose of alpha-cyclodextrin contributed to the inconsistencies in the data. Regarding the type of food in which alpha-cyclodextrin was provided (e.g., sucrose solution versus meals containing starch), we note that the petition suggests that the lack of postprandial blood glucose lowering effect in the study by Gentilcore et al. (2011), in which alpha-cyclodextrin was added to a sucrose solution, may be related to a proposed mechanism of alpha-cyclodextrin (i.e., "amylase inhibition and not any other unspecific effect"; Petition at page 7) and that alpha-cyclodextrin attenuates postprandial blood glucose in response to a starch-based meal (Petition at page 1). The petition cites two *in vitro* kinetic studies to support the assertion of a potential inhibitory effect of alpha-cyclodextrin on amylase activity.[14] However, in an *in vivo* study in an animal model, alpha-cyclodextrin administered with sucrose significantly lowered glucose response compared to sucrose alone.[15] Due to the limited evidence, it is unclear if the proposed mechanism in the petition explains the lack of an effect reported in the Gentilcore et al. (2011) study. Furthermore, there were still inconsistencies in the data from studies in which alpha-cyclodextrin was provided as part of a meal containing starch. Two studies, including three dose comparisons (5 g, 10 g, and 10 g), reported a statistically significant lowering of postprandial blood glucose when alpha-cyclodextrin was consumed with a meal containing starch (Buckley et al., 2006; Bar et al., 2020), and three studies, including three dose comparisons (2 g, 2 g, and 5 g), showed no statistically significant effect of alpha-cyclodextrin on postprandial blood glucose when consumed with a meal containing starch (Buckley et al., 2006; Sugahara et al., 2016; Fletcher, 2013; Jarosz et al., 2013).

We also evaluated whether the dose of alpha-cyclodextrin contributed to the inconsistencies in the data. In the two studies that evaluated the lowest dose of alpha-cyclodextrin (2 g), there were no statistically significant effects of alpha-cyclodextrin on postprandial blood glucose (Buckley et al., 2006; Fletcher, 2013; Jarosz et al., 2013). However, there were inconsistencies in the data at 5 g and 10 g doses, with some studies demonstrating a statistically significant lowering of postprandial blood glucose at 5 g (Buckley et al., 2006) and 10 g of alpha-cyclodextrin (Bar et al., 2020; Buckley et al., 2006) and others finding no statistically significant effect at 5 g (Sugahara et al., 2016) and 10 g (Gentilcore et al., 2011). Due to the limited and inconsistent

[14] Koukiekolo R, Desseaux V, Moreau Y et al. Mechanism of porcine pancreatic α-amylase. Inhibition of amylose and maltopentaose hydrolysis by α-, β- and γ-cyclodextrins. *European Journal of Biochemistry* 2001; 268:841-848; Oudjeriouat N, Moreau Y, Santimone M et al. On the mechanism of α-amylase. Acarbose and cyclodextrin inhibition of barley amylase isozymes. *European Journal of Biochemistry* 2003; 270:3871-3879.

[15] Ishii M, Matsumoto Y, Sekimizu K. Inhibitory effects of alpha-cyclodextrin and its derivative against sucrose-induced hyperglycemia in an in vivo evaluation system. *Drug Discoveries & Therapeutics* 2018; 12:122-125.

findings at different doses, it was not possible to determine whether dose explained the overall inconsistencies in the results for postprandial blood glucose.

We evaluated the data on the effect of alpha-cyclodextrin on the relationship between postprandial insulin and postprandial blood glucose. Four studies (Bar et al., 2020; Buckley et al., 2006; Gentilcore et al., 2011; Sugahara et al., 2016), with six dose comparisons, reported on the effect of alpha-cyclodextrin (2 g, 5 g, and 10 g) on both postprandial insulin and postprandial blood glucose and therefore allowed us to draw scientific conclusions on this relationship.[16] In one study with one dose comparison (n = 12), there was a statistically significant lowering of postprandial insulin after consumption of 10 g of alpha-cyclodextrin when consumed with white bread, which was accompanied by a statistically significant lowering of postprandial blood glucose (Bar et al., 2020). In the other five of six dose comparisons at 2 g, 5 g, and 10 g, there was no statistically significant effect of alpha-cyclodextrin on postprandial insulin (Buckley et al., 2006; Gentilcore et al., 2011; Sugahara et al., 2016).[17]

In summary, there is inconsistent evidence for evaluating the effect of alpha-cyclodextrin on postprandial blood glucose and/or insulin, which weakens our confidence in the relationship between alpha-cyclodextrin and postprandial blood glucose and/or insulin. As described above, we considered whether there were plausible explanations for the inconsistencies in the findings. Due to the limited and inconsistent evidence, we were unable to find plausible explanations for the inconsistencies in the findings or to consider those studies that did not find a statistically significant effect as being less relevant to or less important in determining the strength of the total body of evidence for the effect of alpha-cyclodextrin on postprandial blood glucose and/or insulin. Consequently, we have determined that the strength of the scientific evidence does not support a finding of a beneficial effect of alpha-cyclodextrin on postprandial blood glucose and/or insulin.

III. Conclusion

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 does not show that the consumption of alpha-cyclodextrin has a physiological effect that is beneficial to human health. Consequently, we do not plan to propose to amend the list of nondigestible carbohydrates that meet the definition of dietary fiber to include alpha-

[16] One study evaluated the 2 g dose, two studies evaluated the 5 g dose, and three studies evaluated the 10 g dose. ne study evaluated the 2 g dose, two studies evaluated the 5 g dose, and two studies evaluated the 10 g dose.

cyclodextrin as a dietary fiber based on this scientific evidence. Therefore, in accordance with 21 CFR 10.30(e)(3), we are denying your petition.

Sincerely yours,

Claudine J. Kavanaugh -S

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