Vanguard Regulatory Services, Inc

August 9, 2024

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, Maryland 20852

Citizen Petition Requesting Amendment of the Definition of Dietary Fiber at 21 C.F.R. § 101.9 (c) (6) (i) to Include "Isomaltodextrin (IMD)"

CITIZEN PETITION

The undersigned, Vanguard Regulatory Services, Inc on behalf of Nagase Viita Co., Ltd. (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 "Isomaltodextrin (Fibryxa®)" (referred to in this petition as "IMD" or "Fibryxa®") 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 isomalt dextrin 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)).

B. Statement of Grounds

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]

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prandial blood glucose levels and reducing blood triglyceride levels.

ii. Manufacture of IMD (Fibryxa®)

IMD

iii. Chemical Structure and non-digestibility of IMD

IMD is a polymer exclusively consisting of D-glucose with an average molecular weight of approximately 5,000. It is generally more homogeneous in molecular weight than other resistant dextrins. Another term for this type of substance is an α-glucan because it is made up only of glucose molecules attached together using α-glycosidic linkages, like the starch from which it is produced. IMD is a dextrin of low viscosity, and high-water solubility, having a dietary fiber content of at least 80%. IMD has both linear and branched structures created by α-1,4, α-1,6, and α-1,3 linkages, and combinations of these (α-1,3,6 and α-1,4,6). All these linkages, except α-1,4, inhibit to various extents the amount of digestion by enzymes in the small intestine of humans, making IMD a resistant dextrin, and a candidate dietary fiber.[3]

iv. Review of the Scientific Literature:

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only known studies to the Petitioners on the effects of IMD on postprandial blood glucose and

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

[2]IMD was notified to the Agency as generally recognized as safe (GRAS; GRN 00610, Agency Response Letter, June 6, 2016).

[3] Tsusaki K, Watanabe H, Nishimoto T, et al. 2009. Structure of a novel highly branched α-glucan enzymatically produced from maltodextrin. Carbohydrate Res, 344: 2121-2156. (Appendix 7)

postprandial blood triglycerides in humans. The Petitioners concluded that scientific conclusions could be drawn from all four of the post-prandial blood glucose (Sadakiyo et al., 2017; Ishida et al., 2017; Sakurai et al., 2019; Ishida et al., 2021), and the two postprandial blood triglycerides studies (Takagaki et al., 2018; Ishida et al. 2020). Each study demonstrated consistent and statistically significant physiologically beneficial effects of IMD to human health.

v. IMD (Fibryxa®) consumption provides physiological effects determined by FDA to be beneficial to human health:

a. Lowering post-prandial blood glucose level

1. Sadakiyo, et al. Attenuation of Postprandial Blood Glucose in Humans Consuming Isomaltodextrin: Carbohydrate Loading Studies. *Food & Nutrition Research, 2017; 61: 1325306* (Appendix 1)

Twenty-nine healthy male and female subjects, with a fasting blood glucose level (BGL) ≥ 60 and <126 mg/dL, 2-hour postprandial BGL<189 mg/dL, and random BGL<270 mg/dL participated in a randomized, single-blind, crossover, maltodextrin (MD) loading study followed by a sucrose loading study. Following a 12-hour fast the study groups were randomly assigned to MD or MD plus 9.6 g IMD groups, and the treatments were switched. There was a washout period of at least one week between the tests. Blood samples were collected before, and at 15, 30, 45, 60, 90, and 120 minutes after ingestion in all the studies.

In the MD loading study, there was no significant difference in Δ blood glucose levels at any measuring time between the groups of MD with and without IMD. Neither was there significance in the sucrose loading test. However, in a further analysis of subjects (n = 9) who exhibited a greater increase in Δ blood glucose of 70 mg/dL or more after ingesting only MD, the Δ blood glucose in the group taking MD with IMD was significantly lower (p = 0.04) than when taking only MD at 45 minutes. The AUC (mg/dL·hr) was lower than the control, but not significantly.

Similarly, the sucrose loading study showed no significant benefit in the total cohort between the control and IMD treatment; however, a subgroup (n = 7) with a Δ blood glucose of 75 mg/dL or more after ingesting only sucrose had a significant reduction in Δ blood glucose (p = 0.03) with IMD at 30 minutes. Further the AUC (mg/dL·hr) was significantly lower in the IMD group (p = 0.02).

Another twenty-nine subjects were recruited for a glucose loading study. These subjects were given 50 g of glucose, and their blood glucose and insulin were assayed. Fifteen of the subjects exhibiting the greatest glycemic rise after ingestion were enrolled in the study. The subjects (n = 14) consumed a liquid containing 50 g glucose plus 10 g IMD and were tested for Δ blood glucose and insulin levels. After a washout period of more than one week, the subjects (n = 13) were given a 50 g glucose liquid containing 5 g of IMD and assayed for Δ blood glucose and insulin. The AUC (mg/dL·hr) was also calculated.

In the glucose loading study, the peak Δ blood glucose level was significantly lower ($p = 0.02$) in the 5 g IMD group than in the group without IMD at 45 minutes. The peak Δ blood glucose in the 10 g IMD group tended to be lower ($p = 0.056$) than control at 45 min. Additionally, the AUC (mg/dL·hr) for the 5 g IMD group was significantly lower ($p = 0.046$) with a 13% reduction, while the 10 g IMD group had a 10% reduction but was not statistically different.

Conclusions – These data using three common carbohydrate sources, MD, sucrose, or glucose, demonstrated that IMD significantly suppressed the increase in the peak postprandial Δ blood glucose level in subjects who develop higher blood glucose levels after ingestion of these carbohydrates.

2. **Ishida, et al. The Attenuating Effect of Isomaltodextrin on Post-prandial Blood Glucose Level in Healthy Human Subjects.** ***Jpn Pharmacol Ther, 2017; 45: 1179-85*** **(Appendix 2)**

Forty-five healthy adult male and female subjects, with an average age of 39.9, and fasting BGL≥ 60 and <126 mg/dL, 2-hour postprandial BGL<189 mg/dL, and random BGL<270 mg/dL, participated in a randomized, double-blind, placebo-controlled, crossover study. The subjects ingested a solution containing 50 g of glucose with 2.5 g of IMD or without (control). Blood glucose concentrations were measured before, and at 30, 45, 60, 90, and 120 minutes after ingestion. The process was repeated for the other solution after a washout period of at least one week.

Analysis of all subjects revealed no significant difference in the postprandial blood glucose levels between the control and test diets. However, analysis of the subjects (n = 23) with easily elevated postprandial blood glucose levels (Δ blood glucose ≥ 66 mg/dL) after consuming the control diet demonstrated a significant attenuating effect on blood glucose ($p = 0.0089$) and Δ blood glucose ($p = 0.021$) levels 45 minutes after ingestion.

When the C_{max} and ΔC_{max} of the control diet and IMD groups were compared the IMD group was also significantly lower at $p = 0.0056$ and $p = 0.0057$, respectively. No significant differences in blood glucose AUC and Δ AUC were observed between the test and control diets.

Conclusions – These test results show that ingestion of 2.5 g IMD significantly attenuated peak postprandial blood glucose levels in subjects with easily elevated postprandial blood glucose levels.

3. **Ishida, et al. Suppressive Effect of Isomaltodextrin on Postprandial Blood Glucose Elevation after Ingestion of Cooked Rice in Healthy Adults.** ***Jpn Pharmacol Ther, 2021; 49: 1241-52*** **(Appendix 3)**

Forty-four healthy male and female subjects aged 20 to 64 years with normal to borderline high blood glucose levels (a fasting blood glucose level <126 mg/dL, or a blood glucose level <200 mg/ dL at 2 hours after a 75 g oral glucose tolerance test), participated in a randomized, double-blind, placebo-controlled, crossover study.

The subjects ingested salted rice balls (108 g of carbohydrate) together with a test drink containing IMD (equivalent to 3 g of dietary fiber) or a placebo drink without IMD after fasting for 12 hours following the evening meal. Blood was collected before, and at 30, 45, 60, 90, and 120 minutes after ingestion. Blood glucose and insulin levels were monitored over time. The process was repeated for the other solution after a washout period of 2 weeks.

Statistical evaluation of the IMD treatment as compared to the placebo showed a significant lowering of the blood glucose level ($p < 0.05$) at 60-120 minutes (45 minutes, $p < 0.10$). Similarly, the Δ blood glucose levels at 45, 60, 90, and 120 minutes were significantly lower ($p < 0.05$) with IMD than with placebo. The C_{max} and ΔC_{max} values for IMD and the control diets were compared, and the statistical significance was $p < 0.10$ and $p < 0.05$, respectively. The blood glucose AUC and iAUC of the IMD group compared to the placebo was significantly less at $p = 0.007$ and $p < 0.05$, respectively. Regarding insulin levels, the secondary endpoint, the only significance between the IMD and placebo groups was in the insulin ΔC_{max} $p < 0.05$ ($C_{max,}$ $p < 0.10$).

Conclusions – The study results demonstrated that IMD consumption with a carbohydrate meal significantly suppressed postprandial blood glucose elevation, in healthy individuals predisposed to post-prandial hyperglycemia.

4. **Sakurai, et al. Attenuating Effect of Isomaltodextrin Contained in Bread on**

Postprandial Plasma Glucose Levels in Healthy Humans. ***Med Cons New-Remed, 2019; 56: 358-364*** **(Appendix 4)**

Twenty-eight healthy male and female subjects, with an average age of 41.1, with fasting blood glucose levels ≥60 mg/dL and <126mg/dL, blood glucose levels <189mg/dL at 2 hours after meal, and random blood glucose levels <270mg/dL, participated in a randomized, placebo-controlled, double-blind, crossover study. Overnight-fasted subjects consumed 70 g of a bread, jam and tea breakfast with or without 2.93 g of IMD with jam and tea at breakfast. Blood glucose levels were determined immediately before, and at 30, 60, 90, and 120 minutes after intake of the meal. A washout period of at least one week between the two tests was used.

In the IMD treatment and control total cohort no statistically significant differences in blood glucose levels, Δ blood glucose levels, C_{max}, Δ C_{max}, AUC and Δ AUC values between the meal intake with IMD and non-IMD subjects.

However, in a stratified analysis of subjects (n = 7) whose Δ C_{max} was ≥70 mg/dL after intake of the control diet, at 45 minutes the values of the IMD group were significantly lower (p = 0.02) than the control C_{max} and Δ C_{max}. Further, when the C_{max} and Δ C_{max} of both groups were compared, the IMD group was statistically lower (p = 0.03). The Δ blood glucose levels were also significantly lower at 30 minutes (p = 0.04) with IMD consumption. The AUC and Δ AUC were both significantly lower in the group given IMD than in the control (p = 0.02).

Conclusions – Results of this study demonstrated that IMD, when taken with a meal, attenuates elevated postprandial blood glucose, Δ postprandial blood glucose levels, C_{max} and Δ C_{max} values, and blood glucose AUC and Δ AUC levels in subjects with a tendency for increased higher blood glucose levels after intake of a meal.

Strength

Table 1 (below) summarizes the findings from six studies in four scientific publications that evaluated the relationship between IMD intake and postprandial blood glucose levels.

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individuals with various carbohydrates at breakfast with and without IMD. When the data was analyzed between the IMD treatment and the crossover placebo control of the total cohorts no significant differences in variables associated with a reduction of postprandial blood glucose or insulin was observed. Additionally, the results suggested that IMD is a safe non-digestible carbohydrate that does not have unnecessary effects on the cohorts of generally healthy

individuals with normal postprandial blood glucose levels.[2,4]

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elevated than what is considered a normal response. The fifth study (Ishida, et al., 2021) was populated with subjects having an inclusion criteria of elevated blood glucose response to ingestion of carbohydrates, similar to the forementioned subgroups. Analyses of the total cohorts of the 5 studies showed no significant differences in postprandial blood glucose (PPG) variables of peak PPG (PPPG) and/or ΔPPPG, $C_{max,}$ and/or Δ C_{max}, and AUC and/or Δ AUC (iAUC). No significance in insulin variables were noted in any study, except Ishida et al., 2021. In some studies, the time of the peak value for the control and IMD groups were not the same. Therefore, the definition of PPPG and ΔPPPG used in this document is the time of the PPPG and/or ΔPPPG value of the control group compared to the value of the IMD treated group at the same time point. The C_{max} and Δ C_{max} provide the statistical comparison of the control with the IMD treated groups at their maximum values. Three of the studies (Sadakiyo, et al., 2017) reported ΔPPPG and AUC, but not the other variables.

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demonstrated reduced PPPG and/or Δ PPPG levels, except for one of the treatments (Sadakiyo, et al., 2017) where 10 g of IMD only reduced the Δ PPPG of the 50 g glucose diet to a significance of $p = 0.056$ (Table 1). In the 3 studies (Ishida, et al., 2017; Ishida, et al., 2021; Sakurai, et al., 2019), where C_{max} and Δ C_{max} values were determined all IMD groups were statistically significant in lowering these variables as compared to the control carbohydrate meal/beverage (Table 1). AUC and/or Δ AUC were also examined in the IMD treated groups versus controls. Of the 9 possible study results for AUC and/or Δ AUC for the groups showing exaggerated blood glucose responses to carbohydrate consumption there were 6 that reported significant reduction in the IMD groups as compared to control (Table 1).

The

within a study can increase the strength of the scientific evidence."[5] In the studies presented, doses of IMD ranged from 2.5 to 10 g (Table 1). The only dose that did not demonstrate statistical significance at $p < 0.05$ was the 10 g IMD dose given with 50 g of glucose versus placebo, although it tended toward significance ($p = 0.056$; Table 1). One possibility is that 10 g of IMD is at the upper range of efficacy for this physiological effect.

Examination of the rest of the data from subjects having elevated PPPG after consumption of control carbohydrates, conclusively and consistently demonstrates that all other doses (2.5, 2.93, 3,

[4] Sadakiyo T, Inoue S-I, Ishida Y, et al. 2017. Safety assessment of a soluble dietary fiber, isomaltodextrin, enzymatically produced from starch. Fund Toxicol Sci 4(2): 57-75. (Appendix 8)
[5] Scientific Evaluation of Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.3): Guidance for Industry, February 2018, page 14, footnote 16.

5, 9.6 and 9.6 g) of IMD were significantly beneficial in an IMD-associated reduction of PPPG and/or Δ PPPG, regardless of the study carbohydrate source (Table 1). Regarding the FDA quote above, these data demonstrate the IMD can be used at relatively low doses (2.5, 2.93, 3 and 5 g) and have a positive beneficial physiological effect while minimizing consumer consumption levels. The safety of human consumption is assured by the published data provided in GRAS Notice 00610, and a subsequent publication at doses well above the doses shown to be effective in this document.[5]

Base

carbohydrate, receive significant beneficial physiological attenuating effects when the non-digestible carbohydrate IMD is also consumed. Therefore, The Petitioners. believes that IMD should be considered a dietary fiber under the FDA's proposed definition of dietary fiber.

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Table 1. Summary of Six Studies Supporting Beneficial Physiological Effects of IMD on Post-prandial Glucose Levels

Study	Subjects	Design	IMD Dose	Findings
Sadakiyo (2017) Study 1	n = 29 Healthy men & women Subgroup (n = 9) Δ C_{max} > 70 mg/dL after MD intake	single-blind crossover 12 hr fast	IMD 9.6g MD 46.8g	1. Total cohort Δ PPPG ⊘ PPG AUC ⊘ 2. Subgroup Δ PPPG[1] + (p = 0.04) PPG AUC ⊘
Sadakiyo (2017) Study 2	n = 28 Healthy men & women Subgroup (n = 9) Δ C_{max} > 70 mg/dL after sucrose intake	single-blind crossover 12 hr fast	IMD 9.6g Sucrose 100g	1. Total cohort Δ PPPG ⊘ PPG AUC ⊘ 2. Subgroup Δ PPPG[2] + (p = 0.03) PPG AUC + (p = 0.02)
Sadakiyo (2017) Study 3	n = 13 & 14 Healthy men & women Δ C_{max} > 70 mg/dL after glucose intake	single-blind crossover 12 hr fast	IMD 5, 10g Glucose 50g	1. 5g IMD Δ PPPG[3] + (p < 0.05) PPG AUC + (p < 0.05) 2. 10g IMD Δ PPPG[3] ⊘ (p = 0.056) PPG AUC ⊘
Ishida (2017)	n = 45 Healthy men & women	double-blind placebo-controlled	IMD 2.5 g Glucose 50g	1. Total cohort Δ PPPG ⊘ PPG AUC ⊘

	Subgroup (n = 23) ΔC_{max} > 66 mg/dL after glucose intake	crossover 12 hr fast		2. Subgroup PPPG[4] + (p = 0.009) Δ PPPG[4] + (p = 0.021) C_{max} & ΔC_{max} + (p = 0.006) PPG AUC ∞
Ishida (2021)	n = 44 Healthy men & women With a high-normal OGTT[7]	double-blind placebo-controlled crossover 12 hr fast	IMD 3 g fiber Rice meal (108 g carbohydrates)	Total cohort PPPG[5] + (p < 0.05) Δ PPPG[5] + (p < 0.05) ΔC_{max} + (p < 0.05) PPG AUC + (p = 0.007) Δ PPG AUC + (p < 0.05)
Sakurai (2019)	n = 28 Healthy men & women Subgroup (n = 7) ΔC_{max} > 70 mg/dL after a placebo intake	double-blind placebo-controlled crossover 12 hr fast	IMD 2.93 g in 70 g of bread with jam (80.2 g total carbohydrates)	1. Total cohort Δ PPPG ∞ PPG AUC ∞ 2. Subgroup PPPG[6] + (p =0.02) Δ PPPG[6] + (p = 0.02) C_{max} & ΔC_{max} + (p = 0.03) PPG AUC + (p = 0.02) Δ PPG AUC + (p = 0.02)

PPG AUC = Postprandial glucose area-under-curve; ΔPPPG = Peak postprandial glucose; + = statistically significant attenuation compared to control; ∞ = no statistically significant change compared to control

[1]Δ PPPG for placebo and IMD at 45 min.; [2]Δ PPPGs at 30 min.; [3]Δ PPPGs at 45 min.; [4]PPPGs and Δ PPPGs of control and test diet at 45 min.; [5]PPPGs at 60, 90, and 120 min. and Δ PPPGs at 45, 60, 90 and 120 min.; [6]PPPG at 45 min. and Δ PPPGs at 30 and 45 min.; [7]fasting blood glucose level ≥100 and <126 mg/dL, or a blood glucose level < 200 mg/ dL at 2 hours after a 75 g oral glucose tolerance test

b. Lowering post-prandial blood triglycerides level

1. Takagaki, et al. Effects of Isomaltodextrin in Postprandial Lipid Kinetics: Rat Study and Human Randomized Crossover Study. *PLOS ONE, 2018; 13: e0196802* (Appendix 5)

Forty healthy male and female subjects, aged 20 to 69 with a fasting blood triglyceride (TG) level from 30 to 149 mg/dL, participated in a randomized, double-blind, placebo-controlled, crossover study. The subjects were randomly assigned to 2 groups so that groups had the same sex ratio and change in TG levels (Δ TG) after consumption of a placebo diet. A prospective subgroup analysis was also performed.

A control diet consisting of 20.0 g of butter, 13.9 g of lard and 200.0g of corn potage soup was used as a high fat-loading diet containing a total of 40 g of fat. The test diet was a mixture of the high fat-loading diet and 2.5 g of IMD (equivalent to 2.13 g of dietary fiber).

After fasting for more than 12 hours following the previous evening meal, blood was collected before and at 2, 3, 4 and 6 hours after the subjects consumed the test or the placebo diet.

TG and Δ TG were the primary endpoints. In addition, the area under the curve (AUC and Δ AUC) as well as the maximum concentrations of each subject (C_{max} and Δ C_{max}) were calculated and compared between the IMD containing and placebo diets. In addition to the analysis of all subjects, a subgroup analysis was performed on 14 subjects who had a TG C_{max} of 200 mg/dL or more after consuming the placebo diet.

Analysis of the total cohort showed that TG reached C_{max} at 2 hours after intake of the placebo diet and 3 hours after intake of the IMD diet, and then gradually decreased until 6 hours after intake. A comparison of the TG levels between the diets showed no significant differences at any time after intake. There were also no significant differences in the AUC, Δ AUC, C_{max}, or Δ C_{max} between the diets.

The results of the subgroup analysis showed that the TG levels of the subjects with the IMD diet were consistently, but not significantly, lower than those consuming the placebo diet at every time point. The peak TG level of the placebo diet group occurred 4 hours after intake, while the TG level at 4 hours (not peak) with the IMD diet was significantly lower than that of the placebo diet (p = 0.04). Subjects on the IMD diet trended toward lower AUC values but were not significant. However, the IMD diet demonstrated significantly lower C_{max} (p = 0.009) and Δ C_{max} (p = 0.009) when compared with the placebo diet.

The analysis for remnant-like particle cholesterol (RLP-C) was performed similarly to TG. RLP-C levels in the entire cohort peaked 4 hours after intake of the placebo and IMD diet and then gradually decreased through 6 hours after intake. Comparisons of RLP-C levels at every time point, AUC, and C_{max} showed no significant differences between the diets. A subgroup analysis based on C_{max} of TG showed that the RLP-C levels, AUC, and C_{max} were lower in the subjects on the IMD diet compared with those on the placebo diet, but not significantly.

Conclusions - These results suggest that IMD inhibits postprandial TG increase in subjects who have a normal fasting TG range but a possible high risk of abnormal lipid metabolism.

2. Ishida, et al. Inhibitory Effect of Isomaltodextrin Intake on Increase in Postprandial Blood Triglycerides. *Jpn Pharmacol Ther, 2020; 48: 1437-46* (Appendix 6)

Eighty healthy male and female volunteers aged 20 to 64, with a high-normal to slightly high fasting blood TG level (≥120 mg/dL and <200 mg/dL), participated in a randomized, placebo-

controlled, double-blinded, crossover study.

After fasting for more than 12 hours, the subjects ingested a high-fat diet (43.2 g of fat) together with drinking water containing 5 g IMD (test) or 5 g MD (Maltodextrin, placebo). Blood samples were collected before, and at 2, 3, 4, and 6 hours after intake to determine the level of blood TG and remnant-like lipoprotein particle cholesterol (RLP-C). A subgroup analysis was also performed on these subjects.

The primary endpoints for both the total cohort and the subgroup analyses were the time course of blood TG and Δ TG, and associated area under the curve (AUC) and incremental AUC (iAUC). Secondary endpoints were the same set of variables for blood RLP–C. The TG and Δ TG levels of the total cohort peaked 4 hours after intake of the control diet and then gradually decreased. In the IMD diet group the peak TG and Δ TG was at 3 hours. Comparison of the TG and Δ TG levels at 4 and 6 hours after intake showed that the values of the test diet were statistically significantly lower than those of the control at both times ($p < 0.05$). The AUC and iAUC of blood TG for the test diet was also significantly lower than the placebo diet ($p < 0.05$). RLP-C levels were significantly reduced ($p < 0.05$) at 4 and 6 hours, while the Δ RLP-C levels were not significant ($p < 0.10$). Neither AUC nor iAUC values were significant ($p < 0.10$).

Data from the subgroup analysis of subjects with a normal fasting TG of < 150 mg/dL (n=51) gave similar results to the total cohort. The TG and Δ TG peak values for the control versus the IMD groups were at 4 and 3 hours, respectively. The TG and Δ TG levels at 4 and 6 hours after intake of the IMD test diet were significantly lower ($p < 0.05$) than placebo as well as the TG AUC and iAUC ($p < 0.05$). Statistically significant differences ($p < 0.05$) were observed for RLP-C levels at 4 and 6 hours, while significant differences were found only at 6 hours after intake for Δ RLP-C. No statistical differences were observed for RLP-C AUC and iAUC.

Conclusions – IMD significantly inhibited increases in postprandial blood TG at 4 and 6 hours after consumption, and AUC and iAUC. The data also suggests that IMD lowers RLP-C in subjects with high-normal to slightly high fasting TG levels. IMD also had a similar effect on subjects with normal fasting TG levels.

Strength of the Evidence for IMD on Post-prandial Triglycerides Levels

Table 2 (below) summarizes the findings from two studies that evaluated the relationship between IMD intake and post-prandial triglycerides (TG) levels.

Takagaki (2.5 g) and Ishida (5 g), respectively conducted a comparison of the relationship between IMD consumption and post-prandial blood triglycerides levels with two doses. In these studies, healthy individuals consumed IMD with a high-fat meal at breakfast. In the Takagaki study there were no significant beneficial effects with consumption of IMD on a population of subject with a normal range of fasting blood TG. However, a subpopulation was identified that had an exaggerated C_{max} of > 200 mg/dL to the control high fat meal. This subgroup had a significant lowering of the postprandial blood TG, C_{max} and ΔC_{max}. This supports a conclusion of a beneficial physiological effect of IMD in subjects with normal fasting blood TG but have an excessive response to a high fat diet. Whereas, in the Ishida study cohort, the fasting blood TG was in the high normal to high range where there was significant lowering of postprandial TG, Δ TG, AUC and iAUC. The subgroup included the relatively high normal range of the total cohort (TG ≥120 mg/dL), with a reduction in the high range from <200 mg/dL to <150 mg/dL fasting TG. Comparisons of the IMD treated group with the control meal show significant lowering of postprandial TG, Δ TG, AUC and iAUC. These data suggest that IMD intake with a high fat meal can reduce peak postprandial TG in individuals with high normal and relatively high fasting TG values. Reviewing both studies, it appears to show that individuals with low/medium normal fasting TG levels are not as affected by the action of IMD unless they have an abnormal postprandial response to high fat meals. It also can be stated that the amount of IMD necessary to provide a beneficial physiological effect is very low relative to the documented safety of IMD.[2,3,5]

Based on the totality and strength of the published scientific data the evidence supports the conclusion that generally healthy subjects who exhibit a high normal to high fasting TG or have an exaggerated peak response to a high fat meal receive a significant beneficial physiological effect when consuming the non-digestible carbohydrate IMD with that meal. Therefore, the Petitioners. believes that IMD should be considered a dietary fiber under FDA's proposed definition of dietary fiber.

Table 2. Summary of Two Studies Supporting Beneficial Physiological Effects of IMD on Post-prandial Triglycerides Levels

Study	Subjects	Design	IMD Dose	Findings
Takagaki (2018)	n = 40 Healthy men & women Subgroup (n = 14) C_{max} > 200 mg/dL TG after intake of placebo	double-blind placebo-controlled crossover 12 hr fast	IMD 2.5g with 40g high fat meal	1. Total cohort. PPPTG ⌀ AUC & ΔAUC ⌀ C_{max} & Δ C_{max} ⌀ 2. Subgroup PPPTG + (p = 0.04) AUC & ΔAUC ⌀ C_{max} & Δ C_{max} + (p = 0.009)
Ishida	n = 80	double-blind	IMD 5 g with	1. Total cohort.

(2020)	Healthy men & women fasting TG ≥120 mg/dL and <200 mg/dL Subgroup (n = 51) fasting TG ≥120 mg/dL and < 150 mg/dL	placebo-controlled crossover 12 hr fast	high fat meal	PPPTG & ΔPPPTG + (p <0.05) AUC & iAUC + (p <0.05) 2. Subgroup PPPTG & ΔPPPTG + (p <0.05) AUC & iAUC + (p <0.05)
PPPTG and ΔPPPTG = Comparison of control peak postprandial triglycerides level and change in level versus IMD at the same time point AUC and ΔAUC (iAUC) = Postprandial triglycerides area-under-curve and incremental are-under-curve + = statistically significant attenuation compared to control ø = no statistically significant change compared to control				

c. Conclusions Respecting Requested Agency Action

The foregoing evidence demonstrates that IMD is an "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. As such, it should be included in 21 C. F. R. §101.9 (c) (6) (i)'s list of dietary fibers.

C. Environmental Impact

The action requested is subject to categorical exclusion under 21 C.F.R. §25.30 (h) and therefore does not require the preparation of an environmental assessment.

D. Economic Impact

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

E. Certification

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, that are both favorable and unfavorable to the petition.

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Appendices:

Appendix 1

Sadakiyo, et al. (2017) Attenuation of postprandial blood glucose in humans consuming isomaltodextrin: carbohydrate loading studies.

Appendix 2

Ishida, et al. (2017) The Attenuating Effect of Isomaltodextrin on Postprandial Blood Glucose Level in Healthy Human Subjects.

Appendix 3

Ishida, et al. (2021) Suppressive Effect of Isomaltodextrin on Postprandial Blood Glucose Elevation after Ingestion of Cooked Rice in Healthy Adults.

Appendix 4

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Appendix 5

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Appendix 6

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Appendix 7

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Appendix 8

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