Citizen Petition for Listing Isomaltooligosaccharide as Dietary Fiber Under 21 C.F.R. § 101.9(c)(6)(i)

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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
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Citizen Petition

Undersigned petitions under 21 C.F.R. §10.30 requesting The Commissioner of Food and Drug to include ***Isomaltooligosaccharide*** in the 21 C.F.R. §101.9(c)(6)(i) list of dietary fibers.

A. Action Requested

I. Listing Isomaltooligosaccharide as dietary fiber under 21 C.F.R. 101.9(c)(6)(i)

Isomaltooligosaccharide ("IMO") is glucose oligomers with α-D-(1,6)-linkages, including among others isomaltose, panose, isomaltotetraose, isomaltopentaose, nigerose, kojibiose, and higher branched saccharides with α-D-(1,6)-linkages. While human intestinal enzymes readily digest α-(1,4)-glycosidic bonds, α-(1,6)-linkages are not hydrolyzed and exhibit a digestion-resistant property, and therefore, are not digested in the upper gastrointestinal tract. Because of this digestion-resistant property, IMO helps improve laxation and lower blood cholesterol level. It has long been considered by the scientific community to be a dietary fiber[1] as well as having a prebiotic effect, exhibiting the properties of retaining moisture, and producing a bulking effect.

IMO occurs naturally in foods. In industrial/commercial settings, it is manufactured and consumed throughout the world.

21 C.F.R. § 101.9(c)(6)(i) lists the isolated or synthetic nondigestible carbohydrates determined by FDA to have physiological effects that are beneficial to human health and, therefore, that are authorized to be included in the calculation of the amount of dietary fiber in foods. The undersigned submits this Citizen Petition under 21 C.F.R. §10.30 requesting that the Commissioner include Isomaltooligosaccharide within the listing of dietary fibers contained at 21 C.F.R. §101.9(c)(6)(i).

[1] Tungland BC and Meyer D. 2002. Nondigestible oligo-and polysaccharides (dietary fiber): Their physiology and role in human health and food. Comprehensive Reviews in Food Science and Food Safety 3:90-109.

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B. Statement of Grounds

I. Current Regulatory Environment

The Nutrition Labeling and Education Act of 1990 established mandatory nutrition labeling for packaged foods so consumers could make informed dietary choices by adding Section 403(q)[2] to the FFDCA. Section 403(q) provides in pertinent part:

> ***§ 403. Misbranded Food***
> *A food shall be deemed to be misbranded ----*
>
> *(q) if it is a food intended for human consumption and is offered for sale, unless its label or labeling bears nutrition information that provides ----*
>
> > *(D) the amount of the following nutrients: ... dietary fiber ... contained in each serving size or other unit of measure ...*

21 C.F.R. §101.9(c)(6)(i) defines two categories of dietary fibers:

> *Nondigestible 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.*

To qualify as isolated or synthetic dietary fiber, petitioners are required to provide evidence to FDA in a citizen petition demonstrating nondigestibility and the physiological effects that are beneficial to human health. If FDA grants the citizen, the nondigestible carbohydrate can be considered as "dietary fiber" for declaration on the Nutrition Facts Label.

Petitioner requests the Commissioner to include IMO within the list of dietary fibers identified in 21 C.F.R. §101.9(c)(6)(i) upon the grounds that IMO fits squarely within the statutory definition and therefore should be included in the list of dietary fibers.

II. *Isomaltooligosaccharide* is a "Dietary Fiber" as Defined by 21 C.F.R. §101.9(c)(6)(i).

There are two requirements for inclusion within the list of "dietary fibers" recognized by FDA pursuant to 21 C.F.R. §101.9(c)(6)(i):

> **One:** The food substance must be composed of isolated or synthetic non-digestible carbohydrates with 3 or more monomeric units ***and***

[2] 21 U.S.C. § 343(q)

Two: The food substance must be the subject of a petition submitted to FDA under 21 C.F.R. §10.30 demonstrating that such carbohydrates have a physiological effect that is beneficial to human health.

IMO satisfies both of these requirements as demonstrated below.

a. Isomaltooligosaccharides are composed of non-digestible carbohydrates with 3 or more monomeric units.

i. ***Composition:*** Isomaltooligosaccharides are glucose oligomers containing one or more α-D-(1,6)-linkages. These oligomers include isomaltose, isomaltotriose, panose, isomaltotetraose, isomaltopentaose, and other saccharides with α-D-(1,6)-linkages. Most of IMO's oligosaccharides contain between 3 to 9 glucoses all linked together with α-D-(1,6)-linkages. The balance is made up of disaccharides as well as longer oligosaccharides (up to 9 glucose units) derived from the limit dextrins in high maltose syrups and containing additional α-D-1,6-linked glucose. The disaccharide portion is mainly somewhat digestion resistant α-(1,6) linked isomaltose along with nigerose, kojibiose and maltose. Isomaltotriose, panose, and maltotriose make up the trisaccharide oligomers. Isomaltotetraose, isomaltopentaose, maltohexaose, maltoheptaose, and small amounts of oligomers with 8 or more degrees of polymerization make up the remaining α-D-(1,6)-linked oligomers**.**

ii. ***Production:*** Commercial IMO production begins with natural starch sources such as potatoes, rice, peas, cassava, beans, lentils, barley, corn, oats and wheat. Other starch sources can be used. The first step in IMO production is to convert the selected starch source into high maltose syrup with di-, tri and oligosaccharides (2, 3 or more than 3 glucose units) having α-(1,4) glycosidic linkages which are readily digestible in human intestine. This is accomplished via enzymatic hydrolysis of starch.

These α-(1,4) glycosidic linkages are then enzymatically modified with alpha-transglucosidase to incorporate the more digestion-resistant α-(1,6) glycosidic linkages. It is this key step that confers the property of "iso" linkages between the glucose moieties of oligosaccharides and results in isomalto-oligosaccharides (IMO). Because the product originates from different starch sources (presumably based on seasonal and commodity market pricing considerations), the manufacturing process must control the degree of

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polymerization (dp) and the α-(1,6) linkages to ensure consistent high quality of isomalto oligosaccharides. This degree of control is industry standard practice in IMO production.

Other oligosaccharides, similar in chemical structure and physiological function to IMO, have already been identified as fibers by FDA and other international regulatory bodies. Among these is Promitor® (Tate & Lyle), a corn-based oligosaccharide that FDA, in correspondence to Tate & Lyle, has agreed is a soluble corn fiber. Other oligosaccharides similar to IMO in terms of chemical structure and physiological effects which have already been identified as "fibers" by FDA and other regulatory agencies, include short chain fructooligosaccharides (FOS), and galactooligosaccharides (GOS).

iii. Conclusion: As demonstrated above, IMO contains synthetic non-digestible carbohydrates with 3 or more monomeric units. This satisfies the compositional requirement of 21 C.F.R. §101.9(c)(6)(i).

b. IMO Has Psysiological Effects That Are Beneficial to Human Health:

The second characteristic of dietary fiber under 21 C.F.R. §101.9(c)(6)(i) is that the food substance has a physiological effect that is beneficial to human health. The following evidence demonstrates that IMO fully satisfies this regulatory requirement.

i. Introduction

This is a review of the key clinical studies on IMO that demonstrate its physiological benefits to humans. The petitioner carefully studied FDA's June 13, 2018 letter in response to Top Health's first IMO citizen petition -- -- Docket Number FDA-2016-P-1180. The petitioner is utilizing FDA's input to update and provide additional information to address the Agency's specific concerns about the petitioner's original IMO Citizen Petition and the petitioner has added another study that corroborates the original proposal that IMO be considered a dietary fiber. Translation of a relevant reference that was previously available only as an original foreign language article is attached. Finally, the Agency's questions on statistics have been addressed. The petitioner believes that this updated Petition requesting FDA to consider IMO as a dietary fiber adequately addresses the gaps in the original Petition and focuses only on the most FDA relevant clinical findings about IMO.

The two key physiological benefits this petition is exclusively focusing on include blood cholesterol reduction and laxation. These benefits have been accepted by FDA as relevant

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physiological benefits for evaluation of isolated fiber benefits. Three studies demonstrate reduction in blood cholesterol concentrations and four studies demonstrate improved laxation. For blood cholesterol reduction, FDA previously accepted that the Yen et al. (2011)[3] study that showed reduction in blood cholesterol concentration; a newly submitted study (Lin et al., 2005) demonstrated improvement in cholesterol concentration; and concerns FDA had with the Wang et al. (2001) statistics have been addressed. For laxation, the newly submitted Lin et al. (2005)[4] study shows decreased symptoms of constipation; the concerns regarding statistics for the Wang et al. (2001)[5] paper have been addressed. The validity of the conclusions derived from the 4 presented studies has been confirmed in writing by 2 fiber experts: George C. Fahey, Jr., PhD; and Levinus A. Dieleman, MD, PhD (included as Exhibits 5 and 6, Appendix of Exhibits, Page 34 and 37).

ii. Blood Cholesterol Reduction

Three studies (Yen et al., 2011, Lin et al., 2005, Wang et al., 2001) are presented in this citizen petition to demonstrate the physiological benefits of IMO to humans relative to reductions in total cholesterol (TC) and LDL cholesterol (LDL-C) concentrations. These studies show that IMO lowered both LDL-C and TC and confirm that IMO is a dietary fiber as defined by FDA.

1. **Yen C-H, Tseng Y-H, Kuo Y-W, et al.** Long-Term Supplementation of Isomalto-oligosaccharides Improved Colonic Microflora Profile, Bowel Function, and Blood Cholesterol Levels in Constipated Elderly People: A Placebo-Controlled, Diet-Controlled Trial. Nutr. 2011. 27:445–450. (Exhibit 3, Appendix of Exhibits, Page 20)

   This study was included in Top Health's previous IMO citizen petition.[6] FDA acknowledged that the study demonstrated that "total cholesterol and LDL cholesterol levels were significantly lower after the IMO1 phase of the study (10% and 8%, respectively) ($P < 0.05$)"[7]. The data presented in Table 4 of the paper indicate that the TC and LDL-C concentrations significantly decreased from 4.1 mmol/L to 3.7 mmol/L to 3.6 mmol/L and from 2.4 mmol/L to 2.2 mmol/L to 2.1 mmol/L during IMO1 and IMO2 periods, respectively.

[3] Appendix of Exhibits, page 20 (Exhibit 3)
[4] Appendix of Exhibits, page 2 (Exhibit 1)
[5] Appendix of Exhibits, page 12 (Exhibit 2)
[6] Docket Number FDA-2016-P-1180
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In FDA's Petition response letter[8], it was stated that the study had mixed results as "one comparison showed a statistically significant lowering of total and LDL cholesterol and one comparison showed no statistically significant effect." Looking at the data, total cholesterol and LDL-C were significantly reduced in the IMO1 period, stayed low ($P < 0.05$) through IMO2, and then remained statistically unchanged upon withdrawal, although directionally it increased. The fact that LDL-C did not increase to significance in the four-week washout period was previously viewed by FDA as negative. However, it is respectfully submitted that this simply shows that IMO has a positive carry over effect for a period of time post-consumption. Beyond the 4-week post-period, the statistical effect on TC and LDL-C is unknown. From a clinical point of view, without knowing the subjects' metabolic rates and pharmacokinetic metrics of IMO, it is hard to determine whether 4 weeks are enough as a washout periods especially after 8 weeks of IMO consumption. To reiterate, it is recognized that it would have been good statistically to see blood cholesterol levels rise in the wash out period, however this may be viewed as a clinically positive result.

These data indicate that IMO lowered both LDL-C and TC concentrations and proves that IMO is a dietary fiber as defined by FDA.

2. **Lin S-D, Lim P-S, Wang H-F, et al.** Effects of Isomaltooligosaccharide Chiffon Cake on Serum Biochemical Parameters, Constipation, and Fecal Putrefactive Metabolites in Hyperlipidemic Subjects. Nutr Sci J. 2005. 30(1):108-115. (Exhibit 1, Appendix of Exhibits, Page 2)

   University freshmen were randomized to consume chiffon cake that contained either 10 g/day IMO or sucrose as controls. The subjects were observed for the first week (run-in period) in this 7-week study. Forty-two subjects completed the study. The English translation (with certificate) of this paper is submitted in this petition to address FDA's previous concern that the paper was presented in a foreign language. The non-availability of the English translation previously did not allow complete evaluation of these data thereby not making it feasible to reach a valid conclusion. This study confirms that the ingestion of chiffon cakes containing an average of 10 g/day IMO reduced ($P < 0.05$) TC and LDL-C concentrations.

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Table 2 in the paper shows that after 6 weeks of continuous consumption of chiffon cakes containing IMO or sucrose, serum TC and LDL-C concentrations in the IMO group decreased significantly ($P < 0.05$) from 220.7 to 201.7 and 139.9 to 121.9, respectively, and also differed significantly ($P < 0.05$) from the placebo group. As for the sucrose group, there was no significant difference in the changes in TC, LDL-C, high-density lipoproteins cholesterol (HDL-C), or triglycerides (TG) before or after the experiment ($P > 0.05$). These test results show that after subjects consumed 10 g of IMO in chiffon cake each day for 6 consecutive weeks, the subjects' TC and LDL-C were reduced ($P < 0.05$). The mechanism by which IMO reduces blood lipids is hypothesized to be that, after moderate consumption of indigestible oligosaccharides, and as is the case for many dietary fibers, IMO can shorten the time of passage of food through the digestive tract, thereby reducing the rate of absorption of nutrients. In addition, IMO results in production of short-chain fatty acids including acetic, propionic, and butyric acids, by the action of microorganisms in the intestine, and propionic acid has been shown to reduce serum TC concentrations.

3. **Wang H-F, Lim P-S, Kao M-D, et al.** Use of Isomalto-oligosaccharide in the Treatment of Lipid Profiles and Constipation in Hemodialysis Patients. J Ren Nutr. 2001.11(2):73–79. (Exhibit 2, Appendix of Exhibits, Page 12)

   In a parallel study, 20 individuals with impaired kidney function and with uremic dyslipidemia and chronic constipation consumed 30 g/day of IMO for 4 weeks following a two-week run-in period. The control group consisted of 30 age- and sex-matched hemodialysis patients who did not consume IMO. The subjects in the treatment group were instructed to dissolve the IMO syrup in warm water and to consume it after meals. The recommended dose was 15 g twice daily, but the patients were permitted to increase the dose of IMO according to their bowel movements' frequency.

   This study was previously submitted to FDA in Top Health's IMO citizen petition[9] and was considered by the reviewer for cholesterol reduction. The data show statistically significant decreases in TC and TG and increases in HDL-C that were noted after IMO treatment ($P < 0.05$ compared with baseline and controls). The data presented in Table 4 of Wang et al. (2001) show ($P \leq 0.05$) that the TG and TC concentrations comparison before and after IMO treatment were significantly decreased by 18% from 234.5 mg/mL to 191.2

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mg/mL and 210.0 mg/mL to 174.0 mg/mL, respectively, while the HDL-C concentration increased significantly by 39% from 24.7 mg/mL to 34.3 mg/ml.

As noted, this study was included in Top Health's previous IMO citizen petition[10] and rejected by FDA since "baseline values were reported for the treatment and control groups, but statistical comparisons of the baseline values between the groups were not reported."[11] To respond to FDA's concern, Top Health retained a statistician[12] to review the study data. Utilizing the information presented in Table 4 of Wang et al. (2001), the baseline values including the means of TG, TC, HCL-C and LDL-C before the experiment between the control group and the treatment group were compared statistically. The same procedure was performed for the corresponding means after the experiment. All P-values ≤ 0.05 were considered significant. Table 2 herein shows that there was no significant difference ($P > 0.05$) between the means for the control group and the corresponding patient group mean before the experiment for any of the four studied variables. However, Table 3 herein shows that there was a significant difference ($P \leq 0.05$) between the means for the control group and those of the treatment group for TC, HDL, and LDL after the study.

No significant difference ($P > 0.05$) was found for TG after the experiment between the control group and the treatment group. The data show that the use of IMO significantly affected TC, HDL, and LDL concentrations in blood when the control group was compared to the treatment group.

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[12] Statistician, Dr. Eyrck Silva, has worked and published studies in the field of food science and applied statistics. He was a Professor at the University of Veracruz, Mexico, for almost 20 years, as well as an Assistant Professor and Sessional Professor at the University of Alberta, Canada. In recent years, Dr. Silva has provided statistical consultations to academia and private industry.

Table 1: Comparison of Serum Lipid Before the Intake of Isomaltooligosaccharides (IMO) in Hemodialysis Patients and Controls

Parameters	Control Group Mean Before Study	Control Group Standard Deviation Before Study	n	Upper Critical Value α=0.05	Lower Critical Value α=0.05	Patients Group Mean Before IMO	Z-value	P-value	α=0.05*
Triglycerides (mg/mL)	237.6	148.5	30	290.7	184.5	234.5	-0.1143	0.9092	NS
Cholesterol (mg/mL)	204.0	37.1	30	217.3	190.7	210.0	0.8858	0.1879	NS
HDL-C (mg/mL)	26.8	7.0	30	29.3	24.3	24.7	-1.6432	0.3757	NS
LDL-C (mg/mL)	131.0	39.9	30	145.3	116.7	131.5	0.0686	0.9453	NS

Table 2: Comparison of Serum Lipid After the Intake of Isomaltooligosaccharides (IMO) in Hemodialysis Patients and Controls

Parameters	Control Group Mean After Study	Control Group Standard Deviation After Study	n	Upper Critical Value α=0.05	Lower Critical Value α=0.05	Patients Group Mean After IMO	Z-value	P-value	α=0.05*
Triglycerides (mg/mL)	228.8	180.7	30	293.5	164.1	191.2	-1.1397	0.25470	NS
Cholesterol (mg/mL)	202.1	38.2	30	215.8	188.4	174.0	-4.0291	0.00006	S
HDL-C (mg/mL)	27.6	8.0	30	30.5	24.7	34.3	4.5872	0.00001	S
LDL-C (mg/mL)	137.5	37.7	30	151.0	124.0	114.3	-3.3706	0.00075	S

*NS – Not Significant, S – Significant

Combining the statistical data from the original paper and the additional data extrapolated from it, IMO consumed once a day was found to be effective in

lowering TC and in raising HDL-C concentrations in HD patients, important clinical changes.

iii. Laxation

Four studies (Chen et al., 2001[13], Lin et al., 2005, Yen et al., 2011, Wang et al., 2001) are presented in this petition to demonstrate that IMO consumption significantly decreases symptoms of constipation and improves spontaneous bowel movement frequency and stool output. Subjects include healthy young male and female college freshmen, constipated elderly male and female individuals, and older men with impaired kidney function. IMO supplementation proved to be statistically effective in providing physiological health benefits of improved laxation in humans including improved bowel movement, stool output, and constipation.

1. **Chen H-L, Lu Y-H, Lin J-J, et al. (2001)** Effects of Isomalto-Oligosaccharides on Bowel Functions and Indicators of Nutritional Status in Constipated Elderly Men. J Am Coll Nutr. 2001. 20(1):44–49. (Exhibit 4, Appendix of Exhibits, Page 27)

   Seven nursing home residents (mean age = 75 years) with a history of chronic constipation participated in a 30-day control, low fiber period followed by a 30-day IMO-supplemented (10 g active components) experimental period. Consumption of IMO effectively ($P < 0.05$) improved bowel movement frequency, stool output, and microbial fermentation in the colon without any adverse effects.

   This subject group is an excellent test group as they have ongoing problems with constipation which the petitioner believes is a physiological condition that is a key target of fibers with demonstrable enhanced laxation effects. The first phase of the study did not include IMO (control), while the study subjects consumed IMO during the second phase of the study. The IMO dose was incorporated into a dessert consumed in the afternoon and was gradually increased from 8 g/day (3.3 g of the active component) to 24 g/day (10 g of the active component) during the first 10 days of the experimental period.

   While the spontaneous defecation frequency increased significantly, daily stool output and stool weight per passage also increased significantly with IMO intake. The spontaneous defecation significantly increased from 0.5

[13] Appendix of Exhibits, page 27 (Exhibit 4)

time/5 days (3 times/30 day) to 1.5 times/5 days (9 times/30 days). This laxation effect is also supported by the wet stool weight per day, dry stool weight per day, wet stool weight per passage, and dry stool weight per passage significantly increased by 70% from 47.7 g to 81.1 g, by 55% from 9.2 g to 14.3 g, by 70% from 119.2 g to 202.8 g, and by 55% from 23.1 g to 35.8 g, respectively. That translated to a 3.34 g ± 0.54 g (mean ± SE) increase in wet weight per day for every gram of IMO consumed. The increase in stool bulk was mainly attributed to increased bacterial mass.

FDA[14] expressed a concern about enema use in their June 13 letter. On further study, the data at baseline and during the experimental period were determined to not be statistically different ($P \geq 0.05$), indicating that enema use had no effect on defecation frequency or stool mass. In this study, enema use was tightly controlled by setting criteria of no bowel movement for 3 days and then requiring it be used only based on this criterion for both Control and Test subjects. The subjects were elderly nursing home residents with chronic constipation and enema use was a part of the normal regimen. Enema use leads to voiding of the colon. Therefore, the use of enemas leads to a delay in the time/need to defecate (since much stool has been voided) after its use; or, simply put, enemas are an additional hurdle for the treatment to overcome. In spite of this "handicap", the data indicated that IMO resulted in a positive effect demonstrated by a nearly threefold (from three to nine times) significant increase in spontaneous defecation in the period prior to study initiation compared to the active study period. Spontaneous defecation was not affected by enema use. Stool weights may possibly have been affected by enema use, however this measure is considered only as a supporting evidence. Spontaneous defecation is the physiological key endpoint considered by FDA as the evidence supporting dietary fiber status. Further, there was no statistical difference in number of enemas used by subjects on Control vs. Experimental diets ($P \geq 0.05$) (refer to Table 3 presented in Chen et al., 2001). The increase in spontaneous defecation and stool mass indicated that IMO was effective in improving the symptoms of constipation, and that enema use did not negatively affect the study outcomes.

This study clearly demonstrated that supplementation of IMO in low fiber diets is effective in relieving constipation in the elderly population. The data showed that after elderly individuals with constipation ingested IMO syrup containing 10 g of active ingredient every day for 30 days, not only did the

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frequency of spontaneous defecation increase significantly, but treatment also increased acetic acid and propionic acid concentrations in feces, and wet weights, dry weights, and total bacterial weights of feces ($P < 0.05$). These are typical, well documented physiological responses to dietary fiber ingestion.

2. **Lin S-D, Lim P-S, Wang H-F, et al.** Effects of Isomaltooligosaccharide Chiffon Cake on Serum Biochemical Parameters, Constipation, and Fecal Putrefactive Metabolites in Hyperlipidemic Subjects. Nutr Sci J. 2005. 30(1):108-115. (Exhibit 1, Appendix of Exhibits, Page 2)

   This study is described in the blood cholesterol reduction section. The subjects were observed for the first week (run-in period) in this 7-week study. The dietary records (24-h dietary recall records), intestinal symptoms, and defecation patterns were recorded. The data from this study confirmed that the ingestion of chiffon cakes containing an average of 10 g/day IMO significantly ($P < 0.05$) reduced symptoms of constipation. Subjects consuming approximately the same amount of chiffon cakes containing sucrose did not exhibit these changes.

   Table 3 in the paper indicates that after 6 weeks of consuming chiffon cakes containing IMO, the subjects in the IMO group had a significant decrease in constipation (frequency in times per day) from 0.58 to 0.21 ($P < 0.05$) and decrease in constipation score from 0.36 to 0.18 ($P < 0.05$). The subjects in the sucrose group showed no significant change in constipation frequency or score before or after the experiment ($P > 0.05$). Incomplete defecation was defined as incomplete movement over 5 minutes. This timeframe maybe considered as an objective measurement. When calculating total constipation, “no defecation” and “incomplete defection” were assigned the score of 1, with “smooth defecation” a score of 0. Individual scores were added and then divided by the number of days recorded, and then means and standard deviations were calculated for each group. Compared with the control group which demonstrated no significant change in total constipation, the treatment group achieved the significant decrease in constipation since incomplete or no defection improved to smooth defecation. This calculation method is an objective measure that proves an improvement in laxation frequency.

   Data indicate that daily ingestion of 10 g of IMO had positive effects on symptoms of constipation and this conclusion is consistent with those demonstrated in other studies included in this submission.

3. **Yen C-H, Tseng Y-H, Kuo Y-W, et al.** Long-Term Supplementation of Isomalto-oligosaccharides Improved Colonic Microflora Profile, Bowel Function, and Blood Cholesterol Levels in Constipated Elderly People: A placebo-controlled, Diet-Controlled Trial. Nutr. 2011. 27:445–450. (Exhibit 3, Appendix of Exhibits, Page 20)

   Thirteen nursing home residents (mean age = 83 years) with chronic constipation (lasting for more than 6 months) were provided IMO for two sequential 4-week periods (IMO1 and IMO2). A run-in period and a 4-week placebo period during which the subjects consumed 3 milliliters (mL) of fructose syrup per day (control) preceded the IMO treatment periods. After the 8 weeks of IMO supplementation, there was a 4-week washout period. The study compared the control phase of the study at 4 weeks to the IMO1 treatment phase at 4 weeks and also to the IMO2 phase (4 additional weeks). Further the washout phase (4 weeks) was compared to IMO1 and IMO2 phases, respectively. IMO supplementation of a low-fiber diet improved colonic microflora profile ($P < 0.05$) and spontaneous defecation frequency increased significantly from 1.2 per week in the placebo period to 2.0 per week in the IMO2 treatment period ($P < 0.05$) in constipated elderly subjects. These beneficial effects decreased after discontinuation of the supplements ($P< 0.05$). There was no difference in number of enemas used between placebo, IMO consumption, and post-consumption periods ($P > 0.05$).

   During FDA's review of Top Health's previous IMO citizen petition,[15] this study was included in the blood cholesterol section but not in the laxation section due to enema use. In this study, enemas were allowed if spontaneous defecation did not occur within 3 days, or as requested by the subjects. Given the low rate of defecation in the study population, enema use was allowed for patient comfort and for ethical reasons. As with the study cited previously, enema use in this study was not significantly different amongst the 4 treatment periods during the study ($P > 0.05$), so it did not negatively affect results for defecation frequency or stool mass. As noted above, enema use added an additional hurdle making it more difficult for the treatment group to demonstrate an effect. Table 3 of the paper demonstrates that IMO resulted in a positive effect. Spontaneous defecation increased significantly by about 66% ($P < 0.05$) from an average of 1.2 times to 2.0 times over the course of the two-period study. While enema may affect the stool weight, spontaneous

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defecation was not affected by enema used and it is the physiological key endpoint. Enema use directionally decreased by about 19% from 1.9 times on average to 1.6 times during the same periods. These beneficial effects diminished after discontinuation of the IMO supplements, which adds confidence to the validity of IMO's effect.

The IMO2 treatment phase data were not evaluated or included in Top Health's previous IMO citizen petition[16] because "this represented eight consecutive weeks of treatment, which was not the same duration as the control periods" (4 weeks of placebo and 4 weeks of post-treatment washout). The effects of the IMO on increased defecation in periods 1 and 2 are consistent with the administration of IMO and other oligosaccharide fibers. The difference in washout and administration periods of the placebo had minimal influence on the effects of IMO on defecation in IMO2. The data presented in Table 3 of the paper indicate that IMO positively affected spontaneous defecation frequency and fecal output (g/day). The petitioner respects FDA's conclusion that the IMO2 period is a different time period than placebo; however, notes that both the placebo and wash out period were statistically different ($P < 0.05$) than the treatment period at the end of the IMO2 period and which adds further substantive confidence to the conclusion that IMO improves laxation.

The results demonstrate that IMO supplementation of a low-fiber diet improved bowel movement parameters in a time-dependent fashion in constipated elderly subjects.

4. **Wang H-F, Lim P-S, Kao M-D, et al.** Use of Isomalto-oligosaccharide in the Treatment of Lipid Profiles and Constipation in Hemodialysis Patients. J Ren Nutr. 2001.11(2):73–79. (Exhibit 2, Appendix of Exhibits, Page 12)

   This study is described in the blood cholesterol reduction section. The recommended dose was 15 g twice daily, but the patients were permitted to increase the dose of IMO according to their bowel movements' frequency. The study showed that 30 g IMO ingested once per day was well tolerated and effective in increasing defecation frequency and improving symptoms of constipation of the subjects.

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This study was previously submitted to FDA in Top Health's IMO citizen petition[17] and was considered by the reviewer for cholesterol reduction but not for laxation because the "statistical comparisons of the baseline values between the groups were not reported"[18]. The authors reported that IMO induced a statistically significant increase in the number of bowel movements ($P < 0.05$) and improved the constipation score (Figure 1) by 76.3% ($P < 0.05$). They compared the run-in period to the IMO test period.

Constipation is a common complication for kidney function impaired individuals who are particularly resistant to other therapies. IMO supplementation proved an effective option. IMO induced a significant increase in number of bowel movements ($P < 0.05$) and, hence, improvement in symptoms of constipation.

The authors concluded that 30 g of IMO ingested once per day was well tolerated and effective in increasing defecation frequency and improving symptoms of constipation in individuals with impaired kidney function.

iv. Balance of Evidence

1. Blood Cholesterol Reduction

In FDA's Petition response letter[19], it was stated that BioNeutra Inc. Report (2012)[20] and Chen et al. (2001) did not provide sufficient evidence to demonstrate the beneficial physiological effects on blood cholesterol level reduction. This point is acknowledged, however it is respectfully submitted that the primary objective of the BioNeutra Inc. Report was to evaluate dose tolerance after 4 weeks of treatment. Cholesterol level was a secondary measurement. The non-significant results could be the consequence of an inappropriate experimental design. In the BioNeutra Inc. Report (2012) and Chen et al. (2001), the non-significant difference in the subject's cholesterol level between the two periods could also be explained by the fact that subjects with normal cholesterol level were recruited in these studies. It is obviously harder to demonstrate an effect using this group of subjects.

[17] Docket Number FDA-2016-P-1180

[18] Docket Number FDA-2016-P-1180

[19] Docket Number FDA-2016-P-1180

[20] BioNeutra Inc [unpublished]. Double-blind, randomized, placebo controlled study to investigate the effects of VitaSugar™/VitaFiber™-IMO in healthy adults: final report. Edmonton, AB: BioNeutra Inc. 2012.

2. Laxation

In the response to Top Health Ingredients Inc's petition, it was cited that none of BioNeutra Inc. Report (2012), Bouhnik et al. (2004)[21] nor Kaneko et al. (1993)[22] provided sufficient evidence to demonstrate the beneficial physiological effects on laxation. Both the BioNeutra Inc study and Kaneko et al. (1993) recruited healthy subjects. It is more difficult to demonstrate statistically significant physiological effect on them. In Bouhnik et al. (2004), subjects were given 10g/day in the "pre-screening trial" of 8 days (5g after lunch and dinner). The study subjects reported gastrointestinal symptoms using daily charts which included noting stool frequency. However, the stool frequency data were not presented in the paper. The paper mentions only that "no significant effect was found for the number of stools". There is no discussion or information presented about how stool frequency was measured. The lack of effect with this trial may likely have been the experimental design, although there is so little information, it is hard to say. As with IMO, none of the FDA approved dietary fibers including FOS, GOS, resistant dextrin or inulin, demonstrated any significant effect on laxation in this study.

The 4 studies presented in this petition utilized Taiwanese subjects, but the results can be confidently extrapolated to the US population. As sited in Lin et al. (2005), "in recent years, diet of Chinese people has been influenced by Western diet culture, and intake of sugar, fat and cholesterol has gradually increased, leading to an increase in the population of Chinese people with high cholesterol." Also, constipation is a common complaint of the elderly and hemodialysis patients. Poor chewing ability and a less mobile life style are two reasons of reduced bowel movement in elderly people. Increase in atherosclerosis occurs frequently in hemodialysis patients and they often suffer from constipation due to the low fluid intake, inactivity and the use of aluminum-containing phosphate binders. Diets with dietary fiber to reduce blood lipid level and promote laxation are important. These common health concerns occur in elderly people and hemodialysis patients regardless of their

[21] Bouhnik Y, Raskine L, Simoneau G, Vicaut E, Neut C, Flourié B, Brouns F and Bornet FR. 2004. The capacity of non-digestible carbohydrates to stimulate fecal bifidobacterial in healthy humans: a double-blind, randomized, placebo-controlled, parallel-group, dose-response relation study. *American Journal of Clinical Nutrition* 80: 1658-1664.

[22] Kaneko T, Kohmoto T, Kikuchi H, Shiota M, Yatake T, Iino H and Tsuji K. 1993. Effects of isomaltooligosaccharides intake on defecation and intestinal environment in healthy volunteers. *Journal of Home Economics of Japan* 44: 245-254.

ethnic origins. Thus, the results of these studies are applicable and can be extrapolated to the US population.

Regarding the relevance of the conclusions of the submitted papers to the US population, respected clinical physician, Dr. Levinus A. Dieleman was consulted. He concurred that the conclusions are highly relevant to the US and agreed that enema use did not affect the conclusions that can be drawn on comparing the laxation effects of test diets in comparison to control diets in Chen et al (2001) and Yen et al (2011). All studies presented were further carefully reviewed by noted US fiber expert, Dr. George C. Fahey, who supports the above conclusions and notably that IMO be included as a dietary fiber by FDA. The 4 presented studies' validity is confirmed by the analysis contained in the letters submitted herewith from George C. Fahey, Jr., PhD (Exhibit 5, Appendix of Exhibits, Page 34); and Levinus A. Dieleman, MD, PhD (Exhibit 6, Appendix of Exhibits, Page 37).

v. Chemical Structure

Chemically and structurally speaking, IMO provides the same human health benefits as fructooligosaccharides (FOS) and galactooligosaccharides (GOS) because it is not the monomer in the oligomer that matters, but the fact that the oligomer itself (DP 3 or higher) is indigestible. Fructooligosaccharide is a polymer of fructose linked by β (2-1) linkages with a terminal glucose and where chain length can vary from three to ten fructose units. Galactooligosaccharide is a chain of galactose units with a terminal glucose unit where the chain length could be composed of up to eight monomers. Isomaltooligosaccharide that meets the FDA and Codex fiber definition is a chain of three to ten isomaltose units held together by α (1-6) glycosidic linkages.

When entering the colon in the undigested state, the oligosaccharides activate mechanisms that result in similar physiological activities. For instance, despite their monomeric differences, all of these oligosaccharides arrive in the colon undigested and all are considered prebiotics. FOS and GOS are approved fibers by FDA based on proven physiological health benefits. Thus, IMO should be classified as a dietary fiber as is the case for FOS and GOS.

vi. Analytical Methods

AOAC 993.21 is the optimum method to use for measurement of the non-digestible carbohydrate content of IMO. The dietary fiber content of IMO was determined twice using this method and the results are 58.1 and 66.6 (Table 3 herein). FDA has clearly stated that methods other than the new 2009.01 and 2011.25 can be used to quantitate dietary fiber content of foods and ingredients (21CFR 101.9(g)(10)).

Table 3: Total Dietary Fiber Content of IMO from Two Accredited North American Commercial Laboratories using AOAC 993.21

	IMO content, %	Oligosaccharides content including isomaltose, %	Isomaltose content, %	Proposed dietary fiber content, %
Lots\ Method	HPLC-RI	AOAC 993.21	HPLC	Calculated value[23]
16012632	90.3*	95.1*	28.5*	66.6
17103131	92.1*	90.0**	31.9*	58.1

*Performed by Labs-Mart Inc., Alberta, Canada
** Performed by American Testing Lab, California, USA

Over the years, numerous dietary fiber tests have been approved by AOAC with the goal of more accurate measurement of the fibers. These methods include AOAC 993.21, 2001.03, 2002.02, 985.29, 991.43, 2009.01, 2011.25, and many others. A rapid version of 2009.01 is also being developed. These methods invariably include an enzymatic-gravimetric component and/or a liquid chromatographic component that is used to enhance the methods' versatility to accurately quantitate a wide variety of non-digestible carbohydrates. While the modifications incorporated in 2009.01 and 2011.25 improved upon some of the shortcomings of many of the old methods, these new methods do not accurately measure IMO, resistant starch (RS4, RS2), FOS or several other fibers. Also, although the new 2009.01, 2011.25, and rapid method alleviate many of the shortcomings of previous methods, at least one major issue continues to exist. These new AOAC- and FDA-approved methods replaced bacterial α-amylase used in 991.43 and 985.29 with porcine α-amylase to digest the starch fraction but have not been demonstrated to accurately mimic the α-amylases found in the human gut. Empirically, slight differences could and almost certainly do exist and, consequently, as stated in the literature and discussed in scientific committee

[23] Dietary fiber contents are calculated by subtracted the amount of isomaltose from total oligosaccharides content.

meetings (e.g. AACCI fiber committee), they could possibly be over-digesting some non-digestible carbohydrates such as RS4, FOS, and IMO, leading to under-reporting of the true non-digestible carbohydrate content.

A supporting study published by McCleary and coworkers (2018)[24] found that the total dietary fiber (TDF) content of IMO, as determined using AOAC 2009.01, AOAC 2009.01 + amyloglucosidase, and the rapid method, paired with the increase in amyloglucosidase, decreased from 29.0% to 10.8%, thus demonstrating the lack of ability of AOAC 2009.01 to measure IMO with the rapid test method. The founder of this method is not clear on explaining the reasons why the IMO level dropped analytically in the rapid test vs the original 2009.01.

In addition to an inability to correctly measure the DP3 and greater fractions of resistant IMO, AOAC 2009.01 has shown high inter-lab variability (as may be the case with other fibers). IMO samples were sent to 4 accredited North American laboratories for analysis using AOAC 2009.01. The results range from 3.3% to 34.1%, with an absolute difference of 30.8% or a 10-fold difference (see Table 4 below).

Table 4: Total Dietary Fiber Content of IMO from Four Accredited North American Commercial Labs using AOAC 2009.01

Labs	**Test Report No.**	**Method**	**TDF, %**
Silliker	MRK-37092554-0	AOAC 2011.25	10.5
Medallion*	2011-MED-13241	AOAC 2009.01	34.1
Megazyme	08-Sep-13	AOAC 2009.01	24.1
Labsmart*	39506-1	AOAC 2009.01	3.3

*Denotes same lot

The test results are comprised of three lots with the two asterisked lots being the same lot with the same lot assaying to yield the highest and lowest TDF values (34.1% and 3.3% respectively). The manufacturer's process is highly controlled with a total IMO standard deviation among lots of less than 1%. Thus, the dramatic variation in inter-lab results cannot be attributed to inter-lot variability.

[24] McCleary BV, Sloane N and Draga A. 2015. Determination of total dietary fibre and available carbohydrates: a rapid integrated procedure that simulates in vivo digestion. *Starch* 67: 860-883.

AOAC 2009.01, 2011.25, and the rapid version do not mimic the physiological conditions in the human gastrointestinal tract. The two high temperature steps include 20 min at 95-100ºC to inactivate α-amylase and amyloglucosidase and 30 min at 60ºC for protease treatment. These high temperature treatments that are atypical of human physiological conditions may artificially reduce the quantitated concentration of the fiber portion of IMO. Another problem is the reliance on a fungal enzyme as a proxy for human enzymes. Further, enzymes such as α-amylases from different species are widely known to vary slightly in specificity. The fungal enzyme does not reflect human physiological conditions and, hence, is not able to accurately measure some of the new fibers in the market such as fructans (inulin and FOS), polydextrose, and Fibersol® (Zielinski et al., 2013)[25]. Compared to the enzyme levels observed in the human gut, the rapid method developed based on AOAC 2009.01 dramatically increases the enzyme levels used to reduce the incubation time with pancreatic α-amylase and amyloglucosidase hydrolysis to 4 hours in order to mimic the transit time through the human gastrointestinal tract. However, it is not known if these higher enzyme levels accurately reflect levels of these enzymes found in the human gut. A supporting study published by McCleary and co-workers (2018) reported that the TDF content of IMO determined using AOAC 2009.01, AOAC 2009.01 + amyloglucosidase, and the rapid method are 29.0%, 16.3%, and 10.8%, respectively. These results are proof of the lack of ability of AOAC 2009.01 to precisely quantify IMO using the rapid test method and the others.

FDA has recognized this issue and provided a solution in 21 C.F.R. § 101.9 (g)(10) where it has proposed Records Requirements for Manufacturer's to keep records where no appropriate AOAC method is available. Specifically, section N (3.) states that, "Current § 101.9(g)(2) sets forth requirements for composite sampling and analysis to determine compliance with labeling declarations. Unless a specific analytical method is identified by regulation, composites are analyzed by the appropriate AOAC method (15th edition) or, if no AOAC method is available or appropriate, by other reliable and appropriate analytical procedures." In the same document, FDA also stated that, "In such a case, (presumably where no AOAC method is available) under § 101.9(g)(9), firms must submit a request in writing to FDA for the use of an alternative means of compliance or for a labeling exemption."

[25] Zielinski G, DeVries JW, Craig, A, and Bridges AR. 2013. Dietary fiber methods in Codex Alimentarius: Current status and ongoing discussions. *Cereal Foods World* 58:1-5.

The TDF of IMO may be correctly measured using methods including AOAC 993.21 and several similar validated HPLC methods. By using the validated HPLC test methods, the DP3 and higher fractions can be easily identified and accounted for. Manufacturers in China have two validated HPLC methods (short and long versions) that the Chinese government requires them to use to quantitate DF levels. McCleary and co-workers (2015) also employ HPLC for determining the TDF content of FOS. The petitioner has had experience with quantification of hundreds of IMO commercial lots over nearly a decade using an HPLC method. It is an accurate, reliable, validated test that correlates nearly perfectly with other HPLC methods and is a more suitable method for measuring TDF in IMO vs. the new AOAC methods (2009.01, 2011.25). Alternatively, AOAC 993.21 measures all oligosaccharides including isomaltose. The oligosaccharides contents from 2 lots are presented in Table 3 above. The results show that the AOAC 993.21 provides comparable results with HPLC-RI. AOAC 993.21 over-represents TDF under FDA's new guidelines since a commercial isomaltose mixture includes a DP 2 fraction. To arrive at an accurate TDF value, the isomaltose may simply be subtracted: TDF in the USA and per Codex is quantified using AOAC 993.21 minus the concentration of the DP2 fraction as shown in Table 3 above.

vii. Summary of Regarding Proof of Physiological Effects Beneficial to Human Health

Isomaltooliogosaccharide is chemically and structurally similar to FOS and GOS and similarly provides human health benefits. In the USA, AOAC 993.21 or, in countries other than the USA, additional validated HPLC tests, can accurately determine the TDF content of IMO. To address FDA's concerns and comments on Docket Number FDA-2016-P-1180, four studies are submitted in this citizen petition including a previously unsubmitted, translated paper (Lin et al., 2005).

Three studies demonstrated reductions in blood cholesterol concentrations. Yen et al. (2011) has been accepted by FDA for demonstrating reductions in TC and LDL-C concentrations after IMO supplementation. These results agree with the data presented by Lin et al. (2005), and Wang et al. (2001). Lin et al. (2005) showed that serum TC and LDL-C were decreased significantly after IMO consumption. The statistical data extrapolated from Wang et al. (2001) further illustrate that IMO lowered TC and LDL-C concentrations, and increased HDL-C concentration.

In this citizen petition, four studies demonstrate improved laxation. Lin et al. (2005), demonstrates that after 6 weeks of IMO consumption, the subjects experienced a significant decrease in constipation. Similarly, Chen et al. (2001), showed that

consumption of IMO effectively improved bowel movement frequency and stool output. There was no significant difference in enema use between test and placebo and further, directionally, the frequency of enema use during IMO supplementation was decreased while spontaneous defecation and stool weight were increased. These observations were confirmed by Yen and co-workers (2011) who showed that IMO supplementation to a low-fiber diet improved bowel movement frequency. The petitioner's interpretation is that they are both relevant, well designed and demonstrate a significant laxation effect and that enema use did not negatively impact nor influence the outcome; thus, four strong data points prove that IMO improves laxation. Lastly, the statistical data in the Wang et al. (2001) paper, show that, IMO was effective in statistically increasing the number of bowel movements and improving the constipation score ($P < 0.05$). This study shows that IMO supplementation provides an effective option for individuals with impaired kidney function to increase bowel movement frequency and improve symptoms of constipation.

These studies clearly establish the physiological benefits of IMO to humans to improve laxation and reduce blood cholesterol concentrations consistent with the physiological benefits associated with FDA-recognized dietary fibers. Thus, petitioner respectfully request FDA to recognize IMO as a dietary fiber.

III. Conclusion Respecting Applicability Under The Proposed Regulation

As demonstrated in paragraphs 2.a. and 2.b. above (and the subparts of each), Isomaltooligosaccharide satisfies all of the definitional requirements of "dietary fiber" required by 21 C.F.R. §101.9(c)(6)(i). Accordingly, IMO should be included in the list of dietary fibers set forth in 21 C.F.R. §101.9(c)(6).

C. Environmental Impact

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

D. Economic Impact

An economic impact statement under 21 C.F.R. §10.30(b) is not required at this time.

E. Action Requested of Agency

Petitioner requests the Commissioner determine that

a. *Isomaltooligosaccharide* ("IMO") comes within the definition of dietary fiber stated in 21 C.F.R. § 101.9(c)(6)(i) and,

b. It be included in the list of dietary fibers set forth in 21 C.F.R. §101.9(c)(6)(i).

F. 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 petitioner, which are unfavorable to the petition.

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