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

January 9, 2020

Mr. Kimmo Lucas
Top Health Ingredients Inc.
10045-81 Avenue
Edmonton, AB
T6E 1W7 CANADA

Re: Docket Number FDA-2019-P-1640

Dear Mr. Lucas:

This letter is in response to your citizen petition dated March 4, 2019, requesting that the Food and Drug Administration (FDA or we) "include ***Isomaltooligosaccharide*** in the 21 CFR § 101.9(c)(6)(i) list of dietary fibers" (emphasis in original). (Citizen Petition from Kimmo Lucas, Top Health Ingredients Inc. ("THI"), submitted to the Division of Dockets Management, Food and Drug Administration, dated April 4, 2019 ("Petition") at page 1).

We note that this is the second citizen petition you have submitted requesting that FDA amend 21 CFR 101.9(c)(6)(i) to include isomaltooligosaccharide ("IMO") among the isolated or synthetic non-digestible carbohydrates that have been determined by FDA to have physiological effects that are beneficial to human health, and therefore include IMO in the calculation of the amount of dietary fiber on the Nutrition Facts label. We denied your first citizen petition (see Docket No. FDA-2016-P-1180; dated April 9, 2016) ("original petition"), as explained in a letter ("original denial letter") from FDA to Mr. Kimmo Lucas, dated June 13, 2018.[1]

The only reference in the FDA appendix of the petition not included with the original petition is the English translation of the article by Lin et al., 2005.[2] The other three articles in the FDA appendix (Wang et al., 2001; Yen et al., 2011; and Chen et al., 2001)[3] that were discussed in the petition were also included and discussed in your original petition.

In the *Federal Register* of May 27, 2016, we published a final rule entitled "Food Labeling:

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[1] U.S. Food and Drug Administration, Denial Letter to Top Health Ingredients Inc. (June 13, 2018), available at https://www.regulations.gov/document?D=FDA-2016-P-1180-0046.

[2] Lin S, Lim P, Wang H and Hsiao C. Effects of isomaltooligosaccharide chiffon cake on serum biochemical parameters, constipation, and fecal putrefactive metabolites in hyperlipidemic subjects. *Nutritional Sciences Journal* 2005;30:108-115.

[3] Wang HF, Lim PS, Kao MD et al. Use of isomalto-oligosaccharide in the treatment of lipid profiles and constipation in hemodialysis patients. *Journal of Renal Nutrition* 2001;11:73-79; Yen CH, Tseng YH, Kuo YW 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. *Nutrition* 2011;27:445-450; Chen HL, Lu YH, Lin JJ and Ko LY. Effects of isomalto-oligosaccharides on bowel functions and indicators of nutritional status in constipated elderly men. *Journal of American College of Nutrition* 2001;20:44-49.

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.[4]

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 evidence does not show that the consumption of IMO has a physiological effect that is beneficial to human health.

I. FDA's Consideration of the Scientific Evidence

Your petition requests that FDA add IMO to the list of dietary fibers in 21 CFR 101.9(c)(6)(i) on the grounds that "IMO fits squarely within the statutory definition [of dietary fiber]" (Petition at page 2). You also state that "IMO helps improve laxation and lower [*sic*] blood cholesterol" and that it has "a prebiotic effect, exhibiting the properties of retaining moisture, and producing a bulking effect" (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 discusses the inclusion of studies on diseased populations under certain circumstances as part of our evaluation of the totality of the scientific evidence, 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 and your original petition using the factors identified in the final guidance. In our previous review of your original petition, we evaluated whether the consumption of IMO has the beneficial physiological effects that you had identified as grounds for adding IMO to the list of dietary fibers; these effects included lowering blood cholesterol, increasing frequency of laxation, and improving mineral absorption. We concluded that the strength of the scientific evidence did not show that the consumption of IMO has a physiological effect that is beneficial to human health (original denial letter at page 8).

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[4] For up-to-date information on the additional non-digestible carbohydrates that FDA intends to propose to 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.

In our review of your current petition, we note your intention to "focus exclusively" on the potential physiological effects of IMO consumption on laxation and on blood cholesterol, and "to address [FDA's] specific concerns" with regards to your original petition (Petition at page 4). For example, FDA was unable to draw scientific conclusions from a study by Lin et al. (2005)[5] that we had identified during our review of the literature because this article was published in a foreign language and a verified English translation was not submitted to FDA in accordance with our regulations.[6] In addition, we were unable to draw conclusions about the effects of IMO on total cholesterol in the study by Wang et al. (2001) because statistical comparisons of the baseline values between groups were not reported. Thus, it was not clear whether baseline values between the treatment and control groups in this study were significantly different from each other. You state that "[t]ranslation of a relevant reference that was previously available only as an original foreign language is attached" (Petition at page 4). In referring to this translated article, you say that "the petitioner has added another study[7] that corroborates the original proposal that IMO be considered a dietary fiber" (Petition at page 4).

This response letter addresses the additional data and information provided in the current petition that was not included in your original petition and provides our current assessment of the overall strength of the scientific evidence.

Blood Cholesterol

In our original denial letter,[8] we stated that we could draw conclusions from four human intervention studies that evaluated the effect of IMO consumption on blood cholesterol.[9] We also stated that we could not draw scientific conclusions from the study by Lin et al. (2005) because it was published in a foreign language.

Your petition includes three studies (Lin et al., 2005; Wang et al., 2001; Yen et al., 2011) "to demonstrate the physiological benefits of IMO to humans relative to reductions in total cholesterol (TC) and LDL cholesterol (LDL-C)" (Petition at page 5). As mentioned above, the

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[5] See *supra* note 1.

[6] As stated in 21 CFR 10.20(c)(2), "If a part of the material submitted is in a foreign language, it must be accompanied by an English translation verified to be complete and accurate, together with the name, address, and a brief statement of the qualifications of the person making the translation. A translation of literature or other material in a foreign language is to be accompanied by copies of the original publication."

[7] This additional study is the verified English translation of the study by Lin et al. (2005). In our original denial letter, we identified an additional study that was not published in English and for which we did not have a verified English translation: Lee MR, Lee KA, Ly SY. Improving effects of fructooligosaccharide and isomaltooligosaccharide contained in sponge cakes on the constipation of female college students. *Journal of the Korean Society of Food Science and Nutrition* 2003;32:621-626. We have since been able to obtain an English-language translation of the study by Lee et al., 2003. However, scientific conclusions could not be drawn from this study because it lacked an appropriate control group and statistics were not conducted between the treatment and control groups.

[8] See *supra* note 1.

[9] 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; Chen et al., 2001; Wang et al., 2001; Yen et al., 2011. See *supra* note 1 for full study descriptions.

studies by Wang et al., 2001 and Yen et al., 2011 were included in our evaluation of your original petition.[10]

The study by Lin et al. (2005) was a randomized, double-blind, parallel study in hyperlipidemic college students (mean age = 17 years). Participants consumed chiffon cake with either IMO (n = 22; 10 g of IMO; baseline total- and LDL-cholesterol = 220.7 ± 24.2 and 139.9 ± 33.0 mg/dL, respectively) or sucrose (control; n = 20; 0 g of IMO; baseline total- and LDL-cholesterol = 215.0 ± 12.1 and 139.4 ± 11.9 mg/dL, respectively). After six weeks, total-cholesterol (201.7 ± 21.1 vs. 217.8 ± 15.6 mg/dL) and LDL-cholesterol (121.9 ± 27.1 vs 142.2 ± 15.7 mg/dL) were statistically significantly lower in the IMO group compared to the control group ($P < 0.05$ for both).

In your petition, you state that, in the study by Yen et al. (2011), "it is hard to determine whether 4 weeks are enough as a washout period especially after 8 weeks of IMO consumption" (Petition at page 6). In this study, nursing home residents (n = 13; mean age = 83 years) with chronic constipation were provided IMO for two sequential four-week periods (IMO 1 and IMO 2).[11] A run-in period and four-week period during which the subjects consumed a placebo (Control 1) preceded the IMO treatment periods. After the eight weeks of IMO supplementation, there was a four-week period where IMO was not provided (Control 2). We consider three weeks to be the minimum duration for evaluating the effect of a dietary intervention on serum LDL-cholesterol.[12] This duration allows for study periods that are sufficiently long enough for the endpoint (i.e., measurement of blood cholesterol) to stabilize. In our evaluation of this study, we included the comparisons of the four-week periods without IMO (Control 1 and Control 2) to the four-week IMO l treatment period. We did not consider in our evaluation the IMO 2 period because this represented eight consecutive weeks of treatment, which was not the same duration as the control periods.[13] Compared with Control I, total- and LDL-cholesterol were significantly lower after IMO 1 (10% and 8%, respectively) ($P < 0.05$). Total- and LDL-cholesterol were not significantly different when comparing IMO l to Control 2 ($P > 0.05$). Therefore, our evaluation of this study has not changed in that the results were mixed (one comparison showed a statistically significant lowering of total- and LDL-cholesterol with IMO and one comparison showed no statistically significant effect on total- and LDL-cholesterol).

With regards to the study by Wang et al. (2001), you state that "the Agency's questions on statistics have been addressed" (Petition at page 4) and "[t]o respond to FDA's concern, Top Health retained a statistician" (Petition at page 8). We carefully reviewed the statistical analysis provided in Tables 1 and 2 of the petition (Petition at page 9). However, the petition lacked sufficient details describing the analysis, and we could not replicate the steps taken by your

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[10] See *supra* note 1.

[11] See *supra* note 1 for full study description.

[12] U.S. Food and Drug Administration, 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) (February 2018), available at https://www.fda.gov/media/101183/download. See also ``Memorandum to the File: Scientific Review of the Beneficial Physiological Effects of Non-Digestible Carbohydrates for Meeting the FDA Definition of Dietary Fiber," 2016. 81 FR 33742 at 33856, "Food Labeling: Revision of the Nutrition and Supplement Facts Labels".

[13] See *supra* note 12.

statistician. Therefore, we are unable to determine whether an appropriate analysis was performed. Further, we are unable to draw conclusions from the analysis and unable to draw scientific conclusions about the effects of IMO consumption on total cholesterol from the study by Wang et al. (2001).

Laxation

In our original denial letter, we stated that we could draw scientific conclusions from three human intervention studies that evaluated the effect of IMO on laxation.[14] We also stated that we could not draw scientific conclusions from seven studies for one or more of the following reasons: (1) the study was published in a foreign language and a verified English translation was not submitted to us in accordance with our regulations (Lee et al., 2003; Lin et al., 2005); (2) the study lacked an appropriate control group or statistics were not reported between treatment and control groups (Liu et al., 1994; Qing et al., 2003; Wang et al., 2001); and/or (3) the subjects used enemas and/or laxatives during the fecal collection period, so the independent effects of IMO could not be evaluated (Chen et al., 2001; Yen et al., 2011).[15] As noted above, you have since submitted, as part of your petition, a translation of the study by Lin et al., 2005, and we have since obtained a translation of the study by Lee et al., 2003. However, scientific conclusions could not be drawn from Lee et al., 2003, because it lacked an appropriate control group and a statistical analysis was not reported comparing the treatment and control groups.

The study by Lin et al. (2005) provided data on constipation score, rather than on measures of improved laxation (i.e., elimination of fecal waste/fecal output), as discussed in our final guidance. Such measures include reduced transit time of food through the intestinal tract and increased rates of defecation (e.g., number of stools per day, fecal weight per day).[16] The constipation score[17] is not recognized by FDA as an endpoint for evaluating improved laxation.[18] Therefore, we did not consider the study by Lin et al. (2005) in our evaluation of the effect of IMO consumption on laxation.

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[14] BioNeutra Inc, 2012; Bouhnik Y, Raskine L, Simoneau G et al. The capacity of non-digestible carbohydrates to stimulate fecal bifidobacteria in healthy humans: a double-blind, randomized, placebo-controlled, parallel-group, dose-response relation study. *American Journal of Clinical Nutrition* 2004; Kaneko T, Kohmoto T, Kikuchi H et al. Effects of isomalto-oligosaccharides intake on defecation and intestinal environment in healthy volunteers. *Journal of Home Economics of Japan* 1993. See *supra* note 1 for full study descriptions.

[15] Lee et al., 2003; Lin et al., 2005; Liu S, Ling Y, Tsai C. Biotechnically synthesized oligosaccharides and polydextrose reduce constipation and putrefactive metabolite in the human. *Journal of the Chinese Nutrition Society (Taiwan)* 1994;19:221-232; Qing G, Yi Y, Guohong Jet al. Study on the regulative effect of isomaltooligosaccharides on human intestinal flora. *Journal of Hygiene Research* 2003;32:54-55; Wang et al., 2001; Chen et al., 2001; Yen et al., 2011.

[16] See *supra* note 12.

[17] Constipation score, as defined in Lin et al. (2005), is based on the assignment of values to the number of times a subject experiences episodes of "no defecation," "incomplete defecation," and "smooth defecation."

[18] As discussed in our final guidance, we use subjective measures of laxation, such as self-reported ease of defecation and reduced complaint of difficulty in defecation, to evaluate how changes in these subjective measures are associated with changes in the elimination of fecal waste [see *supra* note 12 at 10]. However, we do not consider subjective measures (such as "incomplete defecation" and "smooth defecation"), which are included in the constipation score, as valid endpoints of laxation.

With regards to the study by Wang et al. (2001), you incorrectly state that the reason we did not consider this study in your original petition was because the "statistical comparisons of the baseline values between the groups were not reported" (Petition at page 15). As stated in our original denial letter to your original petition, and noted above, scientific conclusions could not be drawn from this study because it lacked an appropriate control group or statistics were not reported between treatment and control groups. Specifically, statistical comparisons were made between the beginning and end of the treatment period, but not between the treatment and control groups. As discussed in our final guidance,[19] scientific conclusions cannot be drawn when statistical analyses are not performed between the control and treatment. Furthermore, the study reports constipation score, which we do not consider as a valid endpoint for evaluating improved laxation, as discussed above. It is also not clear if the control group used in the study is appropriate for the evaluation of laxation. The paper describes the control group as "age- and sex-matched 30 [hemodialysis] patients (11 men and 19 women with a mean age of 60.1 ± 10.8 years) with similar lipid profiles" and does not describe the group as having chronic constipation, as is the case for the treatment group. As discussed in our final guidance, the control and treatment groups should be similar, otherwise it is not possible to ascertain whether changes in the endpoint of interest were due to the added non-digestible carbohydrate or to unrelated and uncontrolled extraneous factors.[20]

We carefully considered the letters that were submitted with your petition. Both letters concluded that the use of laxative/enema treatments in the studies reported by Yen et al. (2011) and Chen et al. (2001) had no bearing on the study results because the number of laxative/enema treatments used were not statistically different between the control and experimental phases of the study. The studies by Yen et al. (2011) and Chen et al. (2001) were included with your original petition and were previously evaluated by FDA. These were non-randomized studies conducted in nursing home residents with chronic constipation, in which subjects were permitted to use laxative and/or enema treatments during the intervention. In Yen et al. (2011), the authors noted that "enema usage was not tightly controlled in this study and they could be administered on request of subjects who had relied on them for a long period of time." We stated in our original denial letter that scientific conclusions could not be drawn from the studies by Yen et al. (2011) and Chen et al. (2001) because the subjects in both studies used enemas and/or laxatives during the fecal collection period, so the independent effects of IMO could not be evaluated (original denial letter at page 5).

In our final guidance, we discuss the importance of having a sufficient amount of time for collecting stool samples.[21] There is considerable variability in colonic function (e.g., transit time), both within and between individuals.[22] For most healthy subjects (e.g., individuals without constipation), five days allows for passage of most material for the measuring of spontaneous defecation (i.e., without the use of enemas); however, individuals with constipation

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[19] See *supra* note 12.
[20] See *supra* note 12.
[21] See *supra* note 12.
[22] Wyman JB, Heaton KW, Manning AP et al. Variability of colonic function in healthy subjects. *Gut* 1978;19:146-150.

may have prolonged transit.[23] In the studies by Chen et al. (2001) and Yen et al. (2011), the use of laxative and/or enema treatments throughout the fecal collection period does not allow for an adequate duration of collection, without the use of laxative/enema treatments, for the measuring of spontaneous defecation. Without an adequate collection period, excluding the use of laxative/enema treatments, the independent effect of IMO cannot be evaluated due to the effect of laxative/enema treatments on laxation.[24]

In addition to the inadequate collection time without the use of laxative/enema treatments, statistically comparing the number of laxative/enema treatments between study phases, particularly in these small (n = 7 and n = 13), unblinded and non-randomized[25] studies that were not well controlled (e.g., laxative/enema treatments were administered if spontaneous defecation did not occur in three days and/or as requested by the subjects, and different types of laxative/enema treatments were permitted), would not necessarily negate a potential confounding effect of these treatments on measures of laxation. Furthermore, the number of laxative/enema treatments used throughout the study periods was reported, but the use of these treatments during each fecal collection period was not reported. Therefore, it is unclear if the usage (e.g., frequency, type, timing, and/or dose) of laxative/enema treatments during the fecal collection periods at the end of each study phase was different between the treatment and control phases of the studies, which is important due to the acute nature of the effects of laxative/enema treatments. In addition, in the study by Yen et al. (2011), different types of laxative/enema treatments were permitted, which could affect their impact on measures of laxation (e.g., frequency of bowel movements and fecal output), as different laxative/enema treatments vary in their onset and mechanisms of action (i.e., how they act and how long they take to act).[26] There are also different factors that can impact the effect of enemas (e.g., amount of applied fluid and substances included such as glycerol).[27] The design of these studies did not allow for the control of these different variables related to the use of laxative/enema treatments, which can affect their impact on laxation. For these reasons, we have not changed our view that conclusions cannot be drawn from studies if enemas and/or laxatives are used during the fecal collection period, as the independent effect of IMO consumption on laxation cannot be evaluated (original denial letter at page 5).

In our final guidance, we also discuss studies conducted in subjects who have a disease, condition, undergo a surgical procedure, or receive a treatment that could influence the

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[23] Camilleri M, Thompson WG, Fleshman JW et al. Clinical management of intractable constipation. *Annals of Internal Medicine* 1994;121:520-528; Evans RC, Kamm MA, Hinton JM et al. The normal range and simple diagram for recording whole gut transit time. *International Journal of Colorectal Disease* 1992;7:15-17; Lembo A & Camilleri M. Chronic constipation. *The New England Journal of Medicine* 2003;349:1360-8.

[24] Dinning PG, Hunt L, Lubowski DZ et al. The impact of laxative use upon symptoms in patients with proven slow transit constipation. *BioMed Central Gastroenterology* 2011;11:1-7.

[25] Blinding and randomization reduce the likelihood of potential bias and minimize the effects of other variables or confounders on the results. Confounders are factors that are associated with both the physiological benefit in question and the intervention, and if not controlled for, prevent an investigator from being able to conclude that an outcome was caused by an intervention. See *supra* note 12.

[26] Portalatin M, Winstead N. Medical management of constipation. *Clinics in Colon and Rectal Surgery* 2012;25: 12–19.

[27] Klaschik E, Nauck F, Ostgathe C. Constipation – modern laxative therapy. *Supportive Care in Cancer* 2003;11:679-685.

physiological effect being studied. The subjects in Chen et al. (2001) and Yen et al. (2011) were elderly nursing home residents, with chronic constipation and long-term use of laxative/enema treatments,[28] who were permitted to receive laxative/enema treatments throughout the studies. We cannot draw scientific conclusions from such studies unless evidence is available that allows for extrapolation to subjects who have not received a treatment that could influence the endpoint being measured. Due to the lack of evidence demonstrating that IMO consumption has a beneficial physiological effect on laxation in subjects who are not using laxative/enema treatments, extrapolation of the results from Chen et al. (2001) and Yen et al. (2011) is not scientifically appropriate.

II. Strength of the Scientific Evidence

We evaluated 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 IMO consumption to human health and, therefore, whether to propose to include IMO as a dietary fiber in the dietary fiber definition.

As mentioned above, in evaluating your original petition, we previously concluded that the strength of the scientific evidence did not show that the consumption of IMO had a physiological effect that was beneficial to human health (original denial letter at page 8). We also noted above that your petition included only one additional study that was not submitted with the original petition (English translation of the article by Lin et al., 2005).

In our review of the petition, there were five publicly available studies (BioNeutra Inc. Report, 2012; Chen et al., 2001; Lin et al., 2005; Wang et al., 2001; Yen et al., 2011) from which scientific conclusions could be drawn that measured blood cholesterol. In the one study in healthy individuals, conducted in Canada, (BioNeutra Inc. Report, 2012) (n = 19; mean age = 42 years; mean baseline cholesterol = 4.81-4.91 mmol/L[29]), there was no statistically significant effect of IMO consumption (36 or 54 g/day) on total- or LDL-cholesterol. Three studies (n = 7 to 20) were conducted in Taiwan in non-healthy individuals, e.g., hyperlipidemic individuals, elderly nursing home residents with chronic constipation, and hemodialysis patients with uremic dyslipidemia. One of these studies (Lin et al., 2005; mean age = 17 years), in hyperlipidemic individuals, reported a statistically significant lowering of total- and LDL-cholesterol with IMO consumption (10 g/day). Two of these studies (Chen et al., 2001; Wang et al., 2001; mean age = 75 and 64 years, respectively) demonstrated that there was no statistically significant effect of IMO consumption (24 or 30 g/day) on total- or LDL-cholesterol, and one study (Yen et al., 2011; mean age = 83 years) had mixed results (22 g/day; one comparison showed a statistically

[28] This population may have numerous lifestyle characteristics that differ from the general U.S. population (e.g., diet, exercise, medication use, and long-term use of laxative/enema treatments) and can impact laxation. As you noted in your petition, this population may have impaired mobility/ability to exercise, and poor chewing ability affecting dietary intake of certain foods, which can both impact laxation (Petition at page 16).

[29] To convert cholesterol values in mmol/L to mg/dl, multiply by 38.7.

significant lowering of total- and LDL-cholesterol with IMO, and one comparison showed no statistically significant effect on total- and LDL-cholesterol).[30] In summary, three of the five studies (BioNeutra Inc. Report, 2012; Chen et al., 2001; Wang et al., 2001) showed no statistically significant effect of IMO on total- and/or LDL-cholesterol, including the study in healthy individuals. One study in hyperlipidemic individuals (Lin et al., 2005) showed a beneficial effect of IMO on total- and LDL-cholesterol, and one study in elderly nursing home residents with chronic constipation (Yen et al., 2011) showed mixed results, with a beneficial effect on total- and LDL-cholesterol compared with one control period, but no statistically significant effect compared with the other control period. Further, the one study conducted in individuals that were the most representative of the general U.S. population (BioNeutra Inc. Report, 2012)[31] found no statistically significant effect of IMO on total- and LDL-cholesterol. We considered whether there was a plausible explanation for the inconsistencies between studies that found a statistically significant effect and studies that found no statistically significant effect. We are unable to find a plausible explanation for the inconsistency 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. Consequently, the strength of the scientific evidence does not support a finding of a beneficial effect of IMO consumption on blood cholesterol.

For laxation, we are unable to include the results from Lin et al. (2005) in our current evaluation because an appropriate endpoint for laxation was not used in this study. Our conclusion—that we are unable to draw scientific conclusions from the studies by Chen et al. (2001) and Yen et al. (2011) because the independent effect of IMO cannot be evaluated for the reasons discussed above—has not changed. We are also not able to draw conclusions from the analysis provided on the study by Wang et al. (2001), for the reasons stated above. However, even if we could, a re-analysis of one study would not be enough to shift the overall strength of the scientific evidence on the effect of IMO consumption on laxation, which is described in detail in your original denial letter.[32] Therefore, the overall strength of the scientific evidence for the effect of IMO consumption on laxation in the petition remains the same as in the original petition, and our conclusion that the strength of the scientific evidence does not support a finding of a beneficial effect of IMO consumption on laxation has not changed.

We disagree with your conclusion that "IMO should be classified as a dietary fiber as is the case for FOS and GOS" (Petition at page 17).[33] We note the following in our final guidance: "The guidance addresses the scientific evaluation of synthetic non-digestible carbohydrates and isolated non-digestible carbohydrate ingredients that are produced as a result of processing foods and other sources, to the extent that the ingredients in and of themselves have a specific chemical

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[30] Baseline cholesterol values were not reported in Chen et al., 2001 and Yen et al., 2011. In Wang et al., 2001, mean baseline total cholesterol was 210 mg/dL and 205 mg/dL in the IMO and control groups, respectively.

[31] This study was conducted in Canada in males and females who were 18-65 years of age and generally healthy. Other studies cited in the petition were conducted in Taiwan in subjects who were hemodialysis patients (Wang et al., 2001), constipated elderly men (Chen et al., 2001), constipated elderly men and women (Yen et al., 2011), and hyperlipidemic college students (Lin et al., 2005).

[32] See *supra* note 1, at 8.

[33] FOS, fructooligosaccharides; GOS, galactooligosaccharides.

structure (carbohydrate composition and non-digestible bond linkages)."[34] In other words, we use chemical structure (carbohydrate composition and non-digestible linkages) when categorizing and evaluating the evidence for each isolated or synthetic non-digestible carbohydrate. Therefore, we separately evaluated the scientific evidence for IMO, FOS (as part of inulin and inulin-type fructans[35]) and GOS. Our conclusions that inulin/inulin-type fructans and GOS have a physiological effect beneficial to human health are based on evaluations of the scientific evidence on the endpoint of bone mineral density and/or calcium absorption[36] (we are not aware of publicly available data on the effect of IMO on these endpoints). As discussed above, our conclusion from the evaluation of the publicly available scientific evidence is that IMO does not have a beneficial effect on laxation and blood cholesterol.

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

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[34] See *supra* note 12, at 5.

[35] FOS was evaluated as part of the category "inulin and inulin-type fructans" because of their common β (2,1) linkages.

[36] See our science review titled "Review of the Scientific Evidence on the Physiological Effects of Certain Non-Digestible Carbohydrates," June 2018. Available at: https://www.fda.gov/downloads/Food/LabelingNutrition/UCM610139.pdf.

We recognize, of course, that new scientific information may become available that demonstrates a beneficial physiological effect associated with the consumption of IMO. Although we are denying your petition, we would consider a new petition from you concerning the consumption of IMO that is based on new scientific information.

Sincerely,

Claudine Kavanaugh, Ph.D., M.P.H, R.D
Director
Office of Nutrition
and Food Labeling
Center for Food Safety
and Applied Nutrition