

February 13, 2017

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

RE: Docket No. FDA-2016-N-3389 for “Evaluation of the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates; Request for Scientific Data, Information, and Comments”

Docket No. FDA-2016-D-3401 for “Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-digestible Carbohydrates Submitted as a Citizen Petition; Draft Guidance for Industry”

Dear Division of Dockets Management,

The Infant Nutrition Council of America (INCA) and the Healthcare Nutrition Council (HNC) are jointly commenting on the US Food and Drug Administration’s (FDA), “Evaluation of the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates; Request for Scientific Data, Information, and Comments” (FDA-2016-N-3389), and “Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-digestible Carbohydrates Submitted as a Citizen Petition; Draft Guidance for Industry” (FDA-2016-D-3401), which were published in the *Federal Register* on November 23, 2016. INCA is an association of manufacturers and marketers of formulated nutrition products, e.g., infant formulas and adult nutritionals, whose member companies produce over 95% of the infant formula consumed in the US.\* HNC is an association representing manufacturers of enteral nutrition formulas, parenteral nutritional formulas, supplies and equipment.†

INCA and HNC appreciate FDA’s efforts to update federal nutrition labeling regulations to reflect the latest scientific evidence and better assist consumers in making healthy dietary choices. In addition, we support the FDA’s desire to promote public health by assuring that sources of dietary fiber provide a beneficial physiological effect to consumers. The formulated nutrition industry has always followed this philosophy in the research, development, and manufacturing of our products. We also thank the Agency for extending and aligning the comment periods for these two dockets.

We are concerned, however, that the FDA has excluded a breadth of evidence from its scientific evaluation of the 26 fibers by not considering studies conducted in many non-healthy populations. We believe these studies should be included in FDA’s evaluation because, per the US Department of Agriculture (USDA) and the US Department of Health and Human Services (HHS), about half of the American population is currently living with a preventable chronic disease.<sup>1</sup> Moreover, the mechanism of action of fiber is consistent across populations and thus can be extrapolated to a healthy population even when studied in non-healthy populations. Excluding data from studies on non-healthy populations unduly narrows the totality of available scientific evidence and could significantly narrow the list of approved dietary fibers.

We are also concerned that if FDA’s list of approved dietary fibers remains narrow due to the exclusion of data from studies of non-healthy populations, there may be unintended consequences from the de-listing of substances that are presently considered dietary fibers and the potential removal of these substances from foods, which are contradictory to the US Government’s public health goal of increasing fiber intake. Additionally, a narrower list could impact the nutrition label reform goal of improving consumers’ ability to make healthier dietary choices through a better understanding of the Nutrition Facts Label (NFL), as the de-listed fibers could stay in the food but not be declared as “dietary fiber” on the label. In this scenario, it would be impossible for a consumer to differentiate a product whose level of “Total Carbohydrate” is

\*INCA members are Abbott Nutrition, Mead Johnson Nutrition, Gerber Products Company and Perrigo Nutritionals.

† HNC members are Abbott Nutrition, B. Braun Medical Inc., Nestle Healthcare Nutrition and Nutricia North America.

composed solely of starch compared with one whose level of “Total Carbohydrate” is composed of one or more non-digestible carbohydrates, thus providing a lower glycemic impact.

As associations representing companies that manufacture nutrient-dense formulas for supplemental or sole source nutrition for infants and individuals who cannot meet baseline nutrient intakes or are at risk of or suffering from malnutrition, we are concerned that a narrow fiber list could also result in unintended consequences to fiber-fortified formulas. These therapeutic nutritional formulas, often referred to as Oral Nutritional Supplements (ONS) in the literature, can be orally or tube fed as needed.<sup>2,3</sup> Decades of preclinical and clinical research and product development have gone into the development of these formulas and the specific fibers used to ensure tolerance, efficacy, and suitability for oral feeding or, when indicated, tube feeding. The fibers on FDA’s current approved list are not suitable for these types of liquid nutritional formulas. Furthermore, medical risks could result from patient confusion and misuse of a product if a fiber is no longer appropriately declared as such on the NFL.

We also ask that the FDA consider including the following suggested changes in its scientific review.

**A. We recommend FDA include clinical data conducted in non-healthy individuals in their scientific evaluation of the beneficial physiological effects of isolated or synthetic non-digestible carbohydrates**

FDA has emphasized, “Declarations made on a Nutrition Facts label are intended for the general healthy population,” (81 FR 84516). FDA thus indicated that they would consider data in subjects who have a disease associated with the physiological effect of interest only if the evidence demonstrates that it is appropriate to extrapolate to individuals who do not have the disease (81 FR 84516). As a result, in FDA’s scientific review of an additional 26 fibers, many studies on isolated and synthetic fibers that show a physiological benefit in non-healthy individuals are being excluded from the evidence pool (81 FR 84595). However, it is not clarified why the mechanism of dietary fiber in these populations could not be extrapolated to a healthy population. For example, this approach has led to the exclusion of studies which demonstrated a dietary fiber’s physiological benefit in reducing blood glucose levels in **subjects with diabetes** (as opposed to a non-diabetic population) as well as exclusion of studies which demonstrated a dietary fiber’s physiological benefit in improving laxation in **subjects who suffer from fecal incontinence, had chronic constipation, and/or had irritable bowel syndrome** (as opposed to healthy, regular subjects).

This narrow approach in evaluating the scientific literature ignores the reality that about half of the US population has a preventable chronic disease, which was acknowledged by the USDA and HHS in the 2015-2020 Dietary Guidelines for Americans.<sup>1</sup> Furthermore, the Dietary Reference Intakes Committees of the US and Canadian governments recently held a workshop on “Options for Consideration of Chronic Disease Endpoints for Dietary Reference Intakes.”<sup>4</sup> During this workshop, they considered whether and/or how chronic disease endpoints can be incorporated into the setting of Daily Reference Intake (DRI) values which have traditionally been developed based on the needs of a “healthy” population. We believe that FDA should consider the outcomes of both the Dietary Guidelines and the DRI workshop in its further rulemaking activities on the subject of dietary fiber. As millions of Americans are considered to be non-healthy and buy food products that will be affected by the new Nutrition Facts label regulations, FDA should include studies from non-healthy populations when evaluating ingredients and foods that will be impacted by the regulations.

Perhaps even more germane is the fact that the mechanism of action of dietary fiber is consistent across healthy and non-healthy populations. As such, studies conducted to ascertain the beneficial physiological effect of fiber in a non-healthy population can and should be extrapolated to healthy populations. For example, it has long been known that viscous fibers can attenuate glycemic response.<sup>5-7</sup> Research has shown that viscous fibers attenuate glycemic response by delaying gastric emptying and slowing glucose absorption from the small intestine.<sup>8,9</sup> The scientific community attributes comparable directional effects across all populations (healthy as well as non-healthy populations, including people with diabetes) due to this viscosity-based mechanism of action. In fact, viscous fibers already recognized as dietary fiber by

FDA, such as guar gum and oat beta-glucans, have been shown to attenuate glycemic response in both healthy individuals and people with diabetes.<sup>10-12</sup>

In the case of a beneficial physiological effect on regularity/laxation, fiber must meet two prerequisites to provide a significant benefit, as outlined by McRorie and McKeown (in press). First, the fiber should be relatively resistant to fermentation by the microorganisms that inhabit the large bowel. Second, the poorly fermented fibers should retain a high capacity to hold water. Such fibers would increase stool bulk and result in soft, easy-to-pass stools. Fibers with these attributes support bowel function across populations due to these mechanisms of action (*i.e.*, in healthy populations as well as in populations with fecal incontinence, constipation, irritable bowel syndrome, etc.). Psyllium is a dietary fiber currently recognized by FDA that possesses such attributes and has been shown to improve bowel function in various subjects, healthy and non-healthy.<sup>13-15</sup> Consistent with the dietary fibers currently recognized by FDA in 21 CFR 101.9, many of the fiber substances currently under evaluation (Docket No. FDA-2016-N-3389) demonstrate beneficial physiological effects in both healthy and non-healthy populations. These beneficial physiological effects are well-documented in the individual citizens petitions submitted to FDA by fiber manufacturers, as well as submissions by these same manufacturers to Docket No. FDA-2016-N-3389. These submissions contain additional comments and data pertinent to the review but not yet included in FDA's draft scientific evaluation.

In 2001, the Institute of Medicine (IOM) proposed definitions for dietary fiber. For this work, IOM considered the entire breadth of scientific literature for dietary fiber, including data in healthy and non-healthy populations, as it relates to the evaluation of beneficial physiological effects. While IOM considered disease risk reduction for healthy populations only in establishing DRIs in 2002, the data for non-healthy populations was included in its scientific evaluation of the beneficial physiological effects of fiber for purposes of defining dietary fiber.<sup>6,7</sup> Furthermore, IOM directly recognized a consistent mechanism of action across populations.

In their 2001 report on proposed dietary fiber definitions, IOM stated, "[t]he role of high fiber diets in reducing risk for Type 2 diabetes mellitus and for treatment of both forms of diabetes also relates to viscosity. Viscous fibers from food reduce glycemic response better than sources rich in non-viscous fibers...and increase insulin sensitivity. Increased viscosity results in slower stomach emptying, slower rate of absorption, and changes in the composition of colonic microbial flora... The beneficial physiological effects of viscous fibers on blood glucose concentrations have been consistently demonstrated for over 25 years and are supported by more mechanistic studies." IOM recognized the contribution of a viscosity-related mechanism of action in reducing risk for diabetes for healthy populations and diabetes populations alike. In 2002, IOM conducted a scientific evaluation of many isolated and synthetic fibers in order to explore physiological effects consistent with their proposed definition of dietary "functional fiber."<sup>7</sup> IOM reviewed studies for both healthy and non-healthy populations, including, but not limited to, people with type-2 diabetes, idiopathic constipation, irritable bowel syndrome, and hypercholesterolemia. These two IOM reports are the basis upon which FDA has aligned its new dietary fiber definition on the basis of physiological benefit, and as such, it is unclear why FDA would deviate from the scientific evaluation conducted by IOM and question whether a fiber's mechanism of action is the same in healthy and non-healthy populations.

In addition to IOM, other authoritative scientific organizations have established clinical nutrition recommendations for fiber in non-healthy populations, indicating recognition that fiber plays a comparable role in beneficial health outcomes. For example, the recommendations from the American College of Gastroenterology include use of soluble fiber and psyllium in the medical nutrition therapy for symptom relief of Irritable Bowel Syndrome.<sup>16</sup> Additionally, in their nutrition therapy recommendations for adults with diabetes, the American Diabetes Association recommends people with diabetes consume at least the amount of dietary fiber recommended for the general public.<sup>17</sup>

While the mechanism of action of the fiber is consistent across healthy and non-healthy populations, the detection of a significant effect of fiber, such as improvement in condition, is generally more statistically efficient when using a non-healthy population than an already-healthy population in which fiber helps maintain existing health status. For example, it may take a significantly larger population size and length

of time to detect a statistically significant change in laxation in a population with already regular stools compared to detecting a statistically significant improvement in laxation in a population with constipation. The selection of a non-healthy population can help attain the required statistical power in a clinical trial with a much smaller sample size. Additionally, the potential public health benefit would be greatest for those who have lower intakes or for compromised populations.

This concept is well-recognized by FDA and we encourage the Agency to include those studies conducted in non-healthy populations for the same considerations set out in FDA's "Draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products".<sup>18</sup> In this guidance document, enrichment is defined to be the prospective selection of a study population based on a patient characteristic that makes it more likely to detect a treatment effect relative to an unselected population. Strategies for enrichment include selection of subjects with the disease that the product is intended to treat, subjects with high rate of disease progression, or any other characteristic suggestive of a treatment response. Sponsors routinely employ these strategies in clinical trial design as a way of increasing study power (e.g., minimizing variability through decreased heterogeneity) and decreasing the required sample size (e.g., optimizing the absolute difference between groups). As the draft guidance asserts, "...there are many reasons to use such designs, including an enhanced benefit-risk relationship if a population with an increased likelihood of response can be identified, and efficiency in drug development, as smaller studies can often be used to demonstrate effectiveness." We maintain that these same reasons apply to nutritional studies to ascertain whether a non-digestible carbohydrate provides a beneficial physiological effect. That is, studies of "non-healthy" populations – such as individuals with constipation in the case of laxation or individuals with diabetes in the case of attenuating blood glucose response – are designed as such to increase study power and decrease the required sample size.

Similarly, the concept of extrapolating data from a non-healthy population to a healthy population is not without precedent. Health claims are statements about substance/disease relationships and are directed to the general population with the intent to assist consumers in maintaining healthful dietary practices which reduce the risk of the disease. In FDA's "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final," FDA notes that studies conducted in subjects who have the disease that is the subject of the disease risk reduction health claim can be considered if it is scientifically appropriate to extrapolate to individuals who do not have the disease on the following basis: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations and (2) the substance affects these mechanisms in the same way in both diseased and healthy people.<sup>19</sup> Thus, FDA has allowed for a broader evidence pool for health claims when the mechanism of action is consistent across populations. We therefore suggest the same be applied for the scientific evaluation of the 26 fibers. However, if FDA continues to differentiate between the evidence required for labeling of dietary fiber versus health claims, we urge the Agency to provide clear direction on how the clinical evidence needed to substantiate label declarations differs from that needed to support a health claim.

We encourage FDA to include studies conducted in non-healthy populations for its scientific review of digestible and non-digestible carbohydrates. The mechanism of action for dietary fiber is consistent across populations and data in non-healthy populations can and should be extrapolated to healthy populations in the interest of public health. Therefore, such studies should be included in FDA's scientific review. The exclusion of evidence in non-healthy populations will result in an unnecessary narrowing of the evidence pool because studies which demonstrate a beneficial physiological effect in non-healthy populations will not be considered. Furthermore, exclusion of such data could inadvertently discourage research on the beneficial physiological effects across a broader American population, including non-healthy populations.

**B. We encourage FDA to consider the following unintended consequences of a narrowed fiber list (i.e., de-listing fibers commonly used in foods today due to the narrowing of the scientific evidence)**

If the FDA does not recognize “fiber substances” that are currently used in foods, this will likely result in either removal of the fiber from much of the food supply or consumer confusion on these ingredients.

a. De-listing fibers could result in removal of the fiber substance.

By means of the new regulations, FDA aims to increase the amount of dietary fiber Americans consume in their diets because of the beneficial effects cited by the Institute of Medicine on cardiovascular health. The new fiber guidance and scientific review, however, may ultimately limit the number of “dietary fibers” food manufacturers can use to fortify a food. As a result, companies may decide to remove the fiber ingredients due to cost and the inability to communicate the fiber content to consumers. This would in turn lead to a decrease in availability of fiber-fortified foods, and consequently, a reduction in fiber consumption by the American population.

In the May 2016 final rule on revisions to the NFL, the Agency distinguishes between intrinsic/intact and isolated/synthetic dietary fibers. We would appreciate further clarity on why the FDA is allowing for intrinsic fibers present in plant sources to be considered and labeled as dietary fibers but is requiring scientific and clinical evidence of physiological beneficial effects for those same fibers which are isolated from their plant source. Additionally, further distinction should be made to differentiate between intrinsic and isolated dietary fibers. In the final rule, the assumption is made that non-digestible carbohydrates present in food have inherent physiological benefits while any potential beneficial effects in isolated fibers is diminished.

Many isolated and synthetic fibers have shown physiological benefit in clinical studies. The issue is, however, that showing reproducible beneficial physiological health effects to the standards FDA has proposed can be difficult due to such factors as study design characteristics, selected endpoints, heterogeneous patient populations, exclusion of studies in non-healthy populations, and different fiber dosages. Compounding this difficulty is the fact that these studies must meet the standards of FDA retrospectively, given that the guidance was not available at the time that all of the available clinical research was conducted with a purpose to demonstrate a fiber’s beneficial physiological effect.

Although it is desirable for fibers to show consistent physiological benefit, fibers should not be disqualified prematurely until such nuances, as inclusion of data in non-healthy populations, are appropriately discussed amongst interested stakeholders. Further, the Agency should consider permitting additional physiological benefits in the future as there is ongoing and emerging research in areas such as the impact of non-digestible carbohydrates on gastrointestinal microflora. This would be a public health disservice for the American public, could decrease the availability of fiber-fortified foods, and would oppose FDA’s overall public health goal of increasing dietary fiber intake in Americans.

b. De-listing fibers could result in label confusions.

If a fiber substance remains in the formulation but cannot be declared as a fiber in the NFL, the fiber substance would have to be declared solely as “Total Carbohydrate” in the NFL. Consumers and healthcare practitioners alike may be unable to select a “healthier” option, such as selecting a product for which the glycemic impact is lower (i.e., non-digestible carbohydrates comparative to starches or digestible maltodextrins). Although FDA has emphasized that presence of these substances could be described elsewhere on label outside of the NFL, the reality remains that they cannot be described as fiber.

It is also unlikely that consumers are familiar with individual fiber names (such as short-chain fructooligosaccharides) or understand the term non-digestible carbohydrate, since this has never

before been a consistent term in food labeling and nutrition education efforts. These changes to the clarity of the label would detract from FDA's overall goal of the nutrition label reform, which is to improve consumer access to necessary information in an understandable way so that they can make healthy dietary choices.

**C. We encourage FDA to consider the unintended consequences of de-listing fibers which are extensively researched and technically suitable for therapeutic nutritional formulas such as Oral Nutritional Supplements**

Therapeutic nutritional formulas such as Oral Nutritional Supplements (ONS) are available throughout the patient's lifecycle, in hospital, in long-term care settings, and in the community as they are discharged home. These formulas can be used for sole or supplemental nutritional support for individuals who fail to meet baseline nutrient intakes through the normal diet, and can be orally fed or tube fed. Decades of preclinical and clinical research and product development has been conducted to confirm the efficacy and tolerance of these formulas, including the fibers used, due to the sensitivity of the intended populations and the significant contribution they can provide to the diet.

a. De-listing fibers could result in discontinuation of fiber-fortified therapeutic nutritional formulas.

Providing clear information to patient populations through food labels is a primary necessity for compliance with the nutrition care plan. As patients are discharged from the hospital and re-enter the community, they may still require nutritional support, whether by oral supplementation or tube feeding.

Fiber is a nutrient of public health concern due to insufficient intake by the American population and association of inadequate intake to adverse health outcomes, as noted recently in the 2015-2020 Dietary Guidelines for Americans. Fiber-fortified formulas are available, for sole or supplemental nutrition, for people with or at risk of malnutrition or who cannot meet baseline nutritional intakes through the normal diet.

The fibers which are suitable for a liquid nutritional matrix have been determined through decades of preclinical and clinical research and product development. Those fibers are not currently recognized on the approved fiber list. Without fibers that are suitable and feasible for therapeutic nutritional formulas, fiber-fortified formulas could cease to exist, detracting from the public health goal to increase fiber intake amongst the American population and putting a susceptible patient population at a nutritional disadvantage.

b. De-listing fibers could result in patient and clinician confusion and adverse medical outcomes

Some patients requiring therapeutic nutrition require a no-fiber or low residue diet due to medical necessity. For this reason, therapeutic nutritional formulas that do not contain fiber are also available. However, differentiation of fiber-containing and no-fiber formulas could become difficult if the fibers that are used in these formulas are not approved by FDA.

If the fiber content is no longer clearly declared in the NFL, patients who require a no-fiber formula may be inadvertently switched to a fiber-containing product, and could experience significant adverse medical and clinical consequences, such as impaction, fiber bezoar, or intolerance. Consequently, the new fiber regulation that may exclude many isolated and synthetic fibers from the "Dietary Fiber" declaration may lead to patient and healthcare practitioner confusion and adverse medical impacts. As such, we request that FDA consider studies conducted in non-healthy populations in their evaluation of the 26 fibers currently under review as these fibers have documented efficacy and tolerance in therapeutic nutritional formulas to ensure continuity of these critical patient foods.

**D. We encourage FDA to consider the following points related to the endpoints considered for dietary fiber.**

The FDA has concluded that fermentation is not an acceptable endpoint as it is a process that could result in a beneficial physiological effect and is not, in itself, a beneficial physiological effect. However, there is as much scientific agreement surrounding the benefit of changing the prevalence of fecal *Bifidobacteria* as there is for endpoints such as transit time and other measures of stooling.<sup>20</sup> We suggest that the Agency adopt the standard used by Health Canada, which recognizes “providing energy-yielding metabolites through colonic fermentation” as a physiological benefit. Further, Health Canada does not have an exhaustive list of physiological benefits and recognizes that potential benefits could change as science emerges. Recommendations from the National Academies of Science, Engineering and Medicine (NAS) (formerly the Institute of Medicine (IOM)) are jointly developed by the US and Canada, so downstream use by the NAS should be similar between both countries.

Further, we believe that the Agency should be more explicit in the endpoints considered to provide physiological benefit. For example, for improved laxation, the FDA should note that prevention of diarrhea would be a suitable endpoint to support the benefit of improved laxation.

Additionally, the FDA excluded studies that failed to meet their selected criteria, but they did not weigh those studies which did not meet the criteria. Studies may have been underpowered for the effect measured. Meta-analyses may be needed to avoid making a type II error, which may exclude fibers which could improve health.

**E. We encourage FDA to extend the compliance date of the Nutrition Facts requirements to align with the recently published Uniform Compliance Date for Food Labeling**

On November 25, a straight-to-final rule was published for a Uniform Compliance Date for Food Labeling Regulations (81 FR 85156). While we applaud the FDA’s efforts which were stated to “minimize the economic impact of label changes,” we take this opportunity to comment that the economic impact is not considerably improved by this effort given that the Nutrition Facts reform was not included in the uniform date.

The uniform compliance date of January 1, 2020 pertains only to food labeling regulations published between January 1, 2017 and December 31, 2018 while the NFL final rule was published in May 2016. The Uniform Compliance Date essentially mandates two rounds of label changes for industry. Changes for the NFL, because it requires revisions to every food label that a food manufacturer produces, can equate to a multi-million dollar investment in many cases, which can significantly slow investment in research and innovation. A second round of label changes immediately after the new Nutrition Facts label is in place would be significantly burdensome and economically impactful to industry.

Further, fiber is a complex issue due to the Uniform Compliance Date. Although the definition of fiber was finalized since May, the revision to the regulation to provide a more comprehensive list of recognized dietary fibers will not occur until after January 1, 2017, indicating there could be two different compliance dates depending on the type of fiber. We thus encourage the FDA to extend the compliance date of the Nutrition Facts requirements to align with the Uniform Compliance Date of January 1, 2020, both to ease the burdensome impact to industry and to prevent multiple iterations of food labels and consumer confusion.

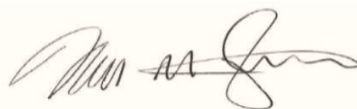
In summary, we applaud FDA’s efforts to improve the public health by ensuring that fibers currently fortified in foods provide a beneficial physiological effect. However, we request that the above concerns be taken into consideration and appropriate time allotted for stakeholder dialogue via an extension of the compliance date for the Nutrition Facts requirements prior to finalizing the list of approved fibers and the guidance.

We appreciate the opportunity to provide comments on these impactful documents. Please let us know if there are any questions.

Sincerely,



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