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VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: 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Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition; Draft Guidance for Industry; Availability. 81 Fed. Reg. 84516-84517 (Wednesday, November 23, 2016). Docket No. FDA–2016–D–3401.

The Council for Responsible Nutrition (CRN)[1] appreciates the opportunity to provide comments on FDA's draft guidance for industry titled, "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition."

General comments

The standard of evidence detailed in the draft guidance is unduly burdensome for listing an isolated or synthetic non-digestible carbohydrate (NDC) as dietary fiber on product labeling. Throughout the scientific evaluation process, from identifying studies that assess a beneficial physiological effect to evaluating these studies and the strength of the scientific evidence, FDA describes in the draft guidance criteria that are unreasonably restrictive in the context of meeting a regulatory definition for claiming nutrient content. FDA should consider the unique challenges in conducting and interpreting nutrition research. Dietary fiber does not exert effects in the body in isolation from the diet or host gut environment; and its effects manifest over many years, as is

[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

the case with all nutrients. Therefore, scientific evaluation of the beneficial physiological effects of dietary fiber should consider quality evidence from studies of both healthy and non-healthy populations and studies of isolated NDCs and NDCs in combination with other food components, among the totality of available evidence.

Further, FDA should recognize that the vast majority of studies that demonstrate a beneficial physiological effect of NDCs currently labeled as dietary fiber were completed prior to the agency's regulatory definition of dietary fiber and issuance of the draft guidance. If FDA applies the evaluation criteria outlined in the draft guidance, decades of scientifically valid and important research would be inappropriately excluded from the body of evidence reviewed and therefore the number of well-researched NDCs that should be labeled as dietary fiber would be substantially reduced.

Unintended consequences of applying the evaluation criteria as written in the draft guidance include the potential removal of NDCs that have a variety of demonstrable beneficial effects from food and dietary supplement products. Companies may remove these NDCs from food and dietary supplement products if they can no longer be labeled as dietary fiber. Currently, these fibers contribute to the overall intake of dietary fiber and reducing their availability in the food supply would detrimentally diminish dietary fiber intake by Americans. Dietary fiber is a shortfall nutrient in the United States and has been identified as a nutrient of public health concern because low intakes are associated with health concerns.[2] Further reductions in dietary fiber consumption by Americans would contradict the public health goal to increase its intake.

Moreover, if an NDC that is determined by FDA not to meet the definition of dietary fiber remains in a food or dietary supplement product, it would not be declared as dietary fiber on the label. Instead, its quantity would be counted toward the "Total Carbohydrate" content, which could lead to confusion. Consumers, as well as health care professionals, would not be able to differentiate between a product with a "Total Carbohydrate" content composed entirely of starch and a product with a "Total Carbohydrate" content composed of an NDC. For example, differentiating between such products is particularly important for consumers and their health care advisors who are seeking low glycemic products.

Intrinsic and intact NDCs

In the summary of the definition of isolated or synthetic NDCs, FDA highlights that NDCs derived from non-food sources are not considered intrinsic and intact. However, the list of "non-food" sources includes seaweed and fungus, both of which have edible varieties and are commonly consumed in the U.S. and around the world[3,4]. CRN encourages FDA to consider any

[2] U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Retrieved from http://health.gov/dietaryguidelines/2015/guidelines/.

[3] Food and Agriculture Organization of the United Nations, 2004. Wild edible fungi - A global overview of their use and importance to people, by E. Boa. Retrieved from http://www.fao.org/docrep/007/y5489e/y5489e06.htm#P624_76235

[4] Food and Agriculture Organization of the United Nations, 2003. A guide to the seaweed industry, by DJ McHugh. Retrieved from http://www.fao.org/docrep/006/y4765e/y4765e04.htm

food source of NDCs as potentially intact and intrinsic based on its composition relative to the source material.

Study subjects

CRN acknowledges that FDA is willing to consider evidence from studies with subjects who have a disease that is associated with the physiological effect of interest if extrapolating to individuals who do not have the disease is scientifically appropriate. FDA further states that evidence from studies of subjects who have disease will be considered only if the evidence demonstrates that the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as those for risk reduction effects in non-diseased populations, and the added NDC affects these mechanisms in the same way in both diseased and healthy people.

CRN strongly encourages FDA to take a flexible approach to evaluating evidence from studies conducted in subjects who have a disease. This would be consistent with the Institute of Medicine's (IOM, currently Health and Medicine Division) activities related to dietary fiber. In its *Proposed Definition of Dietary Fiber*, the IOM evaluated studies conducted in non-healthy individuals, including those with type 2 diabetes and hypercholesterolemia.[5] Further, in establishing the Dietary Reference Intakes (DRIs) for fiber, the IOM reviewed studies conducted in subjects with various diseases or conditions, including type 2 diabetes, hypercholesterolemia, idiopathic constipation, and irritable bowel syndrome (IBS) in its scientific evaluation of the physiological effects of individual isolated and synthetic NDCs for potential classification as "functional fibers."[6] Since the IOM definitions of "functional fiber" (isolated, nondigestible carbohydrates that have beneficial physiological effects in humans) and "dietary fiber" (nondigestible carbohydrates and lignin that are intrinsic and intact in plants) form the basis for FDA's regulatory definition of dietary fiber, the agency should utilize a similar approach as that employed by the IOM in its scientific evaluation.

In some cases, individuals with a disease or disorder may be representative of the general population. An example of this is IBS, which is a group of symptoms, including abdominal pain or discomfort and changes in bowel movement patterns, that occur together.[7] In its guidance for health claims related to gut, immune system, and defense against pathogens,[8] the European Food Safety Authority (EFSA) indicated:

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[5]Institute of Medicine, 2001. Dietary Reference Intakes: Proposed Definition of Dietary Fiber. Washington, DC: The National Academies Press.

[6] Institute of Medicine, 2002. Dietary, Functional, and Total Fiber. In: Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). Washington, DC: The National Academies Press.

[7] The National Institute of Diabetes and Digestive and Kidney Diseases. Digestive Diseases: Irritable Bowel Syndrome (IBS). Retrieved from https://www.niddk.nih.gov/health-information/digestive-diseases/irritable-bowel-syndrome

[8] EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. Guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms. EFSA Journal 2016;14(1):4369. Retrieved from http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4369/epdf

> "Episodes of abdominal pain or discomfort occur both in healthy people and in individuals suffering from IBS, and the difference between the two is the higher frequency and/or greater severity of the symptoms in IBS patients. IBS patients or subgroups of IBS patients (Rome III criteria) are generally considered a suitable study group to substantiate claims on GI discomfort intended for the general population."

FDA should recognize that studies conducted in non-healthy populations contribute to the overall evidence on the beneficial physiological effects of an NDC. It is more feasible to detect a statistically significant change in subjects with a disease or a risk factor for the disease than in healthy subjects. CRN recognizes that the draft guidance states that FDA would consider studies that include individuals at risk of developing a disease or who have an unrelated disease. High quality studies can be conducted in non-healthy populations, including in those with a disease that is associated with the physiological effect of interest, and address relevant research questions using smaller sample sizes and shorter durations than those conducted in healthy people. CRN recommends that FDA consider specific cases in which data studied in non-healthy populations are appropriate evidence in evaluating the beneficial physiological effects of an NDC.

Identification of studies

Section III.A of the draft guidance is titled, "Identifying *Published* Studies That Evaluate a Beneficial Physiological Effect to Human Health" (emphasis added). Further, FDA states, "We will consider the *publicly* available data and written information primarily from intervention studies regarding the beneficial physiological effects of added non-digestible carbohydrates" (emphasis added). Scientific evaluation should not be limited to published studies. Study data may not be published during the development of a new isolated or synthetic NDC. Additionally, data may be proprietary and protected under trade secret or patent laws. Whether the data are publicly available does not necessarily impact the quality of the information. Data from unpublished studies provided by the petitioner should undergo review by the agency, utilizing the same evaluation process as for publicly available data. FDA should clearly state in the guidance that unpublished data will be considered.

Single versus multiple fibers

In Section III.B, FDA indicates that for research studies in support of the petition, the NDC of interest should be provided in its isolated form rather than in a naturally-occurring form in food, and that the added NDC should not be added in combination with other NDCs or other food components that may affect the physiological endpoint being measured. However, using an NDC in isolation may not be practical for studies in which the NDC is added to food. In such cases, the NDC of interest may need to be combined with other NDCs or food components to make the food palatable. Studies that include the NDC of interest in combination with other NDCs may add to the overall understanding of the NDC of interest and should not be automatically eliminated from consideration. If the petitioner can demonstrate that the NDC of interest contributes to the observed beneficial physiological effect, research using the NDC of interest in

combination with other NDCs or other food components should be considered in the scientific evaluation.

Beneficial physiological effects

Fermentation should be considered a beneficial physiological effect. Fermentation of NDCs in the large intestine by gut microbiota produces several metabolites, including short-chain fatty acids (SCFA). These volatile fatty acids, the most abundant of which are acetic acid, propionic acid, and butyric acid, contribute to various physiological processes associated with health benefits. SCFA serve as an energy source, providing approximately 10% of the daily caloric requirements in humans.[9] SCFA are a source of energy for colonocytes, as well as cells in other organs and tissues.[10] They also play a role in energy homeostasis[11] and maintaining gut barrier function.[12] Therefore, CRN recommends that fermentation be considered as a beneficial physiological effect of dietary fiber.

Baseline data

FDA addresses baseline data in Section III.A of the draft guidance:

> "Randomization, however, may result in unequal distribution of the characteristics of the subjects between the control and treatment group…If the baseline values are significantly different, then it is difficult to determine if differences at the end of the study were due to the intervention or to differences present at the beginning of the study."

FDA also states in Section III.B of the draft guidance, "Interpreting the findings of a dietary intervention study is difficult if baseline values for the endpoint being measured are significantly different."

Current standards in the field of clinical trial statistics recognize that randomization can lead to imbalances and are important to consider, especially in past studies in which the statistical analysis approach may not have been adequately adjusted for these covariates *a priori.* CRN agrees that baseline differences should be carefully considered in assessing results from studies that have not used a covariate analysis approach. However, we request that FDA also consider an approach that is consistent with the *International Conference on Harmonisation (ICH) Guideline: Statistical Principles for Clinical Trials E9*[13] [ICH Guideline (E9)], which describes

[9] Bergman, EN. 1990. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. Physiol Rev 70(2):567-90.
[10] Ríos-Covián D, Ruas-Madiedo P, Margolles A, et al. 2016. Intestinal short chain fatty acids and their link with diet and human health. Front Microbiol, 7:185.
[11] Byrne CS, Chambers ES, Morrison DJ et al. 2015. The role of short chain fatty acids in appetite regulation and energy homeostasis. Intl J Obesity, 39:1331–1338.
[12] Ríos-Covián D, Ruas-Madiedo P, Margolles A, et al. 2016. Intestinal Short Chain Fatty Acids and their Link with Diet and Human Health. Front Microbiol, 7: 185.
[13] ICH E9 Expert Working Group. 1998. Statistical principles for clinical trials: ICH harmonized tripartite guideline. Retrieved from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

statistical principles FDA has adopted in guidance.[14] This approach indicates that if randomization is adequately performed and a covariate analysis that includes adjustment for baseline is used in the statistical analysis process, then statistical differences in baseline should not be a factor. That is, studies that have statistical differences in baseline could be considered as data from which conclusions can be drawn if a statistical analysis is performed using an approach that adjusts for baseline differences (e.g., covariate analysis).

The ICH Guideline (E9) also provides guidance for differences in baseline factors not identified *a priori*, which do not invalidate the results of the study, if appropriate statistical procedures are utilized.

Statistical analyses

In Section III.B, FDA states, "When conducting statistical analyses among more than two study groups, the data should be analyzed by a test designed for multiple comparisons (e.g., Bonferroni, Duncan)."

CRN agrees that appropriate statistical analysis of data is critical in determining a beneficial physiological effect. A statistical test that accounts for multiple testing should be considered in order to control the overall Type 1 error rate at an *a priori* defined level; however, including a specific procedure, such as Bonferroni test, may not be applicable in every study, and its use depends on the nature of the design and research question. Also, multiple testing is not only applicable when more than two groups are involved, but also when more than two comparisons are being made on the same variable within or between groups.

Thank you for considering our comments.

Sincerely,

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Director, Scientific & Regulatory Affairs

[14] U.S. Food and Drug Administration. 1998. Guidance for Industry: E9 Statistical Principles for Clinical Trials. Retrieved from http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf