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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): Guidance for Industry

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U.S. Department of Health and Human Services
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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): Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or we) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance listed on the title page.

I. Introduction

This guidance document explains FDA's current thinking on information needed when submitting a citizen petition and the scientific review approach we plan to use for evaluating scientific evidence to determine whether an isolated or synthetic non-digestible carbohydrate that is added to food (hereinafter "added non-digestible carbohydrate") has a physiological effect that is beneficial to human health. The purpose of this guidance is to provide information to those submitting evidence to us to determine if the added non-digestible carbohydrate meets the definition of "dietary fiber" in our regulations for nutrition labeling of food for declaring the amount of dietary fiber on the Nutrition and Supplement Facts labels.

This guidance document addresses our current thinking for: (1) identifying publicly available scientific articles that evaluate a physiological effect of an added non-digestible carbohydrate; (2) evaluating those studies from which scientific conclusions can be drawn; and (3) evaluating the strength of scientific evidence to determine whether there is a physiological effect that is beneficial to human health of an isolated or synthetic non-digestible carbohydrate that is added to foods. This guidance includes revisions that we have made in response, in part, to comments that we received on the draft guidance.[2]

[1] This guidance has been prepared by the Office of Nutrition and Food Labeling in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

[2] We intend to address in a subsequent guidance questions about "intrinsic and intact" fibers, the degree to which a non-digestible carbohydrate can be isolated or synthesized from its original plant source, but still be considered intrinsic and intact, and whether plant cell wall fibers containing a mix or combination of non-

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II. Background

Before 2016, FDA regulations did not define the term "dietary fiber." In the *Federal Register* of May 27, 2016 (81 FR 33742), we published a final rule amending our Nutrition and Supplement Facts label regulations ("the final rule"). 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. The final rule also identifies seven non-digestible carbohydrates that we determined have physiological effects that are beneficial to human health (hereinafter "beneficial physiological effects") (21 CFR 101.9(c)(6)(i)).

We derived our definition of dietary fiber from a 2001 Institute of Medicine (IOM) report that defines dietary fiber as non-digestible carbohydrates and lignin that are intrinsic and intact[3] (i.e., naturally occurring) in plant-based foods. The IOM report also defines the term "added fiber" as isolated, non-digestible carbohydrates that have beneficial physiological effects in humans. Added fibers include synthetic non-digestible carbohydrates or isolated or extracted non-digestible carbohydrates. The IOM's provision of two definitions recognizes the diversity of non-digestible carbohydrates in the human food supply. Finally, the IOM report defines the term "total fiber" as the sum of dietary fiber and added fiber (IOM, 2001). We concluded in the final rule that by defining dietary fiber based on a physiological effect that is beneficial to human health, we will ensure that the dietary fiber declared on the food label will assist consumers in maintaining healthy dietary practices (81 FR 33742 at 33853).

Evidence shows that fiber-containing foods such as fruits, vegetables, and whole grains, provide health benefits, for example, improve laxation and reduce the risk of cardiovascular disease and type 2 diabetes (National Research Council, 1989; IOM, 2002; 21 CFR 101.77). These fiber-containing foods are commonly consumed as part of the U.S. diet, and are part of the USDA Food Patterns (Dietary Guidelines for Americans, 2015-2020) and food composition databases (e.g., USDA Food Composition Database), which have been used for determining the associations between these foods and health outcomes. Fiber-containing foods contain macronutrients, micronutrients, and other biologically active compounds that can have distinct physiological effects in humans. FDA authorized

digestible carbohydrates would be an intrinsic and intact dietary fiber.

[3] The IOM referred to intrinsic fibers as those originating wholly within and intact fibers as those having no relevant component removed or destroyed (IOM, 2001). Intrinsic and intact pertains to non-digestible carbohydrates that are naturally occurring in foods.

a health claim for fruits, vegetables, and grain products that contain fiber (particularly soluble fiber) and risk of coronary heart disease (21 CFR 101.77(a)(3)). The physiological effects of specific isolated or synthetic non-digestible carbohydrates from foods or other sources that are added to foods can only be ascertained by evaluating the non-digestible carbohydrates individually.

This guidance addresses the scientific evaluation of synthetic non-digestible carbohydrates and isolated non-digestible carbohydrate ingredients that are produced as a result of processing of foods and other sources, to the extent that the ingredients in and of themselves have a specific chemical structure (carbohydrate composition and non-digestible bond linkages).[4] These non-digestible carbohydrates may or may not vary in size. If such isolated or synthetic non-digestible carbohydrates are combined to produce an ingredient, for which a firm seeks to declare as a dietary fiber, then each non-digestible carbohydrate that is a component of the ingredient would need to demonstrate a beneficial physiological effect in order for all of the non-digestible carbohydrates in the ingredient to be declared as a dietary fiber. It would not be necessary, under such circumstances, to provide evidence to demonstrate the ingredient has a beneficial physiological effect where there is already evidence to support that each non-digestible carbohydrate that is a component of the ingredient has such an effect.

An isolated or synthetic non-digestible carbohydrate must be declared in the declaration of "Total Carbohydrate" on the Nutrition and Supplement Facts label. If FDA determines it has a physiological effect beneficial to human health and lists it in our regulations in 21 CFR 101.9(c)(6)(i), it must also be included in the declaration of "Dietary Fiber" (21 CFR 101.9(c)(6)(i)). If not listed in our regulation, the declaration of an isolated or synthetic carbohydrate as dietary fiber would misbrand the product (see section 403(q) of the Federal Food, Drug, and Cosmetic Act). Any interested person may ask us to amend our regulations to list a new isolated or synthetic non-digestible carbohydrate as a dietary fiber by submitting a citizen petition (as provided in 21 CFR 10.30) or, if the added non-digestible carbohydrate is the subject of an authorized health claim using the health claim petition process in 21 CFR 101.70,[5] FDA would consider it to meet the definition of dietary fiber and would amend the definition accordingly.

III. Scientific Evaluation of the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates

Our scientific evaluation process involves a series of steps to: (1) assess publicly available scientific studies and other data; (2) eliminate those studies from which scientific conclusions about the physiological effects of an added non-digestible carbohydrate cannot be drawn; and (3) evaluate the strength of the scientific evidence to determine whether the carbohydrate provides a physiological effect that is beneficial to human health.

[4] Examples of isolated non-digestible carbohydrate ingredients with a specific chemical structure include cellulose, guar gum, and pectin. Non-digestible carbohydrate ingredients lacking a specific chemical structure are outside the scope of this guidance.

[5] Guidance to Industry is already available for the scientific review of health claims (FDA, 2009). The significant scientific agreement standard is specific to health claims and does not apply to this guidance.

A. Identifying Publicly Available Studies That Evaluate a Beneficial Physiological Effect to Human Health

We intend to consider the publicly available data and written information, primarily from human intervention studies, regarding the beneficial physiological effect of an added non-digestible carbohydrate. We intend to review intervention studies that are submitted to us in citizen petitions (21 CFR 10.30) requesting the addition of a specific added non-digestible carbohydrate to the list of dietary fibers in 21 CFR 101.9(c)(6)(i). The dietary fibers listed in §101.9(c)(6)(i) are those that we already have determined to have a beneficial physiological effect to human health, and therefore, must be included in the amount of dietary fiber declared on Nutrition and Supplement Facts labels (21 CFR 101.9(c)(6)(i)). Interested parties should submit all publicly available human studies on a specific isolated or synthetic non-digestible carbohydrate as part of a citizen petition, regardless of the studies' findings. Publicly available studies include those studies that are in manuscript form and can be available for the public to review. We may identify additional relevant intervention studies through a literature search. We intend to focus our review primarily on articles reporting human intervention studies because these studies can provide evidence from which scientific conclusions can be drawn about the beneficial physiological effect of a specific isolated or synthetic non-digestible carbohydrate in humans. Observational studies on the beneficial physiological effects of isolated or synthetic non-digestible carbohydrates, for example, are not currently available because food composition databases currently do not provide the content of these types of carbohydrates in food. Therefore, it is not currently possible to assess intake data for added non-digestible carbohydrates in an observational study.

In evaluating the available scientific evidence, we first separate relevant articles on human intervention studies from other types of data and information, for example, review articles and meta-analyses.

- Intervention Studies

In an intervention study, subjects are provided with a specific amount of added non-digestible carbohydrate of interest (intervention group), typically either added to a conventional food or as a dietary supplement. Randomized controlled trials typically have either a parallel or cross-over design. Parallel design studies involve two groups of subjects, the test group and the control group, which simultaneously receive the added non-digestible carbohydrate or serve as the control (without the added non-digestible carbohydrate). In a cross-over design study, all subjects cross over from the treatment to the control, and vice versa, after a defined time period.

In randomized controlled trials, subjects are assigned to an intervention group or treatment sequence by chance. Randomized controlled trials offer the best assessment of a causal relationship between a non-digestible carbohydrate and a physiological effect because they control for known confounders of results (i.e., other factors that could affect the physiological endpoint) (Kraemer et al., 2005). Through random assignment of subjects to the intervention and control groups, these studies reduce the likelihood of selection bias,

that is, the possibility that those subjects most likely to have a favorable outcome, independent of an intervention, are preferentially selected to receive the intervention. Even after randomization, however, there may be an unequal distribution of characteristics of the subjects between the control and treatment groups (e.g., blood [serum or plasma] low-density lipoprotein (LDL) cholesterol levels are significantly different at baseline). In particular, if the baseline values for biomarkers are not measured or are significantly different in a parallel design study, then it can be 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.

Potential bias also is reduced by "blinding" the study so that the subjects do not know whether they are receiving the intervention, or by "double blinding," in which neither the subjects nor the researchers who assess the outcomes know who is receiving the treatment or control. By controlling the test environment, including the amount and composition of non-digestible carbohydrate consumed and other dietary factors, these studies also can minimize the effects of other variables or confounders on the results.[6] Therefore, randomized, controlled intervention studies provide the strongest evidence of whether there is a relationship between an added non-digestible carbohydrate and a physiological effect (Greer et al., 2000).

- Observational Studies

Observational studies can be designed to measure associations between dietary patterns, foods or food components, and physiological and health-related endpoints. Observational studies lack the controlled setting of intervention studies. Observational studies are more reflective of free-living[7] populations and may be able to establish an association between a food component, such as an added non-digestible carbohydrate, and a beneficial physiological effect. Unlike intervention studies, observational studies cannot be used to determine whether an observed association establishes that the food component caused a change in the physiological or health-related endpoint or is a coincidence; that is, observational studies do not establish causation (Sempos et al., 1999). Observational studies generally rely on a dietary intake assessment method to estimate food intake. The nutrient content of reported foods is usually determined using some form of food composition database. While there are limitations in evaluating the association between a food component and a physiological or health-related endpoint (FDA, 2007), if information on the amount of an ingredient added to a food (e.g., an isolated or synthetic non-digestible carbohydrate) is available, information from observational studies could be considered as part of the totality of evidence. Food composition databases, however, currently do not provide the content of individual types of isolated or synthetic non-digestible carbohydrates in foods. Therefore, observational studies that rely on intake data for evaluating the association between an added non-digestible carbohydrate and a beneficial physiological

[6] Confounders are factors that are associated with both the physiological benefit in question and the intervention, and that, if not controlled for, prevent an investigator from being able to conclude that an outcome was caused by an intervention.

[7] Free-living populations represent those who consume diets and have lifestyles (e.g., smoking, drinking, and exercise) of their own choice.

effect are not currently available. If the findings of such observational studies become available, we intend to consider them as part of the totality of evidence.

- Research Synthesis Studies

Reports, such as review articles, which summarize the findings of individual studies, and meta-analyses,[8] that discuss a number of different studies, do not provide enough information on critical elements of the individual studies, such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on the individual studies prevents us from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. Reviewing the critical elements of each study is necessary to determine whether any scientific conclusions can be drawn from it. Therefore, we intend to use review articles and similar publications[9] only to identify reports of additional studies that may be useful to our scientific review and as background information about the beneficial physiological effect of added non-digestible carbohydrates. If we identify additional studies from their description in review articles, we intend to evaluate them individually. Meta-analyses also lack detailed information on the individual studies included in the analysis. Therefore, we intend to use meta-analyses to identify reports of additional studies that may be useful to our scientific reviews, and as background information about the beneficial physiological effect of added non-digestible carbohydrates.

- Animal and *In Vitro* Studies

We intend to use animal and *in vitro* studies as background information regarding mechanisms that might be involved in any physiological effect of an isolated or synthetic non-digestible carbohydrate. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (IOM, 2005). Animal and *in vitro* studies can be used to generate hypotheses, investigate biological plausibility of hypotheses, or to explore a mechanism of action of a specific food component through controlled animal diets. However, these studies do not provide information from which scientific conclusions can be drawn regarding the beneficial physiological effects in humans of a food component, such as added non-digestible carbohydrates.

B. Evaluating Human Intervention Studies

Once we have identified the relevant human intervention studies, we intend to evaluate each study to determine whether any scientific conclusions can be drawn regarding the physiological effect of an added non-digestible carbohydrate. Critical elements of a study, such as design, data collection, and data analysis, may be so flawed that it is not possible to draw scientific conclusions from the study. We do not intend to use studies from which we

[8] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[9] Examples of "similar publications" include book chapters, abstracts, letters, and committee reports.

cannot draw any scientific conclusions about the physiological effect, and we intend to eliminate such studies from further review.

The following are examples of questions that we intend to consider when evaluating whether scientific conclusions can be drawn from an intervention study about the physiological effect of an added non-digestible carbohydrate.

- *Have the studies specified and measured the isolated or synthetic non-digestible carbohydrate?*

The added isolated or synthetic non-digestible carbohydrate of interest should be provided in its isolated form, rather than in a naturally-occurring form in food. The added non-digestible carbohydrate also should not be added in combination with other non-digestible carbohydrates or other food components that may affect the physiological endpoint being measured. When a mixture of non-digestible carbohydrates is added to foods, scientific conclusions cannot be drawn about the role of the individual added non-digestible carbohydrate of interest, unless the other components are controlled by study design. We intend to review studies on added non-digestible carbohydrate ingredients that in and of themselves have a specific chemical structure and source from which they are isolated.

- *Have the studies appropriately specified and measured an endpoint that has a demonstrated beneficial physiological effect?*

There are a number of beneficial physiological effects associated with the consumption of non-digestible carbohydrates. Some examples include attenuation of blood glucose, insulin, and cholesterol concentrations; reduced energy intake; and improved laxation (i.e., the elimination of fecal waste) (81 FR 33742 at 33856, 33858; IOM, 2001; IOM, 2002). It is important that the physiological effect from consuming an isolated or synthetic non-digestible carbohydrate is associated with a specific endpoint that has been shown to have a beneficial physiological effect to human health. When applicable, we intend to include in our review information for subjective measures for a given endpoint (examples are provided below).

Attenuation of blood glucose and/or insulin levels is a physiological effect that is beneficial to human health. Fasting blood glucose concentration provides information on the long-term effects of a dietary intervention and is a surrogate endpoint for type 2 diabetes risk. Insulin resistance is also a surrogate endpoint for type 2 diabetes risk. Attenuation of blood glucose or insulin levels may be measured by assessing post-prandial blood glucose and insulin levels. While not a surrogate endpoint, post-prandial blood glucose[10] provides information on the glycemic response over several hours after consuming a food, beverage, or meal. The rise and fall of blood glucose over several hours after consuming a food, beverage, or meal is often reported as the area-under-the-curve (AUC) (sometimes referred to as an incremental AUC). The serial measurements of post-prandial blood glucose should be recorded up to at least two hours after consumption of the standardized meal.

[10] Post-prandial glucose measures the rise and fall of blood glucose after consuming a meal which reflects the intestinal absorption and clearance of glucose from the blood.

When using post-prandial blood glucose and/or insulin measurements to assess whether an isolated or synthetic non-digestible carbohydrate has a beneficial physiological effect, it is important to include a meal, food, or caloric beverage to determine such an effect. Therefore, we do not intend to consider individual non-digestible carbohydrates that are only added to water as a measure of post-prandial glucose or insulin levels. Because digestible carbohydrates (glucose and other sugars) provide a glycemic response, glycemic index[11] and other measures that compare glycemic responses of added non-digestible carbohydrates to glucose or other sugars do not provide information on how an isolated or synthetic non-digestible carbohydrate affects the glycemic response of a food or beverage that contains nutrients (e.g., starch) that affect blood glucose levels. For this reason, studies that add an isolated or synthetic non-digestible carbohydrate to a food, rather than replacing carbohydrates that have a glycemic response with the non-digestible carbohydrate, provide information about the independent beneficial physiological effect of the non-digestible carbohydrate on attenuation of blood glucose levels. In studies other than addition studies (e.g., substitution/replacement studies), the amount of digestible (or available) carbohydrate should be controlled by design (e.g., the same between the treatment and control). Otherwise, we are unable to determine if there is an independent effect of the non-digestible carbohydrate or if the effect is due to differences in amounts of digestible carbohydrate, which would be expected to impact blood glucose concentrations. In evaluating the strength of the evidence, we intend to consider the AUC and/or the peak glucose level (usually at 30 minutes after consumption), rather than other single data points fixed in time which provide less information.

Reductions in fasting blood total and LDL cholesterol levels are beneficial physiological effects, as well as surrogate endpoints for cardiovascular disease risk. However, post-prandial LDL cholesterol levels are not a valid endpoint to evaluate whether an isolated or synthetic non-digestible carbohydrate has a beneficial physiological effect because of the lack of a rise and fall in LDL cholesterol levels after a meal. Thus, a measure of LDL cholesterol levels taken after a meal would not provide scientific evidence to support the existence of a physiological effect from consumption of an added non-digestible carbohydrate.

Measures of improved laxation (i.e., the elimination of fecal waste/fecal output) are 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) (Topping, 2007). Multiple days of stool collection are needed to measure rate of defecation. We intend to include as part of our review subjective measures of laxation, such as self-reported ease of defecation and reduced complaint of difficulty in defecation from study subjects to evaluate how changes in these subjective measures are associated with changes in the elimination of fecal waste. The ingestion of an added non-digestible carbohydrate can increase stool weight (e.g., grams per stool), but an increase in stool weight does not necessarily indicate improved laxation (IOM, 2002). We intend to consider stool weight data in our reviews but only to

[11] Glycemic index and other measures that compare glycemic responses to glucose or other sugars evaluate the increase in blood glucose after ingestion of a set amount of carbohydrate in a test food, compared to the same amount of carbohydrate from a reference food (white bread or glucose solution) measured in the same individual and under the same conditions, using the initial blood glucose concentrations as a baseline.

evaluate how changes in stool weight, as a result of the consumption of an isolated or synthetic non-digestible carbohydrate, are associated with changes in the elimination of fecal waste.

Increased intestinal absorption of minerals of public health significance, such as calcium, is a physiological effect that is beneficial to human health. Calcium is considered to be a nutrient of public health significance, and the relationship between calcium absorption and the risk of osteoporosis is strong (21 CFR 101.72). Bone mineral density is a surrogate endpoint for the risk of osteoporosis, and we intend to consider it along with calcium absorption and other related endpoints to understand the effects of an added non-digestible carbohydrate on bone health.

Reduced energy intake from food consumption also is considered a beneficial physiological effect. In evaluating the strength of the evidence, we intend to consider studies that measure energy intake either by direct measurement of the food that is left over after an *ad libitum* meal, which is the gold standard, or by 24-hour recalls and food diaries kept by study subjects, which are less reliable, subjective methods. Furthermore, a reduction in energy intake observed at a subsequent meal should not be compensated for at other meals throughout the day. We also intend to consider subjective measures of satiety (a state of "fullness") to understand the mechanism by which a potential reduction in energy intake from food might occur with the consumption of an isolated or synthetic non-digestible carbohydrate. Satiety is often measured using a Visual Analogue Scale that subjectively measures various endpoints such as hunger, appetite, and feelings of fullness.

Fermentation and changes in the microbiota in the large intestine are considered to be processes, rather than physiological effects. Viscosity and fermentability of non-digestible carbohydrates are considered to be physicochemical properties, rather than physiological effects (IOM, 2001). While physiological effects that are beneficial to human health may be an outcome of viscosity, fermentation, or changes in the colonic microbiota, we do not consider these processes or properties in and of themselves to be physiological effects because they are not measures of functions of the human body.

- *Were the study subjects healthy or did they have a disease, condition, undergo a surgical procedure, or receive a treatment that could influence the physiological effect being studied?*

Declarations made on Nutrition and Supplement Facts labels are intended for the general healthy population. We intend to consider evidence from studies with subjects who have a disease that is associated with the beneficial physiological effect of interest when extrapolating to individuals who do not have the disease is scientifically appropriate. If evidence that would allow for such extrapolation is not available, we cannot draw any scientific conclusions from studies with subjects who have a disease or condition, or that had a procedure that is associated with the physiological endpoint (e.g., improved laxation in individuals with an ileostomy, who are tube-fed or non-ambulatory, or have diarrhea or fecal incontinence). However, we intend to consider studies that include individuals at risk of developing a disease (e.g., elevated LDL cholesterol levels, metabolic syndrome, or abnormal glucose tolerance test) or who have an unrelated disease to the physiological

effect being measured because the unrelated disease would not affect the particular endpoint being measured (e.g., individuals with osteoporosis being evaluated for attenuation of blood glucose levels). In some cases, we can consider a study that includes individuals who may have a related disease to the physiological endpoint being measured, and extrapolate the findings to the healthy population because the mechanism of action would not be different in the healthy or diseased populations (e.g., constipation and improved laxation).

• *Did the study include an appropriate control?*

An appropriate control group represents study subjects who did not receive, or consumed a low amount, of the added non-digestible carbohydrate of interest. All other aspects of the study design (e.g., duration, other dietary factors) for the control and treatment groups should be similar. If an appropriate control group was not used, it is impossible to ascertain whether changes in the endpoint of interest were due to the added non-digestible carbohydrate or to unrelated and uncontrolled extraneous factors (Spilker, 1991; National Research Council, 2011). Without an appropriate control, scientific conclusions cannot be drawn about a beneficial physiological effect of an added non-digestible carbohydrate. Therefore, we do not intend to use these types of studies to evaluate whether there is a beneficial physiological effect of an added non-digestible carbohydrate.

When the intervention study involves providing subjects with a whole food, along with an added non-digestible carbohydrate, or a combination of non-digestible carbohydrates or other components, the experimental and control diets should be similar enough that the relationship between the added non-digestible carbohydrate and beneficial physiological effect can be evaluated. The composition of the experimental and control diets should be similar for all food components, except for the added non-digestible carbohydrate of interest. For example, various factors besides non-digestible carbohydrates can influence the glycemic response of a food, including the presence of fat and protein (IOM, 2002).

When evaluating glycemic response, the amount of digestible (or available) carbohydrate should be the same between the treatment and control. Furthermore, the control and test diets should be relevant to diets consumed by the general U.S. population.

When the added non-digestible carbohydrate of interest is provided as a dietary supplement, a placebo should be provided as a control. When the substance is a food, it may not be possible to provide a placebo and therefore subjects in such a study may not be blinded. Although the study may not be blinded in this case, a control group is still needed to draw conclusions from the study.

• *How long was the study conducted?*

Studies that measure a physiological endpoint should be of a duration that is long enough to ensure that any change in the endpoint results from the dietary intervention. If the study is conducted for a time period that is too short to evaluate the effects of the added non-digestible carbohydrate, then scientific conclusions cannot be drawn about the beneficial physiological effect of the non-digestible carbohydrate. Therefore, we would not consider such a study to evaluate whether there is a beneficial physiological effect of an added non-

digestible carbohydrate. For example, we consider three weeks to be the minimum duration for evaluating the effect of a dietary intervention on serum LDL cholesterol (Kris-Etherton and Dietschy, 1997). On bowel function, we consider studies conducted for at least one week to account for adaptation to the diet, passage of fecal material, and a sufficient amount of time for collecting stool samples. More than 80% of markers used for measuring transit time are passed within 120 hours for most healthy subjects (Evans et al., 1992). Measurement of post-prandial blood glucose involves an overnight fast followed by multiple measurements of blood glucose concentrations up to at least two hours after consumption of the test products.

• *How were the results analyzed statistically?*

Appropriate statistical analysis of the study data is critical because it provides the comparison between consuming and not consuming the added non-digestible carbohydrate in order to determine whether there is a beneficial physiological effect. The appropriate statistical analysis will vary depending on factors such as the study design and the research question. For example, when conducting statistical analyses among more than two study groups or when more than two comparisons are being made within and between groups, the data should not be analyzed by a *t*-test and should include adjustments for multiple comparisons (e.g., Bonferroni, Duncan). When statistical analyses are not performed between the control and treatment, or are conducted inappropriately, scientific conclusions cannot be drawn. Therefore, we do not intend to use such studies to evaluate whether there is a beneficial physiological effect of an added non-digestible carbohydrate.

• *Were the relevant baseline data on the physiological endpoint (e.g., LDL cholesterol) statistically significantly different between the control and intervention groups?*

Interpreting the findings of a dietary intervention study can be difficult if the baseline values for the endpoint being measured are statistically significantly different between the control and intervention groups ($P \leq 0.05$). For example, in a parallel-design study on the effect of an added non-digestible carbohydrate on LDL cholesterol, having different baseline LDL cholesterol levels between the intervention group and the control group would lead to uncertainty as to whether any observed effect resulted from the difference in the intake of the added non-digestible carbohydrate, or the difference in the baseline LDL cholesterol levels between the two groups.

Randomization, adequate sample size, and adequate "lead-in"[12] diets or "wash-out" periods[13] for studies with a cross-over design, can help reduce the likelihood of statistically different baseline values. If baseline values are statistically different between groups in a parallel design study, a statistical analysis that includes adjustment for baseline, or calculations of change from baseline, should be used.

• *Where were the studies conducted?*

[12] A "lead-in" diet is one that is provided to all study groups prior to randomization.
[13] A "wash-out" period is the time period within a cross-over design study during which subjects do not receive an intervention.

It is important that the study population is relevant to the general U.S. population. Therefore, we intend to evaluate each study to determine, for example, if the study population lives in an area where malnutrition is common, and/or where the prevalence or etiology of the outcome that is being considered is not similar to that in the United States. Differences in prevalence or etiology of the outcome, as well as nutrition and diet, between the United States and the country where a study was conducted may mean that the study results cannot be extrapolated to the U.S. population. It may be difficult, for example, to draw scientific conclusions about the physiological effects of an added non-digestible carbohydrate in a population that consumes much higher or much lower amounts of dietary fiber, or other nutrients, that have an effect on the physiological endpoint.

C. Evaluating the Strength of the Scientific Evidence

We intend to evaluate the strength of the evidence to determine whether there is a beneficial physiological effect of an added non-digestible carbohydrate using the publicly available studies from which scientific conclusions can be drawn. We intend to conduct this evaluation by considering the number of studies and sample sizes of each study, the dose response data, 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[14,15] of the total body of evidence. These factors are considered when determining whether the evidence is sufficient to support a conclusion that there is a beneficial physiological effect.

Our evaluation of the strength of the evidence considers:

- *Number* of studies and number of subjects per group/study.

- *Doses* provided across studies and *dose-response analyses* conducted within a study.[16]

- The *type of foods,* for example, solid foods, beverages, or dietary supplements, to which the non-digestible carbohydrate was added.

- *Outcome* (i.e., a beneficial effect, no effect, or an adverse effect) and method used to measure the physiological endpoint. For the outcome of an intervention study to demonstrate a beneficial physiological effect, the results of the treatment group would need to be statistically significantly different from the control group ($P \leq 0.05$).

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[14] In this guidance, "consistency" is used to mean the level of agreement among the studies from which scientific conclusions could be drawn about the non-digestible carbohydrate/beneficial physiological effect relationship.

[15] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill, 1965). See also: Agency for Healthcare Research and Quality, Systems to Rate the Scientific Evidence, which defines "consistency" as "the extent to which similar findings are reported using similar and different study designs." [http://www.ahrq.gov/clinic/epcsums/strengthsum.htm#Contents].

[16] We consider the beneficial physiological effects that are observed or not observed for different study doses to understand the relevance of the effective doses to consumer consumption levels. Observed dose-response data within a study can increase the strength of the scientific evidence. Demonstration of a dose-response relationship would depend on the levels provided. For example, a dose-response relationship would not be expected if the dose(s) provided exceed a range of intake for which a linear relationship occurs.

• *Consistency* of findings. In general, the greater the consistency among the studies in showing a beneficial physiological effect, the higher the level of confidence that a relationship between an added non-digestible carbohydrate and a beneficial physiological effect exists. Conflicting results do not disprove an association because the elements of the study design may account for the lack of a beneficial effect in negative studies, but conflicting results tend to weaken confidence in the strength of the association.

• *Relevance* to the general U.S. population. For example,

> *To what extent did the studies that showed a benefit include populations and diets that are relevant to the general healthy U.S. population?*
>
> *Do the studies suggest that the intake level of the added non-digestible carbohydrate that provides a beneficial physiological effect significantly exceeds levels that are typically consumed in the United States or that may cause adverse effects?*

We intend to evaluate whether the scientific evidence supports a beneficial physiological effect to the general U.S. population. If the evidence only supports finding a beneficial physiological effect for a subgroup, for example, only in children one through three years of age, we intend to consider that information to determine whether the beneficial physiological effect is appropriate for the declaration of the added non-digestible carbohydrate as a dietary fiber on the Nutrition and Supplement Facts label on foods represented or purported to be specifically for that subgroup.

IV. References

We have placed the following references on display in the Dockets Management Staff, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You may see them at that location between 9 a.m. and 4 p.m., Monday through Friday. As of February 12, 2018, FDA had verified the Web site address for the references it makes available as hyperlinks from the Internet copy of this guidance, but FDA is not responsible for any subsequent changes to Non-FDA Web site references after February 12, 2018.

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V. Appendix A – Scientific and Technical Review Document

A. Background

In the *Federal Register* of May 27, 2016 (81 FR 33742), we published a final rule which, among other things, defined the term "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" (81 FR 33742 at 33979). We also announced that we had determined that seven isolated or synthetic non-digestible carbohydrates (NDCs) (beta-glucan soluble fiber (as described in § 101.81(c)(2)(ii)(A)), psyllium husk (as described in §101.81(c)(2)(ii)(B), cellulose, guar gum, pectin, locust bean gum, and hydroxypropylmethylcellulose) must be declared as dietary fibers on a Nutrition and Supplement Facts label because they have physiological effects that are beneficial to human health (81 FR 33742 at 33979).

Any interested person may seek to amend the list of NDCs that meet the definition of dietary fiber through our citizen petition process in 21 CFR 10.30 (81 FR 33742 at 33853). In the *Federal Register* of November 23, 2016 (81 FR 84516), we announced the availability of two documents for public comment: (1) a draft guidance titled, "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): Guidance for Industry" (2016 draft guidance); and (2) a document titled "Science Review of Isolated and Synthetic Non-Digestible Carbohydrates" (2016 science review). In addition to requesting comments on these two documents, we published a separate notice in the *Federal Register* requesting any other additional scientific data and information that would help us determine whether any other NDCs should be added to the list of fibers that meet our definition of dietary fiber (81 FR 84595).

B. Summary of the Issues

Based on a science review of the publicly available studies, we identified five isolated or synthetic NDCs (cellulose, pectin, guar gum, locust bean gum, and hydroxypropylmethyl-cellulose) in the final rule that provide a physiological effect that is beneficial to human health and therefore are considered dietary fibers.[17] We also included two other NDCs (beta-glucan soluble fiber and psyllium husk) in our list of dietary fibers because we had previously determined that they have beneficial physiological effects related to the risk of coronary heart disease in one of our authorized health claims regulations (21 CFR 101.81).

1. Consideration of Clinical Studies Conducted in Diseased Populations

The 2016 science review excluded consideration of any clinical studies that were conducted on diseased populations because the Nutrition Facts label is not targeted to

[17] U.S. Food and Drug Administration, Memorandum to the File: Scientific Review of the Beneficial Physiological Effects of Non-digestible Carbohydrates for Meeting the FDA Definition of Dietary Fiber, May 9, 2016.

individuals with a particular acute or chronic disease, but rather is intended to provide the general U.S. population with information to help consumers make more informed and healthy dietary choices (81 FR 33742 at 33750). We have reconsidered this approach and determined that, for certain endpoints, studies conducted on individuals diagnosed with a specific disease can be considered as part of our evaluation of the totality of the evidence when deciding whether an NDC meets our definition of dietary fiber. For example, certain NDCs can attenuate post-prandial blood glucose levels or improve laxation because of their presence in the gastrointestinal tract, rather than systemically (e.g., the failure of cells to respond to insulin (insulin resistance)). Therefore, we can include studies evaluating whether an NDC affects post-prandial blood glucose levels in diabetic individuals or laxation in constipated individuals as part of our evaluation of the totality of the evidence. When evaluating the strength of the evidence, scientific evidence showing a beneficial effect in healthy populations would increase the strength of the evidence for purposes of deciding whether an NDC is a dietary fiber on the Nutrition and Supplement Facts label.

However, exclusion of studies involving individuals diagnosed with a specific disease can be appropriate in other situations. For example, we decline to extrapolate findings on individuals with diarrhea to the healthy population for evaluating improved laxation because there are multiple causes of diarrhea, and most causes of diarrhea are not related to how an NDC might improve laxation. Therefore, as discussed in the 2018 final guidance, we will consider evidence from studies with subjects who have a disease that is associated with the physiological effect of interest when extrapolating to individuals who do not have the disease is scientifically appropriate.

2. Studies Involving a Combination of NDCs

Studies involving a combination of NDCs also may be relied upon to demonstrate a relationship between an isolated or synthetic NDC that is added to food and a physiological effect that is beneficial to human health. A principal consideration is whether the data from such studies can evaluate the independent physiological effect of the individual NDC. We will not consider data from studies in which a combination of NDCs or food components are provided to study subjects if the individual NDC of interest may contribute to a beneficial physiological effect, but cannot be shown to have an independent effect (e.g., the other NDCs or food components are not controlled for).

Thus, the 2018 final guidance clarifies that, if a combination of isolated NDCs is used as an ingredient, each isolated NDC would need to demonstrate a beneficial physiological effect for the NDC combination to be declared as a dietary fiber. Otherwise, a citizen petition can be submitted that provides data on that specific combination, and we will evaluate the data on that specific combination to determine if the combination provides a physiological effect that is beneficial to human health.

3. Physiological Endpoints and Baseline Values

With respect to physiological endpoints, the 2018 final guidance provides additional examples of physiological endpoints that we consider, but this is not an exhaustive list.

For example, we consider fecal output/fecal weight as measured on the basis of grams/day as a measure of laxation.

The 2018 final guidance also clarifies that, if baseline values are statistically different between groups in a parallel design study, a statistical analysis that includes adjustments for baseline, or calculations of change from baseline, should be used. The appropriate statistical analysis will vary depending on factors, such as the study design and the research question posed by the study.

4. Factors FDA Considers in Evaluating the Strength of the Evidence

The 2018 final guidance provides more detail on the factors that we consider when evaluating the strength of the evidence (e.g., types of foods tested). The preamble to the final rule titled, "Food Labeling: Revision of the Nutrition and Supplement Facts Labels" discussed the scientific evidence needed to demonstrate a beneficial physiological effect (see 81 FR 33742 at 33855 to 33856). The 2018 final guidance provides additional information on the scientific evidence we recommend be included in a citizen petition and the approach we intend to use when reviewing the scientific evidence. For example, the 2018 final guidance provides more information on what we intend to consider when evaluating the strength of the evidence, such as, the number of studies, doses provided in a study and dose-response analysis conducted within a study, and type of foods. The factors we identify in the 2018 final guidance for the review of the strength of the scientific evidence to demonstrate a beneficial physiological effect to human health include general, broadly accepted scientific principles and approaches to the review of scientific evidence. In addition, our review of the sufficiency of the scientific evidence for any request to support an NDC as a dietary fiber is a public process and provides an opportunity for interested persons to comment on scientific evidence and our scientific review of the evidence on a case-by-case basis.

5. Consideration of Unpublished Data

We stated, in the preamble to the final rule titled, "Food Labeling: Revision of the Nutrition and Supplement Facts Labels," that a petition to request an amendment to the definition to include an additional dietary fiber should include all publicly available evidence relevant to the review (81 FR 33742 at 33856). A citizen petition is filed by the Dockets Management Staff to which an interested person may submit comments (21 CFR 10.30(c) and (d)). Information submitted to FDA will be handled in accordance with all applicable laws, including the Freedom of Information Act (5 U.S.C. § 552), the Trade Secrets Act (18 U.S.C. § 1905), and applicable FDA regulations (e.g., 21 CFR part 20). Under 21 CFR 20.61(c), data and information submitted or divulged to FDA which fall within the definitions of a trade secret or confidential commercial or financial information are not available for public disclosure. However, we encourage the submission of publicly available information because, if we propose to amend the list of NDCs that meet the definition of "dietary fiber," the proposed rule would be a public rulemaking process, and we would want to provide an opportunity for interested persons to comment on the scientific information we received in a petition or in comments to a petition.