CITIZEN PETITION

To:

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 106
Rockville, MD
20852

Date: March 1, 2022

The undersigned, Chinova Bioworks Inc., submits this petition to the United States (U.S.) Food and Drug Administration (FDA) under Title 21 *Code of Federal Regulations* (CFR) §10.30 to request the Commissioner of Food and Drugs to formally amend their guidance document, *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)*, to consider meta-analyses in their evaluations to support the physiological benefits of dietary fibers, **provided that the meta-analysis includes all studies from which scientific conclusions can be drawn, and sufficient detail on each individual study included in the meta-analysis is provided as part of the submission**.

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A. Action Requested

Chinova Bioworks Inc. requests that the U.S. FDA amend their *Guidance for Industry: 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)* (hereinafter also referred to as the "Guidance Document") (U.S. FDA, 2018), as indicated below in bold font, to consider meta-analyses in their evaluations, provided that the meta-analysis includes all studies from which scientific conclusions can be drawn, and sufficient detail on each individual study included in the meta-analysis is provided as part of the submission.

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> "*Reports, such as review articles, which summarize the findings of individual studies, and meta-analyses, 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 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*. ***As part of the scientific review, a high quality meta-analysis that is conducted and included in the petition may be considered in evaluating the strength of the evidence, provided that all publicly available studies from which scientific conclusions can be drawn are included in the meta-analysis, and sufficient detail on each individual study included in the meta-analysis is provided as part of the petition***".

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> "*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.* ***A high quality meta-analysis that is conducted and included in the petition may also be considered in evaluating the strength of the 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 < 0.05).* ***In cases where a meta-analysis is appropriate, the pooled effect size would need to be statistically significant (P<0.05).***

- *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.*

- ***A high quality meta-analysis that is conducted as part of the petition, using all publicly available studies from which scientific conclusions can be drawn. To be considered a high quality meta-analysis, transparent and adequate documentation of the objective, study eligibility criteria, statistical methodology, and sub-group analyses should be prepared prior to the conduct of the meta-analysis and provided in the petition; as well, sufficient detail on each individual study included in the meta-analysis must be provided as part of the petition***".

Chinova Bioworks Inc. is requesting that the U.S. FDA consider the results of meta-analyses as part of future scientific evaluations of the beneficial physiological effects of isolated or synthetic non-digestible carbohydrates.

B. Statement of Grounds

B.1 Regulatory Background

In May 2016, Nutrition Facts and Supplement Facts Label regulations were amended, as per the *Federal Register* of 27 May 2016 (hereinafter referred to as the "Final Rule"); among the changes was the definition of dietary fiber (U.S. FDA, 2016). Dietary fiber was newly defined 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*".

Correspondingly, isolated or synthetic non-digestible carbohydrates are required to have physiological effects that are beneficial to human health. At the time, 7 non-digestible carbohydrates were determined to have physiological effects that are beneficial to human health (*i.e.,* that met the definition of dietary fiber), and interested parties were advised to submit a citizen petition under 21 CFR 10.30 to add other isolated or synthetic non-digestible carbohydrates that meet the definition of dietary fiber.

In February 2018, the FDA finalized and published *Guidance for Industry: 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*) (U.S. FDA, 2018). The Guidance Document provides insight into the FDA's current thinking on the type of scientific evidence that will be required, and the scientific evaluation approach in determining whether an added isolated or synthetic non-digestible carbohydrate has a beneficial physiological effect in humans.

According to the Guidance Document, the FDA's scientific evaluation process involves the following steps:

A. *Assess publicly available scientific studies and other data;*

B. *Eliminate those studies from which scientific conclusions about the physiological effects of an added non-digestible carbohydrate cannot be drawn;*

C. *Evaluate the strength of the scientific evidence to determine whether the carbohydrate provides a physiological effect that is beneficial to human health.*

With regards to the types of publicly available scientific studies that the FDA would consider (Point A above), it is stated that:

- "*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*";
- "*Publicly available studies include those studies that are in manuscript form and can be available for the public to review*";
- "[…] *randomized, controlled intervention studies provide the strongest evidence of whether there is a relationship between an added non-digestible carbohydrate and a physiological effect*";

- "*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*[…] *Therefore, observational studies that rely on intake data for evaluating the association between an added non-digestible carbohydrate and a beneficial physiological 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*";

- "*Reports, such as review articles, which summarize the findings of individual studies, and meta-analyses, 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 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*"; and

- "*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*[…]".

To summarize, randomized, controlled intervention studies are primarily considered in the determination of whether isolated or synthetic non-digestible carbohydrates have physiological effects that are beneficial to human health, while observational studies are currently not considered due to limitations in accurately estimating the amount of isolated or synthetic non-digestible carbohydrate consumed during the study by the study participants. Meta-analyses cannot be considered in determining the strength of the scientific evidence because they lack detailed information on the individual studies included in the analysis.

In contrast, in their *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims* (U.S. FDA, 2009), the U.S. FDA explicitly states that they would consider a submitted meta-analysis as part of the evidence-base, so long as the submitted meta-analysis is based on the totality of publicly available human evidence, and the included studies are consistent with FDA's expectations in terms of study quality:

> "[…] *FDA intends to use review articles and similar publications to identify reports of additional studies that may be useful to the health claim review and as background about the substance/disease relationship. If additional studies are identified, the agency intends to evaluate them individually. Most meta-analyses, because they lack detailed information on the studies summarized, will only be used to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship. FDA, however, intends to consider as part of its health claim review process a meta-analysis that reviews all the publicly available studies on the substance/disease relationship. The reviewed studies should be consistent with the critical elements, quality and other factors set out in this guidance and the statistical analyses adequately conducted*".

It should be noted that the FDA received 2 comments following the publication, in November 2016, of the Draft Guidance Document (*i.e.,* during the commenting period) related to the consideration of meta-analyses in determining whether isolated or synthetic non-digestible carbohydrates have a physiological effect beneficial to human health. The American Herbal Products Association (AHPA) and International Life Sciences Institute (ILSI) North America noted that the value of meta-analyses may extend beyond identifying additional studies relevant to the scientific review (AHPA, 2017; ILSI, 2017). Given that no notable changes were made regarding the use of meta-analyses between the Draft and Final Guidance Documents, the petitioner assumes that the FDA does not consider meta-analyses because of the reasons cited in both the Draft and Final versions of the Guidance Documents; namely, meta-analyses lack detailed information on the individual studies, preventing the FDA from determining the methodological robustness of each study (included in the meta-analysis).

B.2 Factual Grounds for this Petition

B.2.1 Definition of a Meta-analysis

The definition of a meta-analysis provided in the Guidance Document is, "*the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated*" (Spilker, 1991). The Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health and Human Services, in their *Nutritional Research Series: Advancing the Role of Evidence-based Reviews in Nutrition Research and Applications*, provide the following definition: "*Meta-analysis uses statistical methods to combine two or more studies addressing the same question*. *It is often part of a systematic review and can identify significant results when individual studies are inadequately powered*" (Lichtenstein *et al*., 2009a,b). In other words, a meta-analysis is a component of a systematic review where statistical methods are used to combine the results of multiple studies to yield an overall statistic (*i.e.,* calculation of the pooled effect).

Relative to individual intervention studies, potential benefits of meta-analyses include (Cochrane – Deeks *et al*., 2021):

- Improvement in precision—*i.e.,* intervention studies are often too small to yield strong evidence so an estimation based on multiple studies can improve precision;

- The ability to answer questions (that cannot be answered with individual studies)—*i.e.,* each individual intervention study is conducted in a specific setting (such as a specific study population), and meta-analyses can be conducted to compare the effects of studies with different characteristics (and offer possible explanations to differences observed across individual studies);

- Settling studies that appear to be contradictory or to generate new hypotheses—*i.e.,* the overall statistic (pooled effect) settles contradictory results between studies and the reasons for the contradictory results can be explored.

B.2.2 Challenges in Nutrition Studies

Although the randomized controlled trial paradigm was developed for the clinical investigation of pharmaceuticals, it is increasingly being applied to the clinical investigation of foods and food constituents. However, nutrition or dietary intervention studies are associated with challenges that pharmaceutical intervention studies often do not face. Major challenges that are unique to nutrition or dietary studies include confounding with baseline/habitual exposure to the nutritional intervention; displacement of other

nutrients/changes in dietary patterns; effects of the food matrix used (and differences in bioavailability); inaccurate intake assessment; use of meaningful or relevant control; and inability to blind research investigators and/or subjects (Lichtenstein *et al*., 2008; Weaver and Miller, 2017). These challenges translate into greater variability between studies and within studies (*i.e.,* in the subjects), and greater variability within studies leads to a decreased ability to detect statistically significant differences between control and active groups.

Due to regulatory requirements, nutrition or dietary intervention studies are generally conducted in healthy or borderline-healthy individuals, while drug studies are conducted in unhealthy subjects with specific diseases or conditions. Coincidently, effect sizes of nutrition or dietary interventions are generally small relative to the effect sizes of pharmaceuticals. With smaller effect sizes and greater variability, nutrition or dietary intervention studies require a greater number of subjects to be adequately powered; however, nutrition or dietary intervention studies are typically smaller than pharmaceutical studies (given the economics and funding differences) (Frestedt, 2017).

Therefore, meta-analyses (as stated in B.2.1) can potentially directly address the challenges associated with clinical nutrition studies, as meta-analyses help obtain a more precise estimate of the effect size and address potential differences observed across studies.

B.2.3 Uses of Meta-analyses in Regulatory and Policy-related Initiatives

Given the potential benefits of addressing the challenges in nutrition research, meta-analyses are widely used by national and international scientific and/or regulatory bodies.

B.2.3.1 AHRQ

The Office of Dietary Supplements (ODS) at the National Institutes of Health (NIH) have used the Evidence-based Practice (EPC) Reports program developed by AHRQ to address the congressional mandate to better understand the efficacy and safety of dietary supplements. Through the program, over 17 evidence reports have been prepared related to the efficacy and/or safety of B-vitamins, ephedra, multivitamin/mineral supplements, *omega*-3 fatty acids, soy, and vitamin D. In addition to the evidence reports that relied on systematic reviews to derive the conclusions, given the challenges involved in conducting systematic reviews on nutrition-related research questions, Technical Reports were prepared, in order to:

(a) "*identify the challenges, advantages, and limitations of conducting nutrition-based systematic reviews;*

(b) *work with a panel of experts to explore approaches for integrating systematic reviews into processes associated with the derivation of nutrient intake reference values;*

(c) *identify the breadth and quality of currently available nutrition-related systematic reviews against generally accepted quality guidelines within the context of the unique needs for nutrition topics; and*

(d) *critically explore the consistencies and inconsistencies in results between observational and intervention studies and evaluate how the formulation of research questions may have contributed to these discrepancies"* (Lichtenstein *et al*., 2009a).

On the topic of the use of meta-analyses in nutrition-related applications, the following was noted in the Technical Report:

"*The ability to combine small studies with meta-analysis increases the statistical power available to address specific questions. This is particularly useful for systematic reviews of nutrition topics where the availability of large trials is relatively limited or lacking. Meta-analyses may have potential usefulness in simulating dose-response curves across intervention studies that individually evaluated only one or two intake levels*".

Consequently, AHRQ recommends the synthesis of results by performing meta-analysis (if appropriate) as part of conducting a systematic review in nutrition research (Lichtenstein *et al*., 2009b).

B.2.3.2 WHO

The World Health Organization (WHO) recommends the use of meta-analyses in developing WHO Guidelines. In the WHO's *Handbook for Guideline Development,* which is a step-by-step instruction on developing WHO Guidelines, the WHO recommends the use of a meta-analysis to combine the results across comparable studies, and only when it is not feasible or appropriate (*e.g.,* due to heterogeneity or the nature of the data), it recommends that the evidence be qualitatively presented (WHO, 2014).

An example of a guideline based on meta-analyses is the WHO's guideline on sugar intake (WHO, 2015). The WHO recommended the reduction of free sugar intake, and the basis of the recommendations were the effects of free sugar on body weight and dental caries. The following results were observed from the meta-analyses[1]:

- A reduced intake of free sugars, in 5 adult studies in which diets were consumed *ad libitum*, was associated with a statistically significant decrease in body weight (pooled effect of -0.80 kg, 95% confidence interval: -1.21, -0.39 kg). Based on the results of the individual studies, there was a high level of consistency (with 100% of the studies favoring decreased body weight with reduced intake of free sugars) in the direction of effect; however, statistically significant decreases in body weight were observed in only 1 of the 5 studies (Te Morenga *et al*., 2012).

- An increased intake of free sugars in 10 studies was associated with a statistically significant increase in body weight (pooled effect of +0.75 kg, 95% confidence interval: 0.30, 1.19 kg). Based on the results of the individual studies, there was a high level of consistency (90% of the studies favoring increased body with increased intake of free sugar) in the direction of effect and statistically significant increases in body weight were observed in 6 of the 10 studies (Te Morenga *et al*., 2012).

- Isoenergetic exchange of free sugars with other carbohydrates was not associated with significant changes to body weight (0.04 kg; 95% confidence interval: -0.04, 0.13). Statistically significant changes in body weight were observed in 1 of the 13 studies (Te Morenga *et al*., 2012).

The above findings are examples of where consistency of the findings among the individual studies did not always agree with the findings of the meta-analyses. The WHO concluded that there was low- and moderate-quality evidence on body weight to support the recommendation to reduce intakes of free sugars.

[1] The relationship between free sugar and dental caries was not examined *via* meta-analysis because of a high degree of variability in the outcome being reported. In addition, randomized controlled trials were not identified in the systematic review; rather, the systematic review was based on 2 non-randomized intervention trials in adults, 2 observational studies in adults, and 50 observational studies in children. Thus, the results pertinent to dental caries are not discussed herein.

B.2.3.3 Health Canada

In Canada, meta-analysis is an optional step in preparing a submission to Health Canada for a food health claim (Health Canada, 2009). Health Canada acknowledges that meta-analyses can be helpful in estimating the effect size or in comparing the effects across different studies; however, it is not a mandatory requirement of a health claim application because it can be resource-intensive, and it is not easy to conduct meta-analyses well (Health Canada, 2015). The scientific standard for supporting a food health claim is "a high level of certainty", which is reached when statistically significant improvements are observed in the majority (≥75%) of the high-quality human studies or when the pooled effect from a meta-analysis is statistically significant.

For example, in reviewing the scientific support for the claim related to ground whole flaxseed and lowering blood cholesterol, decreases in total cholesterol and low-density lipoprotein (LDL) cholesterol were observed in all 8 included studies; however, improvements in total cholesterol were statistically significant relative to the control in only 2 of the studies, while improvements in LDL cholesterol were not statistically significant from control in any of the studies (Health Canada, 2014). In a meta-analysis conducted by Health Canada's Food Directorate, statistically significant pooled effects were observed for total and LDL cholesterol and the health claim relationship was approved by Health Canada.

In Health Canada's *Questions and Answers about Preparing Submissions for Food Health Claims*, it is explicitly stated that "*meta-analyses are a significant undertaking and can be difficult to do well. If a company possesses the resources to perform or commission a meta-analysis of the studies included in the health claim submission, Health Canada encourages the company to submit it as part of their application*" (Health Canada, 2015).

B.2.3.4 Food Standards Australia New Zealand

In Australia and New Zealand, new health claims must be supported by a systematic review, regardless of the claim type (*i.e.,* high level or general level health claim) and regulatory route (*i.e.,* approval or notification – FSANZ, 2018[2]). The systematic review should be conducted in accordance with Schedule 6 of the Australia New Zealand *Food Standards Code*. Although the conduct of a meta-analysis is not a requirement, as per Schedule 6 in the Australia New Zealand *Food Standards Code*, the Ministry for Primary Industries (MPI)[3] does recommend the conduct of a meta-analysis if it is possible to do so, as meta-analyses are "*a more straightforward way to assess the consistency of the association*" (FSANZ, 2015; MPI, 2016).

B.2.4 Limitations and Important Considerations in Conducting Meta-Analyses

Although meta-analyses serve as a beneficial tool in conducting systematic reviews on nutrition-related topics, important limitations and considerations in conducting and interpreting results of meta-analyses have been raised by the regulatory or scientific bodies that utilize meta-analyses. A summary of the limitations and considerations provided by AHRQ, Cochrane Collaboration, and the WHO is provided in Table B.2.4-1.

The primary consideration or limitation of meta-analyses was noted to be whether the studies are similar enough such that an appropriate response would be ascertained from combining the study results. For example, the investigational and comparative products, the outcomes of interest, and the study populations

[2] A health claim application must be submitted to Food Standards Australia New Zealand (FSANZ) for any new high level health claim (*i.e.,* a claim that refers to a serious disease or a biomarker of a serious disease), while general level health claims (*i.e.,* a claim that is not a high-level health claim) have an option of either notification of the food-health relationship to FSANZ (or obtaining pre-market approval from FSANZ).

[3] MPI is a regulatory enforcement body of New Zealand.

should be sufficiently similar. Another important consideration in conducting and interpreting the results of meta-analyses is that the minor differences in the methodology used (*e.g.,* eligibility criteria, statistical analyses) to conduct the meta-analysis may impact the results and conclusion.

These considerations are critical in conducting a high-quality meta-analysis; however, in terms of using the meta-analysis to determine whether synthetic or isolated non-digestible carbohydrates have a physiological effect that is beneficial to human health, many of these considerations are already evaluated by the scientific evaluation principles laid out in the Guidance Document. The scientific evaluation of whether synthetic or isolated non-digestible carbohydrates have a physiological effect that is beneficial to human health requires a systematic, comprehensive, and transparent review process; therefore, by following the scientific guidance, studies most relevant to the objective, studies with equivalent or similar investigational products (*i.e.,* the isolated or synthetic non-digestible carbohydrate of interest), studies with similar valid and relevant outcomes, and studies with similar study populations would be selected. The only considerations that are not currently captured under the Guidance Document relate to pre-defining the statistical methodology (including sub-group analyses, sensitivity analyses, and handling of publication bias) of the meta-analysis, which can be resolved by requiring *a priori* protocol registration in a systematic review and/or meta-analysis repository.

Table B.2.4-1 Summary of Limitations or Key Considerations for Conducting and Interpreting Meta-analyses

Regulatory or Scientific Body	Comments Regarding the Limitations or Considerations of Conducting and Interpreting the Results of a Meta-analysis	Reference
AHRQ	AHRQ recommends that a meta-analysis be conducted only if appropriate. Key considerations in conducting a meta-analysis are the appropriateness of combining the studies and the methodology used to combine the studies. Different results can be obtained (albeit sometimes small) from meta-analyses with similar objectives when there are slight differences in the questions asked, the eligibility criteria applied, method of assessing the quality of the included studies, and applicability of the included studies. Therefore, the interpretation of meta-analyses requires the understanding of the nature of the data, question, and methodology. In AHRQ's *Method Guide for Effectiveness and Comparative Effectiveness Reviews*, a decision tree is provided on whether a meta-analysis should be conducted. Factors that are considered include: (i) clinical and methodological similarity between studies[4]; (ii) the composition of the evidence base (*i.e.,* presence of "best-quality" trials); (iii) risks for misinterpretation or misleading results (*e.g.,* wide-ranging effect sizes, reporting bias, small study effect); (iv) the number of studies available for the meta-analysis; and (v) the presence of statistical heterogeneity.	(Lichtenstein *et al*., 2009a) (Morton *et al*., 2018)
WHO	Meta-analysis should be conducted when certain requirements are met, one of the conditions being a high level of homogeneity between studies (in design, study population, intervention and comparator, and outcomes). In addition, any sub-group or sensitivity analyses should be defined *a priori.*	(WHO, 2014)
Cochrane Collaboration	Appropriate consideration has to be given at each step of the meta-analysis (*i.e.,* when formulating the review question; determining eligibility criteria; performing the literature selection; collecting appropriate data; considering methodological robustness of studies; planning intervention comparisons; and deciding what data would be meaningful to analyze). Inappropriate practices related to meta-analysis include: (1) Combining clinically-diverse studies in the meta-analysis. (2) Including individual trials that have a high risk of bias in the meta-analysis. The pooling of the studies with high risk of bias may compound the errors and may produce an inappropriate result.	(Cochrane - Higgins and Green, 2011; Deeks *et al.*, 2021)

[4] It is noted that there is no universally accepted standard to define "similarity"; therefore, "similarity" is based on judgement.

Table B.2.4-1 Summary of Limitations or Key Considerations for Conducting and Interpreting Meta-analyses

Regulatory or Scientific Body	Comments Regarding the Limitations or Considerations of Conducting and Interpreting the Results of a Meta-analysis	Reference
	(3) Using existing meta-analyses that contain serious publication and/or reporting biases. Results of such meta-analyses should be interpreted with caution.	

AHRQ = Agency of Healthcare Research and Quality; WHO = World Health Organization.

B.2.5 Use of Meta-analyses in Evaluating the Strength of the Evidence

According to the Guidance Document, the factors that the FDA considers in evaluating the strength of the evidence include the number of studies, the number of subjects in the studies, doses and dose-response relationships, the vehicle or matrix to which the non-digestible carbohydrate was added, the outcomes assessed, consistency of the results, and the relevance of the evidence to the general U.S. population. With respect to the outcome and consistency, it is noted that statistically significant differences relative to the control group must be observed to demonstrate a beneficial physiological effect and that consistency[5] across studies increases the level of confidence. Further, the Guidance Document references the Bradford Hill causality criteria and AHRQ's *Systems to Rate the Scientific Evidence* wherein the consistency is defined as "*the extent to which similar finds are reported using similar and different study designs*".

In AHRQ's *Methods Guide for Comparative Effectiveness Reviews: Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update* (Berkman *et al*., 2013), consistency can refer to (1) the direction of the effect, or (2) similarity in the effect sizes (*i.e.,* magnitudes of effect) across studies. The consistency in the direction of effect is determined by the line that distinguishes superiority from inferiority (*e.g.,* mean difference of zero or an odds ratio of one). Meanwhile, consistency in the effect sizes can be estimated by statistical tests (*e.g.,* Cochran's Q or I^2 statistic) for meta-analysis results (where meta-analysis is appropriate) or by reviewers' judgement when meta-analysis results are unavailable.

Therefore, results of meta-analyses can be used to evaluate the strength of the evidence in a manner similar to that of FDA's current approach; namely, statistical significance of the difference between the treatment group and the control group can be assessed and consistency in the direction of effect and the magnitude of effect can be assessed.

B.2.6 Standard of Scientific Evidence

In the Guidance Document, the FDA does not define the scientific standard required to conclude that an isolated or synthetic non-digestible carbohydrate has a beneficial physiological effect, as the FDA has previously done for health claims or structure/function claims (*e.g.,* "significant scientific agreement" for authorized health claims, "credible scientific evidence" for qualified health claims, and "competent and reliable scientific evidence" for structure/function claims on dietary supplements and infant formula).

[5] Consistency was not further defined to indicate whether consistency referred to statistically significant effects or to the direction of effect (regardless of the statistical significance).

In the Final Rule (page 33,855), the FDA responded to a comment requesting that the FDA provide an "evidentiary standard" and that the scientific standard should not be equivalent to the significant scientific agreement standard for an authorized health claim (rather the comment suggested that evidence from animal or *in vitro* studies be considered) (U.S. FDA, 2016). As part of the response, the FDA differentiated "health claims" from "physiological effects that are beneficial to human health", the latter which are required for nutrient declaration on a food label (*i.e.,* for dietary fiber). While health claims can be substantiated by studies showing a reduced risk in chronic disease or a health-related condition, physiological effects that are beneficial to human health may be substantiated with well-established physiological endpoints (*e.g.,* postprandial blood glucose, improved bowel function). In addition, the FDA responded that the "*strength of the total evidence should demonstrate a specific beneficial physiological effect and that the beneficial effect should be replicated*". It is the petitioner's understanding that no "evidentiary standard" was provided by the FDA in response to the comment.

In Appendix A of the Guidance Document (under "Factors FDA Considers in Evaluating the Strength of the Evidence"), the FDA again noted that, "*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*** [emphasis added]". A high quality meta-analysis is a broadly accepted scientific principle and approach to the review of the scientific evidence.

C. Environmental Impact

This Citizen's Petition relates to an action that is categorically excluded from environmental impact considerations under 21 CFR §25.30(h) (U.S. FDA, 2021a), thus an environmental assessment was not included.

D. Economic Impact

An economic impact assessment is to be submitted only when requested by the Commissioner following review of the petition, as indicated in 21 CFR §10.30 (U.S. FDA, 2021b).

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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