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Division of Dockets Management (HFA-305)
Food and Drug Administration
5360 Fishers Lane
Rm. 1061
Rockville, MD 20852

RE: Docket: FDA-2016-D-3401

Dear Madam or Sir,

The North American Branch of the International Life Sciences Institute (ILSI North America) appreciates the opportunity to share scientific perspectives from ILSI supported scientific publications in response to the Food and Drug Administration's (FDA) proposed guidance on the *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* (Docket No. FDA-2016-D-3401).

ILSI North America is a public, non-profit organization that actively collaborates with government and academia to identify and resolve scientific issues important to public health. The organization carries out its mission by sponsoring relevant research, professional education programs and workshops, seminars and publications, as well as providing a neutral forum for government, academic, and industry scientists to discuss and resolve scientific issues of common concern for the wellbeing of the general public. ILSI North America programs are supported primarily by industry member companies.

ILSI North America's Technical Committee on Carbohydrates submits these comments in response to draft guidance by FDA describing the "scientific review approach planned for use in evaluating scientific evidence to determine whether an isolated or synthetic non-digestible carbohydrate that is added to food has a physiologic effect that is beneficial to human health."

FDA's guidance addresses three areas noted here in brief: (1) identify relevant articles, (2) evaluate studies from which conclusions can be drawn, and (3) evaluate the strength of evidence to determine whether there is a physiologic benefit to human health. In the first of these areas, FDA guidance focuses on identifying primary evidence from human studies and cites the role of "research synthesis studies" such as reviews and meta-analyses as a way to identify primary human research and for use as background information. The role of meta-analyses and pooled studies is not addressed in the guidance on evaluating the strength of scientific evidence.

An ILSI Europe monograph by Lillian Langseth provides perspective on a wide-range of epidemiologic research, including population based human intervention studies (Langseth, 1996). Of particular relevance to the FDA guidance is information on the useful role and limitations of meta-analyses, which directly addresses several factors noted by FDA to be considered in

evaluating the strength of scientific evidence. The Langseth monograph notes that meta-analyses are particularly useful when results from studies conflict:

> *In this situation, the inconsistency can sometimes be resolved through a meta-analysis – a quantitative technique in which the statistical results of separate studies are pooled to yield overall conclusions*
>
> *Meta-analysis may be more objective than traditional critical reviews of the literature and it can help make sense out of studies too small to provide reliable answers when analyzed individually. However, decisions about which studies to include in a meta-analysis can be difficult. Opinions differ on whether flawed studies and unpublished studies (often the ones that give negative results or no effect) should be included in meta-analyses and on whether studies of better quality should be given greater weight than those of lesser quality.*
>
> *Studies that are to be combined in a meta-analysis should be similar in terms of the types and amounts of exposures and the types of outcomes assessed. If the studies differ in these respects, the meta-analysis may yield erroneous results. For example, a meta-analysis that supposedly indicated that vitamin C has no effect on the common cold has been questioned because it included studies that employed low doses of vitamin C (200 mg/day or less) as well as those that used mega-doses (1–5 g/day). The negative results of the low dose studies may have diluted the more positive results of the high-dose studies, leading to an incorrect conclusion. Critics have argued that it would have been better to analyze the two groups of studies separately.*

This perspective suggests a useful role of meta-analysis based on relevant human studies in the third area of guidance, namely evaluating the strength of scientific evidence

<u>In conclusion, the Langseth monograph states:</u>

> *{S}cientists must consider whether findings may have been due to chance and whether a study had sufficient power to detect an association if it was present. When the results of epidemiological studies conflict with one another, it may be possible to resolve the inconsistency through meta-analysis – a quantitative technique in which the statistical results of separate studies are pooled in an attempt to yield overall conclusions. Even if a study or a meta-analysis shows a statistically significant association, epidemiologists should use caution when extrapolating findings from one group of people to other, very different population groups.*

Based on this conclusion, meta-analyses can be used in appropriate and relevant conditions to assess the evaluate strength of evidence for specific fibers in determining whether there is a physiologic benefit to human health, beyond its use to "identify reports of additional studies."

Respectfully submitted,

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References

Langseth, L. "Nutritional Epidemiology: Possibility and Limitations." ILSI Europe Concise Monograph. http://ilsi.org/publication/nutritional-epidemiology-possibilities-and-limitations/ (Last accessed January 19, 2017).