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Advancing probiotic research in humans in the United States: Challenges and strategies

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ABSTRACT

This is a summary from a workshop convened as part of the 13th annual meeting of the International Scientific Association for Probiotics and Prebiotics. A group of 24 stakeholders, including clinical experts, researchers, federal government officials, funding agencies, lawyers and industry experts met to review the challenges of the current regulatory approach to human research on probiotics in the USA and to discuss ways to move research forward. There was agreement that some of the current regulatory requirements imposed on probiotic research in the United States hindered research progress and increased cost without improving study subject safety. Many situations were outlined by clinical investigators demonstrating the impact of regulatory delays on research progress. Additionally, research is compromised when study designs and outcomes require manipulation so as to invoke less burdensome regulatory requirements. These responses by investigators to regulatory requirements have placed United States' researchers at a disadvantage. The public ultimately suffer when research to clarify the role of these products on health is stalled. Workshop participants concurred that regulatory oversight should balance study subject vulnerability with documented safety for the intended use for the probiotic strain, and that human research on foods and supplements should not be be regulated as drug research. Challenges and potential improvement strategies are discussed.

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Introduction

The intent of the workshop was to discuss with multiple stakeholders the challenges of the current regulatory approach to human research on probiotics in the United States and to consider potential strategies to reduce the regulatory burden without compromising subject safety. The key challenges were (1) establishing a clear path for human research on probiotics for foods, supplements and medical foods that does not require the Investigational New Drug (IND) framework; (2) providing a path for human research that does not automatically require safety studies if adequate documentation of safe use exists for the conditions of use; and (3) streamlining the IND process to facilitate investigator-initiated research. The 24 participants (listed in acknowledgments section) comprised clinical experts, researchers, federal government officials, funding agencies, lawyers and industry experts.

Through a period that has seen rapid global expansion of probiotic research, human studies in the United States are few. A search of PubMed revealed that of 27 human studies on probiotics published January through September 2015, only 3 were conducted in the United States. Furthermore, industry appears to be less likely to fund human studies on probiotics compared to other substances in the United States. A search of www.clinicaltrials.gov on September 24, 2015 indicated that 59%, 49% and 46% of industry-funded studies conducted on omega-3 fatty acids, vitamin D and antioxidants, respectively, were conducted in the United States, in comparison to only 23% for probiotic studies. Although we cannot prove the cause of these associations, one explanation is that regulatory oversight is discouraging probiotic research in humans in the United States. We believe this is largely due to regulators viewing probiotics as drugs, even when research endpoints can clearly be considered legitimate for foods, and subsequently requiring that the research with them be conducted under an IND framework. This requirement extends to the study of

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probiotic foods, dietary supplements or medical foods that are not intended to be marketed as drugs. This approach has hindered progress and increased cost without improving study subject safety. Additionally, research is compromised when study designs and outcomes are manipulated in an effort to avoid burdensome regulatory requirements.

As part of the IND process, the Food and Drug Administration (FDA) has required investigators to conduct safety studies prior to efficacy studies.[1,2] Safety assessments have been mandated even when the probiotic is widely marketed, is the subject of a Generally Recognized as Safe notification, or has otherwise been tested or used with a reasonable certainty of no harm.

Although this situation has beset probiotic research for a decade, a final guidance for clinical investigators, sponsors, and Institutional Review Boards (IRB) was issued in 2013 by the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research and Center for Food Safety and Applied Nutrition (CFSAN) of the FDA.[3] The scope of this guidance went beyond probiotics, covering all substances being investigated by human research. The guidance was titled "Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND."[3] This guidance indicated FDA's intent to require INDs for most foods and dietary supplements. In response to comments from the nutrition community in which they delineated ways that this guidance would hinder nutrition research, the FDA reopened portions of the guidance for comment through April 2014.[4] On October 30, 2015, the FDA issued an administrative stay, under which FDA will refrain from enforcing certain food-related sections of this guidance as the agency continues to consider the issues.

The combined effect of these actions by the FDA has resulted in many IRBs requiring INDs from investigators proposing research with a probiotic. Many industry sponsors intending to market foods or dietary supplements (and not drugs) have elected to conduct their probiotic clinical trials in non-United States settings or not at all to avoid the burdensome and non-applicable requirement for an IND. In addition to the challenges of complying with IND requirements if the investigated product is not manufactured at a pharmaceutical grade facility, companies worry that once research on a new probiotic commences as an investigational new drug, their product may be precluded from being marketed as a food or dietary supplement in the future. This is a reasonable concern for investigational foods or supplements not previously marketed, since the FDA Amendment Act of 2007 prohibits the sale of food containing a biological product for which "substantial clinical investigations" have been instituted.[5]

Furthermore, workshop stakeholders emphasized that the IND requirement to conduct probiotic clinical research ignores the statutory distinctions between "foods" and "drugs" and narrows the scope of "nutrition" and understanding of "food" to include only items consumed primarily for taste, aroma, or nutritive value. This imposes a drug process that is not applicable to foods and does not consider that foods and all its subcategories are lawfully legitimate subjects of human research. Under law, foods may impact the structure or function of the human body, reduce the risk of disease, or provide for the specific dietary management of a disease or condition. As these are appropriate uses for foods, research designed to establish the role of foods in these functions should not legally be required to be conducted under an IND. The current version of the FDA guidance will require modification to clarify this point for stakeholders.

Suggested solutions

The discussion resulted in support for the following measures that would facilitate progress with probiotic research in human subjects in the United States:

- The panel suggested that a process for uniform guidance for probiotic research harmonization between CBER and CFSAN would be helpful.
- Better intra-agency communication between CBER and CFSAN is needed. A single point of contact with both CBER and CFSAN or a cross-center committee would serve as a resource for researchers and industry seeking to conduct probiotic research in human subjects. This would assist in the process of determining if an IND is necessary for the research, and if so, facilitate the IND process.
- A reassessment by FDA is needed regarding when an IND should be required for probiotic

research in human subjects. A path to conduct such research without an IND on endpoints legally allowed for foods (including reduction of risk of disease, structure and function of the human body and dietary management of a disease) should be possible for probiotic foods, including dietary supplements and medical foods.

- The degree of regulatory oversight should balance study subject vulnerability and documented safety for the intended use for the probiotic strain.
- A requirement to conduct a safety study before any efficacy studies should depend on the information available and should not be automatic. Safety studies should be waived if evidence of probiotic strain safety for the intended use is sufficient. Existing information and documentation should be considered in judging probiotic safety, including Generally Recognized as Safe evaluations, New Dietary Ingredient Notifications, history of safe use, scientific studies and safety evaluations from other countries (such as Qualified Presumption of Safety in the EU, licensure in Canada as a Natural Health Product, recognized Novel Food in the EU). Safety for the intended study population, and not the nature of the research endpoint, should determine the need for a safety study. If a new probiotic strain does not have documented safety, then it must be tested in safety tests and then in human studies with proper oversight.
- The proposal by CBER put forth for public comment would ease the path to conducting research under an IND on commercialized probiotics by allowing the product label to serve as chemistry, manufacturing and control information.[6]

Conclusions

The outcome of this workshop was tremendously positive. Although past difficulties were acknowledged, effective strategies to streamline the process of conducting human studies were proposed. The FDA can reasonably require that human studies be conducted in a manner that will assure the safety and rights of subjects in all phases of an investigation. However, such oversight does not need to be executed under the guise of an IND when foods and supplements are the subject of investigation.

Abbreviations

FDA	Food and Drug Administration
CBER	Center for Biologics Evaluation and Research
CFSAN	Center for Food Safety and Applied Nutrition
IND	Investigational New Drug
IRB	Institutional Review Board
ISAPP	International Scientific Association for Probiotics and Prebiotics.

Disclosure of potential conflicts of interest

DJM has been a scientific expert about marketing claims for a probiotic product for General Mills, Bayer, Procter & Gamble and Nestle. Dannon, Lifeway, Nestle and Cargill have provided Georgetown funding for separate clinical trials. MES has been a consultant for numerous probiotic food and supplement companies and receives financial remuneration from ISAPP for her role as Executive Science Officer. ALS received a research grant through Emory University from the Gerber Foundation and an unrestricted donation of probiotic and placebo product from BioGaia from 2012-2014 for a research study.

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