Establishing and Evaluating Health Claims for Probiotics[1,2]

Sharon M. Donovan,[3*] Barbara Schneeman,[4] Glenn R. Gibson,[5] and Mary Ellen Sanders[6]

[3]Department of Food Science and Human Nutrition, University of Illinois, Urbana, IL; [4]Office of Nutrition, Labeling, and Dietary Supplements, Center for Food Safety and Applied Nutrition, Food and Drug Administration, College Park, MD; [5]Department of Food and Nutritional Sciences, University of Reading, Reading, UK; [6]Dairy and Food Culture Technologies, Centennial, CO

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (1). The potential for probiotics to treat or prevent disease conditions, to maintain health and to reduce the risk of future disease is an active area of investigation (2). However, there is neither a legally recognized definition of, nor a standard of identity for, the term probiotic in the US or Europe (3). Currently, products containing this label must comply with safety, labeling, and good manufacturing requirements stipulated for the applicable product category (e.g., foods, dietary supplements, medical foods or drugs), but no standards unique to probiotics exist in the US. Under the federal Food, Drug, and Cosmetic Act, health claims on foods or dietary supplements can be authorized by the FDA (4–7).

Successful and responsible introduction of probiotic products into the marketplace requires labeling for health benefits that adheres to regulatory standards and accurately conveys scientific evidence (3,7). Health benefit claims must be supported by well-conducted human trials in the targeted population (3,6). However, studies to support claims for probiotic products may be confounded by the health status of the consumers and their resident microbiota (3,6). Additionally, human trials to show efficacy are expensive, and obtaining optimal physiological samples from intestinal sites is difficult (4). Regulations differ among countries, but underlying all is an emphasis on scientific credibility of any statements of health benefits (6). Therefore, the goal of this workshop was to review the scientific evidence underlying US and European Union (EU) regulations affecting health claims for probiotics and the process for developing evidence to substantiate their health effects.

In the first presentation, Glenn Gibson reviewed approval of health claims by the European Food Safety Authority (EFSA) and recent recommendations regarding designs for probiotic trials with the goal of substantiating health claims. EC Regulation No. 1924/2006 was established to generate approval of health claims made for food, including an evaluation of dossiers by EFSA. Potential probiotic claims have not met with a favorable reaction from EFSA. Therefore, a panel of independent academic scientists with proven track records in probiotic research made the following recommendations for the design of probiotic studies intended to substantiate health claims in EU (8):

- Discriminate between a trial to test a hypothesis compared with a trial to substantiate a health benefit claim.
- Use a dose available in commercial products.
- Ensure that trials are appropriately powered with an adequate sample size, based on the expected magnitude of effect. Otherwise, statistically significant conclusions cannot be obtained and meaningful conclusions drawn. Therefore, >1 recruitment site may be needed.
- Ensure that trials are of appropriate duration to determine endpoints that are tested
- Avoid evaluation of multiple parameters unless they are hypothesis driven.
- Volunteers should reflect the general population (e.g., age, sex, BMI)
- Characterize the probiotic product, including demonstration of viability at beginning, middle, and end of study, as well as detailed biological and genetic description of the probiotic strain(s).
- Ensure that strain(s) used in studies is (are) the same as those in the intended product.
- Use multiple sample times.
- Take and store additional physiological samples for future tests.
- Preferably use validated endpoints with clinical support, e.g., eczema, immune aspects, lipids, microbiota, transit, gut assessments, metabolites, geno/cytotoxicity, other biomarkers.
- Include biomarker(s) to help mechanisms/causality.

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*To whom correspondence should be addressed. E-mail: sdonovan@illinois.edu.

The panel agreed that there is a need to address generally accepted biomarkers (e.g., information generated by the EU-funded European Commission Concerted Action on Functional Food Science in Europe and the EU Commission on Concerted Action program, the Process for the Assessment of Scientific Support for Claims on Foods projects), which aim to resolve some of the ongoing issues of validation, scientific substantiation of claims, and communication to the consumer.

Next, Barbara Schneeman reviewed how health claims are evaluated by the FDA. Health claims describe the relationship between a food or food component and reducing the risk of a disease or health-related condition; they are not intended as claims to cure, treat, mitigate, or prevent disease (6). The FDA developed a process for qualified health claims that characterize the quality and strength of scientific evidence because these claims are not based on considerable scientific agreement; since 2003, it has published several letters of enforcement discretion for qualified health claims. In January 2009, the FDA published guidance for the food industry on the process and approach that it uses to evaluate scientific evidence in support of health claims (9).

In reviewing the scientific evidence, the FDA considers studies that are relevant to the claim, the quality of the studies, and the strength and consistency of the body of evidence (6,9). For example, review articles, book chapters, and in vitro and animal studies are not useful for drawing scientific conclusions relevant to the health claim (9). The guidance points to certain fatal flaws in study design such as the lack of a control, lack of relevant statistics, use of nonvalidated biomarkers, lack of intake validation, and use of malnourished populations (9). The regulatory framework for use of health claims include specifications that may disqualify a product from bearing such a claim.

The final speaker, Mary Ellen Sanders summarized some of the regulatory challenges facing the probiotic field. First is communication of the scientific evidence substantiating probiotic products. Although the science behind probiotics is progressing at a rapid rate [reflected in part by >60 meta-analyses or systematic reviews published through 2011 and by practice guidelines published by the World Gastroenterology Organization (10)], translating this science into claims that are truthful, do not mislead the public, and conform to the regulatory requirements of different countries worldwide has proved difficult.

This challenge is primarily faced by probiotics marketed as foods or dietary supplements, which are the majority of probiotic products in the US and Europe. In Europe, where all health benefit claims must be government approved, only 1 claim (yogurt cultures improving lactose digestion) submitted by companies for their probiotic products has been deemed adequately supported. The challenge in the US takes a different form. US claims that speak to the normal functioning of the human body (known as "structure/function" claims) do not require government approval. Such claims are used with great frequency on probiotic foods and supplements, making it difficult to differentiate products that are scientifically backed from those with little evidence.

Making general function claims requires that the research be designed to have a health impact on the general population, not to mitigate disease in people already sick. Such research is challenging as magnitudes of effects may be small and difficult to discern in the variations inherent to a human study. Studies likely will require large numbers of subjects. Better characterization of the microbiota and host genome of subjects might help differentiate the responders and nonresponders.

Another challenge is that probiotic research is often controlled by the FDA Center for Biologics Evaluation and Research. This Center considers intended use to determine whether human studies where the research targets are the cure or treatment of disease should by conducted under an investigational new drug application. To date, the Center for Biologics Evaluation and Research has concluded that probiotic uses are drug uses. In cases in which the intent is to determine the effects of probiotics on maintaining health or reducing the risk of disease, such a requirement is not justified. Such requirements have effectively stymied research progress on probiotics in the US and may inadvertently drive companies to conduct their research outside the US where such restrictions are not imposed.

Regulatory agencies in US and Europe must continue to protect consumers from misleading labeling and advertising; however, these agencies currently believe that the scientific evidence for probiotics does not meet the standards for approved health claims. Therefore, investigators wishing to conduct studies that will substantiate health claims for probiotics should carefully consider the study design, study populations, and select relevant experimental outcomes (3,6–8).

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