10-18-2013

# Probiotics: Finding the Right Regulatory Balance

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**Title:** Probiotics: Finding the right regulatory balance

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**Abstract:** The recent proliferation of probiotics in supermarkets, drugstores and on the Internet requires consideration of their unique properties in establishing an appropriate framework for their regulation. Although a separate regulatory category at the Food and Drug Administration is not justified, certain reforms should be considered to achieve more efficient regulation and greater reliability on probiotic product claims.

**Main Text:**

Initial findings of the Human Microbiome Project (HMP), an NIH Common Fund initiative, to characterize the microorganisms that live in and on the human body and analyze their role in health and disease, were published a little over a year ago (*1*). While the findings raise more questions than they answer about the role and variation of microorganisms within individuals and across populations, they have already begun to promote the development of probiotics, substances containing live microorganisms

that have a beneficial effect when taken in sufficient quantities (*2*) and "designed to intentionally manipulate microbiome and host properties"(*3*). The findings will also provide a "baseline" by which to measure changes in an individual's microbiome produced by the consumption of probiotic products.

Most probiotics currently on the market are sold as foods or dietary supplements. Probiotics have been consumed for centuries in the form of yogurts and fermented milks. In recent years the variety of probiotic foods on supermarket shelves has significantly expanded, and probiotic dietary supplements are being aggressively marketed in retail stores and on the Internet. Although no probiotic has been approved for therapeutic purposes, a number are undergoing clinical trials and may soon be marketed as biologics or other drugs (*4*). There is already a body of published evidence of the potential benefit of some strains and species of probiotics for a variety of indications (*5*).

In addition to promoting the development of novel clinical therapies, the HMP is likely to increase the number of probiotic foods and dietary supplements available to consumers as well as the claims made about them (6). Consumer demand for these products is growing in large part because of their health and wellness claims (*7*). Reid *et al.* (*8*) and others (*9*) have asserted that while some of these claims may have merit, others do not. Many probiotics have not been adequately tested for efficacy yet "make claims that lead consumers . . . to believe that they are using reliable products"(*8*).

One of the goals of the HMP was to study the ethical, legal and social issues (ELSI) raised by human microbiome research. One such issue is whether the current regulatory framework for probiotics: 1) adequately addresses issues of safety and effectiveness; 2) provides sufficient information to consumers to make informed choices about purchasing probiotic products; and 3) sufficiently allows for, or at least does not discourage, research on the potential therapeutic benefits of probiotics. These questions were addressed as part of an NIH HMP-funded ELSI study which brought together a Working Group (WG) of human microbiome researchers, legal academics,

food and drug law attorneys, consumer advocates, bioethicists, industry representatives, an official from the US Federal Trade Commission (FTC) and a representative from Health Canada's Natural Health Products Directorate (*10*). (Although officials from the US Food and Drug Administration (FDA) were invited to participate as members of the WG, they declined to do so because of the perceived problem of a conflict of interest arising from a project that might result in recommendations to change the FDA's approach to regulating probiotics (*11*)). This article reports on several of the WG's observations about the regulatory process for probiotics and potential areas for reform.

To date, FDA's approach to probiotic products has relied entirely on its existing regulatory framework. That is, FDA has no definition of probiotics and regulates them based on whether they fall into one of the existing regulated product categories (*12*), i.e., drugs, biologics, foods, food additives, medical foods, foods for special dietary use, dietary supplements, medical devices, or cosmetics. (See Table 1.) Because probiotics fall into multiple categories, expertise about them is spread unevenly across multiple centers at the FDA without a single authoritative agency voice on the issue. This has led to inter-center inconsistencies in interpretation and application of regulations, data requirements, and the content of potentially relevant guidance documents. There appears to be uncertainty at times about whether a probiotic product should be regulated by the Center for Food Safety and Applied Nutrition, the Center for Biologic Evaluation and Research or the Center for Drug Evaluation and Research.

Apart from classification uncertainty, regulatory approaches developed for other products may not be a good fit for probiotics or may need to take into account some of the unique features of probiotics. By their very nature, probiotics are live organisms that are dynamic and unlike chemicals. Probiotics are also likely to lose viability and degrade under certain circumstances. Probiotic research and manufacturing involve consideration of variables such as the effect of the environment on the viability and effectiveness of the probiotics and the interaction between the human body's biology

and biochemistry and the human microbiome, including factors within the human body that may activate or deactivate the probiotics. Without stringent manufacturing procedures and quality controls, specific probiotics may lose the properties that once formed their isolation and selection criteria (*13*). Animal models may be of limited utility because of the significant differences between human and animal microbiomes and immune systems. Finally, many probiotics are consumed by individuals on a daily basis as foods making dosing of probiotics for therapeutic purposes challenging.

An example of the questionable fit between traditional regulatory concerns and probiotics is a 2010 FDA guidance document that sets forth requirements for chemistry, manufacturing, and controls for early clinical trials using live biotherapeutic products (LBP) (*14*). Without using the word "probiotic", the guidance and its definition of LBP appear to include probiotics intended to be used as drugs (*15*). As written, the requirements are not adequately customized for probiotics. Specifically, the current LBP guidance requires a summary of the phenotype or genotype of the strain with specific attention to the genetic loci that may indicate activity or potency. It is very difficult to pinpoint the genetic loci for probiotics, especially in early clinical trials. Furthermore, the guidance refers to genotypic methods that are inadequate and outdated. Given the reduction in their costs, current genome sequencing technology should be required. Moreover, LBP characterization standards are focused on the product; this may be inappropriate for probiotics because safety and effectiveness may be dependent on both the characteristics of the product *and* the microbiome of the consumer.

While probiotics do have some distinctive characteristics, they arguably are not unique enough to warrant their own regulatory pathway, in large part because probiotic products are so varied, potentially being marketed as foods, dietary supplements, medical foods, foods for special dietary use, or drugs. Two changes in the current regulatory framework, however, could improve how probiotics are addressed by FDA.

The HMP is driving studies by academic researchers of probiotic products traditionally sold as foods or dietary supplements to determine whether certain therapeutic claims

are, or could be, valid. Under the current regulatory framework, if the intent of the study is to substantiate a drug claim (a claim that a substance can diagnose, cure, mitigate, treat or prevent disease), researchers are required to submit an Investigational New Drug Application (IND). The IND may include results of pharmacologic and toxicity studies; chemistry, manufacturing and controls data as well as a clinical plan. It also generally includes three phases of human studies for the development of the new drug product. This means that researchers attempting to establish, for example, that a yogurt currently available on supermarket shelves reduced the incidence of diarrhea in the elderly, would be subject to the expansive full drug approval process, including phase 1 clinical safety studies. In some cases, the high costs of the IND have been an obstacle to such research.

While we agree that probiotic products that wish to make therapeutic claims generally should be subject to the same rigorous requirements as other products making drug claims, including adequate and well-controlled investigations supporting such claims, under limited circumstances we recommend an abbreviated IND process for some probiotic products, allowing them to bypass Phase 1 clinical safety studies. Probiotics that would be eligible for an abbreviated IND process are probiotic foods, dietary supplements, and dietary ingredients for which there is adequate evidence of safety in the target population; approved food additives; and substances generally recognized as safe (GRAS).

The probiotic that is the subject of the abbreviated IND would be required to be studied in essentially the same dose (or amount) and delivery system as the probiotic previously deemed to be safe, so as not to raise safety concerns. Under the abbreviated IND process, if the sponsor wished to conduct a study to support a therapeutic benefit for an at-risk population, such as premature infants, FDA would need to make a determination as to whether the available information on safety is suitable for this new target population. The abbreviated IND would provide a mechanism for products currently in the food and dietary supplement category to make drug claims by moving into the drug category, albeit with a slightly less burdensome IND process.

A second recommendation targets the regulation of unsubstantiated claims. Probiotic claims are currently regulated by both FDA and the FTC. FDA regulates advertising claims for prescription drugs and labeling claims for essentially all FDA regulated products, including prescription and over the counter (OTC) drugs, dietary supplements, medical devices, cosmetics and food. FTC regulates advertising claims for OTC drugs, foods, dietary supplements, medical devices and cosmetics. FDA regulation of claims differs based on which category a product falls within. Drug claims or health claims, i.e., claims of a reduction of risk of disease, require FDA approval prior to marketing. Foods and dietary supplements, however, may make structure/function claims without premarket approval, thus presenting an opportunity for misleading and unsubstantiated claims. Such claims describe the role of a nutrient or dietary ingredient intended to affect normal structure or function of the body in humans. The manufacturer is responsible for ensuring the accuracy and truthfulness of these claims. Often these claims are vague and difficult to understand.

In addition to providing an opportunity for making unsubstantiated claims, structure/function claims may be difficult to substantiate. For example, a number of probiotics make claims that they maintain or promote a healthy "balance" of micro-organisms in the body (often in the digestive system). This concept of promoting "balance" is not part of the disease-focused paradigm that has governed regulation of health-related products in the U.S., in large part because of a paucity of measurable outcomes to determine balance and whether such "balance" is beneficial. Some authors, however, have suggested conceptual approaches to the measurement of balance. For example, Sanders *et. al.* have proposed the concept of homeostasis as a focus of health studies and provide a rationale based on solid statistical theory as a way to measure wellness or health maintenance (*16*). Yet, much more scientific work needs to be done before such a concept can be implemented, including identifying appropriate biomarkers for study.

The existence of unsubstantiated claims in the marketplace is due in part to lack of agency enforcement resources but also to the difficulty of policing advertising on the Internet and to the lure of profit by potential probiotic manufacturers. In order to address the problem, in addition to greater enforcement efforts, we recommend that FDA establish a monograph for probiotic foods and dietary supplements similar to that adopted in Canada for natural health products. Unlike the U.S., Canada has taken a proactive role in regulating probiotic products. Most probiotic products that would be considered dietary supplements in the United States are regulated in Canada as natural health products and fall under probiotics and live micro-organisms monographs (*17*)—a set of requirements that cover acceptable ingredients, doses, formulations, quality specifications and labeling/claims. Under Health Canada's probiotics monograph, all probiotic natural health products require pre-market assessment and licensing and must be supported by evidence of strain-specific safety and efficacy under recommended conditions of use. Compliance with the monograph requirements leads to expedited review of the application for marketing the product. The Canadian probiotics monograph allows four specific claims for four specific strains of live microorganisms and limited generalized claims for combinations of strains that meet all additional requirements. (See Table 2.) Natural health products are not limited to these claims; however additional evidence supporting the product's safety and efficacy is required for claims not specified by the monographs. (See Figure 1.)

FDA could create probiotics monographs for those strains it believes are generally recognized as safe and effective for a particular benefit and could utilize expert panels as it did in the development of the OTC drug monographs. Similar to the FDA monographs for most OTC drug products, a probiotics monograph would include a list of active ingredients found to have achieved a specified benefit; levels of active ingredients needed to achieve the benefit; product claims that the FDA believes fairly communicate that benefit; mandatory warnings for this category of products; purity standards for active ingredients; a listing of permissible excipient and/or inactive ingredients; and methods and standards of testing. Ideally, a monograph would reduce the number of

structure/function, and arguably unsubstantiated, claims that could be made about probiotic products and thereby help the consumer make more informed decisions when purchasing these products.

Adoption of the abbreviated IND and monograph procedures would provide more balance in the regulation of probiotic products, leading to more reliable quality standards and properly substantiated efficacy claims that better reflect the nature of probiotics.

| Table 1. FDA Product Categories and Regulating Centers for Probiotics for Human Use | | | | | | |
|---|---|---|---|---|---|---|
| **Product Category** | Foods | Dietary Supplements | Cosmetics | Drugs | Biologics | Medical Devices |
| **Included in category** | All food products including bottled water, food additives, infant formula, medical foods, and foods for special dietary use. | Vitamins, minerals, herbs or other botanicals, amino acids, or dietary substances used to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent or extract of the above | Products used to cleanse or beautify the body. | Over the counter and prescription drugs. | Vaccines, blood products, and other biologics. | Instruments, machines, or other articles which do not achieve their primary intended purposes through chemical action within the body. This encompasses electronic products including any product that gives off radiation. |
| **Regulating Center** | Center for Food Safety and Applied Nutrition (CFSAN) | Center for Food Safety and Applied Nutrition (CFSAN) | Center for Food Safety and Applied Nutrition (CFSAN) | Center for Drug Evaluation and Research (CDER) | Center for Biologics Evaluation and Research (CBER) | Center for Devices and Radiological Health (CDRH) |

| Table 2. Probiotic product claims allowed by Health Canada probiotics monograph | |
|---|---|
| Microorganism | Eligible Specific Claims |
| • Lactobacillus johnsonii La1<br>• L. johnsonii Lj1<br>• L. johnsonii NCC 533 | An adjunct to physician-supervised antibiotic therapy in patients with Helicobacter pylori infections |
| • Lactobacillus rhamnosus GG | • Helps to manage acute infectious diarrhea.<br>• Helps to manage antibiotic-associated diarrhea.<br>• Helps to reduce the risk of antibiotic-associated diarrhea |
| • Saccharomyces boulardii | Helps to reduce the risk of antibiotic-associated diarrhea |
| | Eligible General Claims |
| • Lactobacillus johnsonii La1<br>• L. johnsonii Lj1<br>• L. johnsonii NCC 533<br>• Lactobacillus rhamnosus GG | • Probiotic that forms part of a natural healthy gut flora.<br>• Provides live microorganisms that form part of a natural healthy gut flora.<br>• Probiotic that contributes to a natural healthy gut flora.<br>• Provides live microorganisms that contribute to a natural healthy gut flora. |
| • Saccharomyces boulardii<br>• Lactobacillus johnsonii La1<br>• L. johnsonii Lj1<br>• L. johnsonii NCC 533<br>• Lactobacillus rhamnosus GG | • Probiotic to benefit health and/or to confer a health benefit.<br>• Provides live microorganisms to benefit health and/or to confer a health benefit. |

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[10] D. Hoffmann et al., White paper submitted to NIH pursuant to NIH Grant Number: 5R01HG005171-02, *Federal Regulation of Probiotics: An Analysis of the Existing Regulatory Framework and Recommendations for Alternative Frameworks*, November, 15, 2012 (revised August, 2013)

[11] Two representatives from FDA did attend the first meeting as observers but declined to attend subsequent meetings.

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[15] The Guidance (*12*) defines a "live biotherapeutic product as "a biological product that: 1) contains live microorganisms, such as bacteria or yeast; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine."

[16] M. E. Sanders et al., Health claims substantiation for probiotic and prebiotic products. *Gut Microbes* **2**, 127 (2011); http://www.landesbioscience.com/journals/gutmicrobes/Sanders-GMIC2-3.pdf?nocache=2119325585.

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**Acknowledgment**
The research leading to this paper was supported by Award Number R01HG005171 from the National Human Genome Research Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Human Genome Research Institute or the National Institutes of Health.