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Probiotics: Finding the Right Regulatory Balance

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Indings of the Human Microbiome Project (HMP), funded by the U.S. National Institutes of Health (NIH), raise important questions about the role and variation of microorganisms within individuals and across populations (1). One related area of growing research and commercial interest is the development and use 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). We offer observations about the regulatory process for probiotics and potential areas for reform.

Most probiotics—consumed for centuries as yogurts and fermented milks—are sold as foods or dietary supplements. In recent years, the variety of probiotic foods on supermarket shelves has 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, some are undergoing clinical trials and may soon be marketed as biologics or other drugs (4). There is 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 new clinical therapies, the HMP is likely to increase the number of probiotic foods and dietary supplements for 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). Although some of these claims may have merit, others do not (8, 9).

Under an NIH-HMP funded ELSI (Ethical, Legal, and Social Issues) study, we convened a group (10) to examine whether the current U.S. regulatory framework for probiotics: (i) adequately addresses issues of safety and effectiveness; (ii) provides sufficient information to consumers to make informed choices; and (iii) sufficiently allows for, or at least does not discourage, research on potential therapeutic benefits (11).

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The U.S. Food and Drug Administration (FDA) has no definition of probiotics and regulates them based on whether they fall into one of the existing regulated product categories (e.g., drugs, biologics, foods) (12). Yet, regulatory approaches for other products may not cover some unique features of probiotics. Probiotics are live, dynamic organisms, likely to lose viability and degrade over time. Their research and manufacturing involve a greater number of variables than does research with many other substances. These include the effect of the environment on the viability of the probiotic and interaction with the human genome and microbiome. Without stringent manufacturing procedures and quality controls, specific probiotics may lose the properties that once formed their isolation and selection criteria (13). Animal models are limited because of differences between human and animal microbiomes and immune systems. Many probiotics are consumed by individuals on a daily basis as foods, which makes dosing for therapeutic purposes challenging.

An example of the questionable fit between traditional regulatory concerns and probiotics is 2010 FDA guidance for early clinical trials using live biotherapeutic products (LBP) (14). Without using the word “pro-biotic,” the guidance appears to incorporate probiotics into this category. But the requirements are not entirely relevant for probiotics, in that they require a summary of the pheno-type or genotype of the strain with specifi c “attention to biological activity or genetic loci that may indicate activity or potency” (14). It is difficult to pinpoint genetic loci for probiotics, especially in early clinical trials. LBP product characterization standards may be inappropriate for probiotics, as safety and effectiveness may depend on both the product and the microbiome of the consumer.

Changing FDA’s Regulatory Framework

Although probiotics have some distinctive characteristics, they arguably are not unique enough to warrant their own regulatory path way, largely because probiotic products are so varied and may be marketed as foods, dietary supplements, medical foods, foods for special dietary use, or drugs. In addition to changes regarding characterization, two modifications to the regulatory framework could improve how probiotics are addressed by FDA.

Abbreviated application process.

Under the current regulatory framework, if the intent of a study is to substantiate a drug claim (that a substance can diagnose, cure, mitigate, treat, or prevent disease), researchers must submit an Investigational New Drug Application (IND) to FDA. The IND may include results of pharmacologic and toxicity studies; chemistry, manufacturing and controls data; and a clinical plan. It generally includes three phases of human studies for development of the new product. In some cases, high costs of the IND have been an obstacle to research.

Probiotic products that include drug 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. But, under limited circumstances, we recommend an abbreviated IND (AIND) process for some probiotic products that would allow them to bypass phase 1 clinical safety studies (11). Eligible for this process would be 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 AIND probiotic would be required to be studied in the same dose (or amount) and delivery system as the probiotic previously deemed safe. Under the AIND process, if the sponsor wished to conduct a study to support a therapeutic benefi t for an at-risk population, FDA would need to determine whether the available safety information is suitable for this target population. The AIND would provide an abbreviated pathway for some probiotic foods and dietary supplements to make drug claims, albeit by moving them into the drug category.

Regulating claims.

FDA regulates advertising claims for prescription drugs and label ing claims for essentially all FDA-regulated products, including prescription and over the counter (OTC) drugs, dietary supplements, and food (15). FDA regulation of claims differs according to which category a product falls within. Drug claims or health claims, i.e., claims of a reduction of risk of disease, require FDA approval before marketing. Foods and dietary supplements may make claims, without premarket approval, about 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; however, lack of prior approval presents an opportunity for misleading and unsubstantiated claims.

Structure-function claims may be difficult to substantiate. For example, unique to probiotics are claims that they maintain or promote a healthy “balance” of microorganisms in the body. This balance concept is not part of the disease-focused paradigm that has governed regulation of health-related products in the United States, in large part because, although some have suggested conceptual approaches to measurement of balance [e.g., (16)], there is a paucity of measurable outcomes to determine balance and whether it is beneficial.

Problematic advertising claims including unsubstantiated structure-function and unap-proved drug or health claims are due to lack of agency enforcement resources, the diffi - culty of policing advertising on the Internet, and to the lure of profit by potential manufacturers. In addition to greater enforcement, we recommend that FDA establish a monograph for probiotic foods and dietary supplements that could be modeled on that adopted in Canada for natural health products or FDA’s monographs for OTC drugs (11).

The benefits of the monograph approach are twofold. Because claims permitted by a monograph would be evidence-based, unsubstantiated structure-function claims would likely be reduced. Further, mono graph-approved drug or health claims could be made without subjecting the product to the current and more costly IND process.

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 microorganisms monographs (17) that cover acceptable ingredients, doses, formulations, and quality specifications, and specify the claims that can be made about these products. Under Health Canada’s probiotics monograph, all probiotic natural health products require

premarket 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 monograph allows specific and general claims for strains that meet all additional requirements [see table, based on (17)]. Natural health products are not limited to these claims, but additional evidence supporting safety and efficacy is required for claims not specified by the monographs.

Unlike Canada's monograph, FDA's OTC drug monographs do not require pre-market approval. FDA could create probiotics monographs for strains it believes are GRAS and effective for a particular benefi t and could use expert panels as it did in developing OTC drug monographs. Similar to most FDA OTC drug monographs, a probiotics monograph would list, among other things, active ingredients, acceptable product claims, labeling, and dosages. Ideally, a monograph would reduce the number of unsubstantiated probiotic claims and thereby help consumers make more informed decisions.

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References and Notes

1. Human Microbiome Project Consortium, Nature 486, 215 (2012). [PubMed: 22699610]
2. Joint Food and Agriculture Organization of the United Nations–World Health Organization Expert Consultation, "Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria" (FAO-WHO, Rome and Geneva, 2001); www.who.int/food-safety/publications/fs_management/en/probiotics.pdf.
3. Gordon JI, Science 336, 1251 (2012). [PubMed: 22674326]
4. Olle B, Nat. Biotechnol. 31, 309 (2013). [PubMed: 23563425]
5. Floch MH et al., J. Clin. Gastroenterol. 45 (Suppl), S168 (2011). [PubMed: 21992958]
6. Slashinski MJ, McCurdy SA, Achenbaum LS, Whitney SN, McGuire AL, BMC Med. Ethics 13, 28 (2012). [PubMed: 23110633]
7. Satine LA, Food Drug Law J 63, 537 (2008).
8. Reid G, Jass J, Sebulsky MT, McCormick JK, Clin. Microbiol. Rev. 16, 658 (2003). [PubMed: 14557292]
9. Schardt D, "Helpful bacteria: should you take probiotics?" Special Feature, Nutrition Action Healthletter, 12 2006.
10. The study (*11*) brought together human microbiome researchers, legal academics, food and drug law attorneys, consumer advocates, bioethicists, industry representatives, and representatives from the U.S. Federal Trade Commission (FTC) and Health Canada's Natural Health Products Directorate. Officials from the U.S. FDA were invited to participate but declined to do so because of perceived conflict of interest arising from a project that might result in recommendations to change the FDA's approach to regulating probiotics.
11. Hoffmann DE et al., "Federal regulation of probiotics: An analysis of the existing regulatory framework and recommendations for alternative frameworks," (White paper submitted to NIH pursuant to NIH grant 5R01HG005171–02, Univ. of Maryland Carey School of Law, Baltimore, MD, rev. 2013); www.law.umaryland.edu/ProbioticsWhitePaper.

12. Vaillancourt J, in Ending the War Metaphor: The Changing Agenda for Unraveling the Host-Microbe Relationship—Workshop Summary (National Academies Press, Washington, DC, 2006), pp. 229–237.
13. Grześkowiak Ł, Isolauri E, Salminen S, Gueimonde M, Br. J. Nutr. 105, 887 (2011). [PubMed: 21059281]
14. FDA, Guidance for Industry, Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information (FDA, Washington, DC, 2010); www.fda.gov/downloads/BiologicsBloodVaccines/Guidance-ComplianceRegulatoryInformation/Guidances/General/UCM292704.pdf.
15. The Federal Trade Commission (FTC) regulates advertising claims for OTC drugs, foods, dietary supplements, medical devices, and cosmetics.
16. Sanders ME et al., Gut Microbes 2, 127 (2011). [PubMed: 21646865]
17. Health Canada, Probiotics (2012); http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=probio&lang=eng.

Some products marketed as drugs should be excused from Phase I trials, but safety and efficacy claims for dietary supplements should be more tightly regulated.

Probiotic product claims allowed by Health Canada probiotic monograph

Eligible General Claims	***Lactobadttus johnsonii La1***	***L. johnsonii Lj1***	***L. johnsonii NCC 533***	***L. rhamnosus GG***	***Saccharomyces boutardii***
Probiotic to benefit health and/or to confer a health benefit.	●	●	●	●	●
Provides live microorganisms to benefit health and/or to confer a health benefit.	●	●	●	●	●
Probiotic that forms part of a natural healthy gut flora.	●	●	●	●	
Provides live microorganisms that form part of a natural healthy gut flora.	●	●	●	●	
Probiotic that contributes to a natural healthy gut flora.	●	●	●	●	
Provides live microorganisms that contribute to a natural healthy gut flora.					
Eligible Specific Claims					
An adjunct to physician-supervised antibiotic therapy in patients with *Helicobacter pylori* infections.	●	●	●		
Helps to manage acute infectious diarrhea.				●	
Helps to manage antibiotic-associated diarrhea.				●	
Helps to reduce the risk of antibiotic-associated diarrhea.				●	●