Probiotic Foods and Drugs: Impact of US Regulatory Status on Design of Clinical Trials

Patricia L. Hibberd1,2 and Lisa Davidson1

1Department of Geographic Medicine and Infectious Diseases, Tufts New England Medical Center, and 2Tufts University School of Medicine, Boston, Massachusetts

Probiotics have been in widespread use since ancient times and are increasingly being consumed to maintain health and to prevent and treat a wide range of conditions. In the United States, probiotics are considered to be foods or biologics, depending on their intended use. This article addresses the similarities and differences between approaches to conducting clinical trials of probiotics as foods (which leads to health claims) or as biologics (which leads to therapeutic claims). Most probiotics are manufactured as foods, which makes it challenging for academic investigators in the United States to meet the requirements of an Investigational New Drug application that enables them to study the therapeutic effects of these novel agents. Although it is important to ensure the safety and quality of probiotic products, there also may be value in adapting the US Food and Drug Administration’s Guidance for Industry for Botanical Products to probiotic products, in part to allow the research agenda to move forward with products for which there are no safety concerns.

Shortly after birth, we become colonized by bacteria and other microbes. The commensal bacteria in our gastrointestinal tract are crucial to maintaining the integrity and health of the intestinal mucosa [1, 2]. However, these beneficial effects are not limited to the gastrointestinal tract [3–7]. The ability of commensal bacteria to interact with both the local and the systemic immune systems holds great promise for the use of nonpathogenic organisms for prevention and treatment of a range of diseases [8–12].

Probiotics have been in use since ancient times. In the early 20th century, Metchnikoff promoted his theory that the fermentation of bacteria in dairy products promotes good health and longevity [13]. Today, probiotics are used to prevent and treat a wide variety of conditions. The evidence is strongest in support of their use for gastrointestinal disorders, including diarrhea, pouchitis, inflammatory bowel disease, traveler’s diarrhea, antibiotic-associated diarrhea, and Clostridium difficile infection [14–17]. Other uses have been discussed in other articles of this supplement.

Many consider probiotics to be “complementary” or “alternative” medicine. The use of complementary or alternative medicine is increasing rapidly in the United States. In a 2002 survey, the National Center for Complementary and Alternative Medicine, National Institutes of Health, found that 36% of all adults used some form of complementary or alternative medicine in the previous year [18], and US $36–$47 billion is spent yearly. Natural products (which include probiotics) account for 19% of the complementary or alternative medicines used annually. US sales of probiotics are estimated at $764 million (in 2005 US dollars) and are expected to rise to $1.1 billion by 2010 [19]. In recent years, the number of published articles on probiotics has increased exponentially (figure 1), but, despite scientific interest in and the widespread and growing use of probiotics, few articles are about randomized clinical trials. However, the number of National Institutes of Health grants for probiotic research (figure 2) and the number of ongoing clinical trials of probiotics (figure
3) have also increased exponentially, from 1 registered trial in the United States in 2000 to 20 trials in 2006.

Widely available in pharmacies, supermarkets, and health food stores, most probiotics that are being studied are sold as foods or dietary supplements. Are the articles tested in these studies foods or drugs? This is a critical question. Most clinical studies designed and implemented in the United States evaluate probiotics to prevent, treat, mitigate, or cure various conditions—meeting the conditions for filing an Investigational New Drug (IND) application with the US Food and Drug Administration (FDA). However, few United States–based trials have been conducted under an IND application.

Because patients also have access to these products, the safety and efficacy of probiotics as they are being used by patients (i.e., as manufactured in accordance with food standards), rather than the safety and efficacy of probiotics specifically manufactured as drugs, should be evaluated. Alternatively, few would argue against a regulatory review that ensures the quality of both a product and the clinical trials that are conducted [22]. Although the scientific community may view the US regulatory system as confusing and as obstructing of scientific advancement, these regulatory challenges are an opportunity to improve the rationale for, approach to, and quality of clinical trials of probiotics that involve patient populations, by asking the following questions.

1. Do we need to understand the precise biological basis of the immunomodulatory effects of probiotics and the effects of these agents on the gastrointestinal microbiota in animal models before human studies are conducted?

2. Are preclinical toxicity studies of probiotics that are in widespread use and that are “generally regarded as safe” necessary or useful before development further proceeds with clinical studies?

3. How necessary is it to study the effects of probiotics in animal models of disease before clinical trials are conducted for specific conditions?

4. Is more information on the safety and effects of probiotics in healthy people needed, and, if so, how should studies to obtain this information be designed?

5. How should probiotic trials be conducted with “at-risk” populations (e.g., pregnant women, neonates, children, and immunosuppressed and critically ill patients)?

6. Does the dose of probiotics matter, and should it be studied?

7. Is it necessary to use live probiotic organisms, or can benefit be achieved with dead organisms?

8. Should individual probiotic strains be studied separately, or can safety and efficacy profiles be predicted for similar organisms?

9. What are the fundamental requirements to ensure the consistency, quality, and safety of probiotic products used in clinical trials? In general use?

10. For probiotic trials, why are well-recognized standards for conducting clinical trials [23] not being followed? Do the standards differ depending on whether the probiotic is studied as a dietary supplement or as a biologic?

Randomized clinical trials to evaluate the effects of interventions (e.g., through diet, behavior, drugs, biologics, and devices) are believed to contribute to evidence-based medicine only when they meet standards (e.g., as described in the CONSORT statement) for methodological rigor and high-quality conduct. The main difference between studies of foods or dietary supplements and studies of drugs and biologics are the specific questions addressed and the nature of the product (e.g., the manufacturing practices required for foods, dietary supplements, or drugs). Most manufacturers of probiotic foods...
and supplements are unwilling to meet or are disinterested in meeting the requirements for good manufacturing practices for drugs or biologics. These standards are necessary to support the IND application for their product to be tested for a “disease end point.” As a result, academic clinicians are unable to investigate these products, even though their patients can continue to consume these foods without evidence of safety or efficacy.

In 2004, the FDA published a guidance document [24] about botanical products to assist the industry and researchers in understanding the US regulatory process and requirements for such products. In this document, the FDA defines botanical products as finished, labeled products that contain vegetable matter, which may include plant materials, algae, macroscopic fungi, or combinations of these. Similar to probiotics, most botanicals (e.g., ginkgo) have been in widespread use in the United States for many years and are often marketed as dietary supplements. Key features of this 2004 botanical-policy guidance document include statements that (1) botanicals that have a documented history of safe prior use in humans, either as foreign drugs, foods, or supplements, are allowed to enter initial clinical trials under an IND application and to proceed without prior safety studies in animals; (2) pilot studies are allowed to proceed in the absence of the product meeting the marketing requirements for chemistry manufacturing and controls for a drug; and (3) the initial clinical trial of a botanical product that is already widely available to the public may not require the typical phase 1 study design used for agents that have never been used in humans. The guidance document describes what is necessary to meet the requirements for quality control and assurance at different points in the process of product development. This document for botanicals may provide a valuable
starting point for the FDA to develop a similar guidance document for probiotics that have been in widespread use for many years. As it does with botanicals, the FDA should consider the product-specific “track record” of safety for a probiotic submitted under an IND application.

The scientific community is at an important crossroads—namely, the determination of whether probiotics are safe and effective in the treatment of many conditions for which they are already in widespread use. The growing public interest in probiotics for disease management necessitates a review of the most basic issues: dosing, safety, and mechanisms of action of these agents. Since it is unclear whether data from one strain may be extrapolated to another, each strain may require separate assessment. This holds true for multistrain combinations as well. With the promise of genetically engineered microorganisms for production of “designer” probiotics, it is even more critical that the current regulatory impasse be resolved to allow clinical investigations to guide basic, translational, and clinical research in this novel therapeutic area.

Acknowledgments

Financial support. National Institutes of Health (R13AT003805, K24AT003683, R21AT002133, and R21AT002388).

Supplement sponsorship. This article was published as part of a supplement entitled “Developing Probiotics as Foods and Drugs: Scientific and Regulatory Challenges,” sponsored by the Drug Information Association, the National Institutes of Health National Center for Complementary and Alternative Medicine (1R13AT003805-01 to Patricia L. Hibberd), the California Dairy Research Foundation, Chr. Hansen, the Dannon Company, General Mills, Institut Rosell, and Yakult International.


References