

Executive Summary: Scientific and Regulatory Challenges of Development of Probiotics as Foods and Drugs

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Probiotics have a long global history of traditional use. Although they are currently sold mostly as ingredients in foods or nutritional supplements, recent research has explored the potential of probiotics to treat or prevent disease conditions, to maintain health, and to reduce the risk of future disease. A workshop held in Maryland on 16–17 October 2006 examined historical and current uses of probiotics along with current knowledge of probiotic organisms, their properties, and their mechanisms of action. The program included scientific presentations about advances in understanding of the relationship between the gastrointestinal microbiota and the development of the innate and adaptive immune system, as well as the implications of this relationship for current uses of and research on probiotics (table 1). Unlike other workshops held to date, the program examined the critically important interface between science and regulation. Speakers addressed the impact that science has on the way in which products are regulated and the equally important impact that regulations have on how research is planned and conducted, how product information is conveyed to consumers and health care professionals, and how products are ultimately marketed. The articles and discussions in this supplement address these topics that were presented in each panel. This article summarizes the findings of the conference and the recommendations made for future directions relating to research on probiotics.

FINDINGS

Need for adoption of definitions and standards.

As a relatively new subject of scientific research and product development, probiotics need internationally accepted definitions and precise language to describe the products and their impact on health and disease. Workshop participants endorsed the Joint Food and Agriculture Organization/World Health Organization Working Group's definition of probiotics: "Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [1, p. 8]. This definition may need to be revisited as knowledge expands regarding the mechanisms of action of probiotics and as novel formulations and genetically engineered microorganisms become available.

It is time to require that all microorganisms used as probiotics be identified by genus, species, and strain with the use of current methods. Conference participants noted that some products that are claimed to be probiotics are marketed with taxonomically incorrect or fictitious microbial names. They recommended use of only the most current nomenclature codes that govern the naming of bacteria and fungi. It is also time for implementation of standards to report the number of microorganisms in the product, which may include the maximum number at the end of the manufacturing process and the minimum number anticipated at the end of the shelf life. The viable number of microorganisms needs to relate to the suggested dose or serving size. Standards for marketing should include descriptions of acceptable methods of storage to maintain the product viability. Manufacturers of probiotics should be required to adhere to a set of minimal standards

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Table 1. Program advisors and speakers at the 1st International Drug Information Association Conference, entitled “Developing Probiotics as Foods and Drugs—Scientific and Regulatory Challenges,” held at the University of Maryland, Adelphia, on 16–17 October 2006.

Group	Names and titles or affiliations
Program chairs	Patricia Hibberd, MD, PhD, ^{a,b} Director, Center for Global Health Research, Tufts University School of Medicine; James Heimbach, PhD, ^{a,b} President, JHeimbach; Freddie Ann Hoffman, MD, ^{a,b} CEO, HeteroGeneity
Program Planning Committee	Jonathan Berman, MD, PhD, ^b National Center for Complementary and Alternative Medicine, NIH; Johanna Dwyer, DSc, RD, ^{a,b} Office of Dietary Supplements, NIH; Gregor Reid, PhD, ^{a,b} Director, Canadian Research and Development Centre for Probiotics, University of Western Ontario, Canada; Donna Jean Robie, PhD, Science Policy Analyst, Center for Food Safety and Applied Nutrition, FDA; Mary Ellen Sanders, PhD, ^{a,b} Executive Director, International Scientific Association for Probiotics and Prebiotics; Carmen Tamayo, MD, ^{a,b} Chair, Natural Health Products Special Interest Area Community, Drug Information Association, and Clinical Consultant, Flora, Canada
Program advisors	Daniel Fabricant, PhD, ^a Vice President, Scientific Affairs, Natural Products Association; Carey Frye, Vice President of Scientific and Regulatory Affairs, International Dairy Foods Association; Sherwood Gorbach, MD, ^{a,b} Chief Professor of Public Health and Family Medicine, Microbiology, Medicine and Immunology, Tufts University School of Medicine; Maya Pineru, PhD, Food and Agriculture Organization; Jon Vanderhoof, MD, ^a Vice President, Global Medical Affairs, Mead-Johnson Nutritionals; W. Allan Walker, MD, ^a Director, Division of Nutrition, Harvard Medical School
Speakers	Harunobu Amagase, PhD, Director, Research and Development, Wakanuga, Japan; Frederick H. Degnan, Esq, Partner, King & Spalding; Robert Garfield, Executive Director, National Yogurt Association; H. Rex Gaskins, PhD, Professor of Immunobiology, University of Illinois; M. Nicolas Gausseres, PhD, Director, Nutrivaleur Department, Danone, France; Marguerite Klein, MS, ^{a,b} Program Officer, National Center for Complementary and Alternative Medicine, NIH; David M. Klurfeld, PhD, National Program Leader, Human Nutrition, USDA; Antonia Mattia, PhD, Director, Division of Biotechnology and GRAS Notice Review, Center for Food Safety and Applied Nutrition, FDA; Simin Nikbin Meydani, DVM, PhD, Director, Nutritional Immunology Laboratory, Tufts University; Maria Oria, PhD, Food and Nutrition Board, Institute of Medicine; Patricia Rohan, MD, ^c Medical Officer, Center for Biologics Evaluation and Research, FDA; Jennifer Ross, PhD ^{b,c} Regulatory Reviewer, Center for Biologics Evaluation and Research, FDA; Maija-Liisa Saxelin, PhD, Research Manager, Valio, Finland; Barbara Schneeman, PhD, ^{a,b} Director, Office of Nutritional Products, Labeling, and Dietary Supplements, Center for Food Safety and Applied Nutrition, FDA; David Snyderman, MD, Chief, Division of Geographic Medicine and Infectious Diseases, Tufts New England Medical Center; Iryna Sorokulova, MS, PhD, DS, Visiting Professor, Auburn University School of Veterinary Medicine, and Head, Department of Standardization of Biological Products of the National Control Authority for Biological Products, Ukraine; Ann Sutton, MPH, Senior Consultant, Biologics Consulting Group; Julienne Vaillancourt, RPh, MPH, ^c Regulatory Reviewer, Center for Biologics Evaluation and Research, FDA

NOTE. CEO, Chief Executive Officer; FDA, US Food and Drug Administration; GRAS, Generally Recognized as Safe; NIH, National Institutes of Health; USDA, US Department of Agriculture.

^a Speaker.

^b Session chair.

^c Invited speaker.

such as these, to ensure consumer confidence in the products that are purchased.

Need for preclinical and phase 1 studies to provide the biological basis of and justification for design of later-phase clinical trials. Growth of the global market for probiotics is stimulating their recognition and use by consumers. Currently, most probiotics are sold as food ingredients, particularly in fermented dairy products and in capsules, as dietary supplements. In 2005, US sales of probiotic-containing products reached only \$764 million [2], representing <5% of the dietary supplement market. In contrast, the probiotic markets of both Japan and the European Union are much larger and more mature than the US probiotic market, because of long histories of traditional use, consumer comfort with microbial ingredients

in food, different regulatory frameworks, and perceived health benefits from probiotic products in those regions.

For specific well-characterized probiotics, a long history of use as food ingredients provides support for safe use in humans as well as some of the evidence needed to make general health claims. However, to establish preventive or therapeutic claims for patient populations, it is time to reconsider the biological basis of the effects of probiotics and whether there is a need to address new issues that may have a positive or negative effect on the safety and efficacy of these products in these populations. Advances in the understanding of the relationship between the microbiota and the development of the innate and adaptive immune system provide an important new opportunity to understand the mechanisms by which particular probiotic strains

exert specific clinical effects and to revisit dose-response characteristics. Validated methods in preclinical studies, such as the use of in vitro and in vivo animal models of disease, may provide important new data and surrogate markers of both safety and efficacy of probiotics. These may translate into better-designed phase 1 studies of both healthy subjects and patients, as well as increasing the success rate of phase 2 and 3 clinical studies. There is also an important need to assess how the probiotic properties of adherence, agglutination, and up- and down-regulation of cytokines relate to and/or affect maintenance of health or therapeutic effects. Given the large number of available probiotics and probiotic “candidates,” there is an urgent need to understand which characteristics pertaining to safety and efficacy can be generalized to a species or genus and which cannot.

Need for well-conducted studies evaluating safety and efficacy of probiotics. The National Institutes of Health (NIH) Office of Dietary Supplements selects 25 exceptional articles for publication in a bibliography of dietary-supplement research. This process involves the canvassing of journal editors and experts about their views regarding significant articles on dietary supplements. Of 175 outstanding articles selected over the past 7 years on various dietary-supplement topics, only 2 addressed probiotics (J. Dwyer, personal communication). One reason for the lack of notable studies of probiotics is the prevalence of poorly conducted research. Studies of probiotics often lacked control groups, blinding, validated outcomes, or standards for reporting adverse events. Other reasons were fewer absolute numbers of publications. This may represent fewer submissions or a lack of interest in the topic on the part of the journals. Finally, the lesser quality of those studies that were published could reflect inconsistent review policies for probiotic research among mainstream peer-reviewed journals.

The number of research studies that are being funded by the NIH and the US Department of Agriculture is continuing to increase. Requests for research proposals have been issued by the National Center for Complementary and Alternative Medicine [3] and are stimulating interest among the scientific community. On 18 May 2007, the Human Microbiome Project was added to the NIH Roadmap. The goal of this project is to evaluate the relationships among the entire microbial flora that exist within the human body and the relationship of this flora to health, disease, and response to therapy. This project will no doubt further stimulate research in this area.

One key issue that needs to be addressed is the establishment of standards for recognizing and reporting adverse events, particularly the detection of invasive infection caused by probiotics. Other factors that may affect outcomes of probiotic use, including comorbid conditions, composition of the diet, and concomitant use of medications, also need to be explored. Administration of probiotics to neonates may “prime the gut” for

life, but the safety and efficacy of this strategy needs to be evaluated further.

Although many investigators are providing rigorously designed studies that follow the Consolidated Standards of Reporting Trials (CONSORT) recommendations [4], new issues have arisen from both the clinical and the regulatory perspective. These include a detailed understanding of how strain-specific effects versus generalizable effects within a species, variations in formulation, and product stability and viability affect product safety and efficacy.

Need for clarity in the regulations for clinical research and manufacturing of probiotics. The regulation of probiotics is not internationally harmonized. In the United States, probiotics can be marketed as ingredients for use in the following regulatory categories: conventional foods, dietary supplements, foods for special dietary uses (including medical foods), drugs, and veterinary products (animal feed ingredients and animal drugs). A product’s regulatory category is determined not only by intended use (which is largely defined by the nature of the claims made) but also by formulation (e.g., beverage, pudding, capsules, or pills), route (topical vs. oral administration), target consumers (general public vs. those with special conditions or requirements), and safety (safe vs. unsafe for the consumer to take in the absence of a “learned intermediary”). These factors, in turn, dictate which regulations are imposed on the clinical research, development, manufacturing, and marketing processes.

Manufacturers are charged with determining how their products will be packaged, labeled, and marketed. They are also responsible for maintaining the appropriate level of scientific support for claims made on the product label and in promotional materials, on the basis of the regulatory category. Clinical studies are often required to support many types of label and marketing claims.

Regardless of how a probiotic is marketed, when it is studied clinically, the regulatory category (i.e., food or drug) depends on the regulations in the country where the product is being tested. In the United States, drugs are legally defined by their intended use as “(a) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease...and (b) articles (other than food) intended to affect the structure or any function of the body of man or other animals” [5]. It is important to note that both foods (including dietary supplements) and drugs can “affect the structure or function of the body.” However, only if a product is also intended to be used to diagnose, cure, mitigate, treat, or prevent disease does it meet the legal definition of a drug. In this latter scenario, an Investigational New Drug (IND) application may need to be filed with the US Food and Drug Administration (FDA) to conduct a clinical trial in the United States. Filing an IND for a probiotic product requires not only time but also sufficient

human and financial resources. Because the manufacturing process for a drug must be vetted by the FDA, detailed product information needs to be included as part of an IND. Submission of such information requires a probiotic manufacturer that is willing to participate in the application process.

The above issues were discussed in depth at the workshop, as were the differences in regulations for probiotics within and outside the United States. The following recommendations were made. Regulators must be open to and forthcoming in policy discussions concerning this product area and must actively participate in the scientific debate. US funding agencies need to become more conversant with US regulatory requirements so that they avoid stipulating requirements beyond those imposed by law. Sufficient resources must be made available to those investigators or sponsors who are legally required to file INDs. Federal agencies should work toward making the regulatory process more transparent by providing appropriate guidance to both researchers and manufacturers with regard to the development process and the design of research studies of probiotics.

Need for standards in communication of information about probiotics to physicians and consumers. Although products claiming to contain probiotics are widely consumed, most consumers and health care professionals have little knowledge about them and are unfamiliar with the different strains of probiotic organisms available and their benefits. Recommendations for the uses of probiotics must be driven by consistent products and solid evidence-based data.

RECOMMENDATIONS

Further scientific review and assessment.

1. There is a need for an NIH “State-of-the-Science” conference for probiotics that includes reports on probiotic mechanisms, the role of intestinal microbiota in human health, understanding of the physiological significance of immune responses invoked by probiotics, the most-promising therapeutic and health effects of probiotics, the range of organisms that can be considered to be probiotics, and the safety of probiotics.

2. When sufficient clinical information is available, an NIH “Consensus Conference” may also be useful, to provide direction to health care professionals.

Regulatory needs.

1. The NIH, in collaboration with the FDA, should develop a guidance document that will assist clinical researchers in traversing the US regulatory system.

2. The FDA should develop an agencywide “guidance for industry” document for probiotics that includes input from the Center for Food Safety and Applied Nutrition, the Center for Biologics Evaluation and Research, and the Center for Veterinary Medicine, among other units of the organization. This

guidance document, similar in nature to the FDA’s “Guidance for Industry—Botanical Drug Products” [6], should focus on the differences and similarities among the various regulatory categories in terms of manufacturing requirements, safety testing and monitoring, and general testing requirements. In addition, it should specifically address differences between testing and marketing a product that has documented prior use in humans versus marketing one that is novel, and it should discuss whether probiotics should be tested as ingredients, as final formulations (i.e., as the product to be marketed), or as both.

3. Clarification of what constitutes “newness” or “separateness” of probiotic products is urgently needed. Under the Dietary Supplement Health and Education Act, a substance sold as a dietary supplement or that was in the food supply before 15 October 1994 is not considered “new” and can continue to be marketed. However, any substance introduced after that date requires the filing of a New Dietary Ingredient notification. The FDA should provide clarification as to how it applies this concept to probiotics—that is, for a specific strain, how it determines whether the strain is new or is considered to already be in the food supply. The same issue also needs to be addressed with respect to Orphan Product Designations and other regulatory applications.

Need for infrastructure.

1. Standards for identification and biobanks of microbial strains that are considered to be probiotics should be made in collaboration with existing international collections of strain types.

2. Federal funding should address the critical need for excellence in the assessment of potential probiotics with regard to treatment of illness and promotion of health.

3. Governmentwide collaboration is needed among federal agencies (Department of Health and Human Services, US Department of Agriculture, Department of Defense, Department of Homeland Security, etc.) to develop complementary programs in probiotics.

4. Public-private partnerships (among industry, scientific and health care communities, and regulatory authorities) are needed to address ongoing issues and new challenges relating to probiotics, as well as communication of information to consumers and health care professionals.

5. The FDA should establish an internal agencywide working group to provide leadership, policy determination, and internal consistency with regard to the regulation of probiotics as ingredients in conventional foods, foods with special dietary uses, medical foods, dietary supplements, drugs, and veterinary products.

6. For those NIH-sponsored clinical investigations of probiotics assessed to be of high priority in the peer-review process, the NIH should make appropriate resources available to address the regulatory filings with the FDA that are mandated by law.

Areas for future research.

1. By use of state-of-the-art technologies, the intestinal microbiota should be further evaluated. Studies should explore how the microbiota develops after birth, how the microbial species interact within gastrointestinal lumen as well as with the mucosal surface, how the microbiota are altered by the nutritional status of the host and by various disease states, and whether probiotics can alter the microbiota, and, if they do, the consequences of altering the microbiota.

2. Properties of probiotics should be explored to determine how generalizable the effects are from a specific strain to the genus and the species.

3. Rational *in vitro* and *in vivo* animal models need to be developed to study the mechanisms of action of probiotics and biomarkers to assess the biologic effects of probiotics.

4. How product formulation affects the safety and efficacy of probiotics and the biological basis for these effects should be examined further.

5. The dose-response relationships of probiotic products should be further characterized, in addition to ways of optimizing the administration of these products.

6. Optimal and cost-effective methods of evaluating probiotic combinations versus single-strain products need to be determined.

7. Further studies are needed to determine whether there are high-risk populations that should use probiotics only under the supervision of a qualified health care professional.

8. When there is a sound biological basis for conducting phase 2–3 studies of specific probiotic strains, careful assessment of high-quality preparations needs to be performed to establish product safety and efficacy in disease states.

9. Selection of appropriate study outcome measures and other methodological challenges of conducting clinical trials still need to be addressed.

CONCLUSION

An understanding of the science relating to probiotics is an essential foundation for good regulatory decisions, and an un-

derstanding of the regulations and their impact on product development and marketing is crucial if the exciting potentials of probiotic-containing products—foods, dietary supplements, and biological drugs—are to be fully realized.

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