Meeting Summary

Federal Regulation of Probiotics: An Analysis of the Existing Regulatory Framework and Recommendations for Alternative Frameworks – Meeting #1

June 14, 2010

University of Maryland Baltimore

On June 14, 2010, a team of researchers at the University of Maryland Baltimore held the first of three meetings that are being funded by a grant from NIH’s Human Microbiome Project (HMP). The HMP is a $150 million, five-year NIH initiative. A portion of HMP funds were set aside to study the Ethical, Legal, and Social Implications (often referred to as the ELSI issues) of the Project’s scientific goals. The probiotics project is an interdisciplinary collaboration between faculty members from the University of Maryland Schools of Law, Pharmacy and Medicine. The members of the University of Maryland team are listed in Appendix A.

One of the most significant implications of the HMP is a potential expansion of the number of consumer and clinical probiotic products. Although probiotics have existed in certain foods for centuries, the HMP and the understanding it will provide regarding the mechanisms underlying probiotic action promises to increase the development of probiotic products dramatically – a reality that is already obvious on supermarket shelves but may soon be more common in the doctor’s office as physicians begin to recommend or prescribe probiotic therapies. The use of probiotics in commercial products has skyrocketed in recent years. Because this is a relatively new area of study, new claims are being made about the role and value of probiotics in promoting human health and wellbeing and there is a great deal of uncertainty about how these products should be regulated. The goal of this collaborative project is to create a healthy debate among the experts, study the legal and regulatory issues surrounding probiotics, and attempt to come to a consensus on how they should be regulated.

The University of Maryland research team convened a group of stakeholders and experts (the “Working Group”) in the area of probiotics to work with them on the project. The Working Group includes NIH-funded researchers and administrators, food and drug law attorneys, government regulators, legal academics, consumer advocates and industry representatives. A list of Working Group members appears in Appendix A. In addition to their participation in the June 14th meeting, the Working Group will participate in at least two additional meetings to discuss and develop recommendations as to how probiotics should be regulated at the federal level. The first meeting focused on the science of probiotics; a preliminary look at how drugs, foods, dietary supplements and other products are regulated by the FDA under current law; and whether the current regulatory structure is a good fit for probiotics. The agenda for the meeting appears in Appendix B.

1 NIH Grant Number: 5R01HG005171-02, PD/PI Name: Diane E. Hoffmann.
2 The FAO/WHO definition of probiotics is “live microorganisms which when administered in adequate amounts confer a health benefit on the host.”
3 The second meeting will focus on the adequacy of the current regulatory framework in the United States to ensure that probiotics products are safe and effective for consumers and that the regulatory framework encourages the type of scientific research that most appropriately elucidates the safety and efficacy of probiotic products. At the third meeting, the Working Group will compile its conclusions and work together to develop recommendations for the most appropriate framework to regulate probiotics.
During the morning session of the meeting, Dr. Mary Ellen Sanders, a food science microbiologist and consultant in the area probiotics, provided attendees with an overview of the history of probiotics – from their earliest use in products such as fermented milk to current commercial formulations. Dr. Claire Fraser-Liggett, Director of UMB’s Institute for Genome Sciences and recipient of two HMP grants, gave an update on the HMP and discussed her thoughts on how HMP-funded research will influence the development of probiotics in the future. Finally, Dr. Patricia Hibberd, an infectious disease physician, epidemiologist and clinical probiotic researcher at Massachusetts General Hospital for Children, described the current state of probiotic research, gaps in that research, and potential products that might develop from current and future research. After these talks, the Working Group divided into small mixed-profession discussion groups to discuss the following predetermined questions:

- What concerns relating to probiotics do participants have that they hope this project will address?
- From each participant’s professional vantage point - what are the gaps in the science relating to the risks and benefits of probiotics?
- Is there anything we should consider regarding risks and benefits that is not addressed in the literature, e.g., family, community, environmental concerns?

Responses to these questions can be roughly grouped into the following categories – concerns with current FDA regulation of probiotics, gaps in the current research on probiotics, probiotic research-related concerns, ethical issues, consumer and claims issues, and issues for future consideration of the Working Group. A detailed list of issues raised within each category appears below. These collated concerns and issues reflect individual contributions to the discussion and, unless otherwise indicated, they are not to be taken as consensus statements or recommendations.

**Concerns with current FDA regulation of probiotics:**

1. The current regulatory framework is focused on the drug model and doesn’t contemplate the role of foods in preventing and treating disease. Because the FDA generally views probiotics as drugs, an IND is required. Manufacturers are reluctant to file INDs because of the regulatory burden associated with submitting an IND application. This reluctance on the part of industry results in fewer clinical trials – although these trials are necessary to understand the effects of probiotics.
2. Stakeholders need clarity from FDA regarding the scope and type of claims that can be made about a product especially with regard to “structure/function” claims and the distinction between the concepts of “risk reduction” (a structure/function claim) and disease prevention (a drug claim).
3. The current FDA regulatory structure influences how researchers define outcomes and endpoints in research and this limits probiotic research. It is difficult to study probiotic effects on healthy subjects without defined endpoints. Further, it is challenging to design and conduct studies to support general “wellness” claims.
4. Phase 1 clinical trials (as they are defined currently) may be of limited utility for probiotic research. The typical drug development process may not be appropriate for probiotics.
5. A serious area of concern is getting “locked into” the drug category -- which is what happens if a new product is first researched under an IND. That product can never be marketed as a food or supplement after falling under an IND.
6. The ability of researchers to conduct studies on foods or dietary supplements may be restricted by inability to obtain access to the product’s “master file.”
7. Because these are live products, probiotics are often regulated by CBER instead of CFSAN which is not necessarily a good fit.
Gaps in the current research on probiotics:

1. There are insufficient rigorous probiotic studies that include: (1) a study group; (2) a placebo group; and (3) a non-intervention group.
2. There is insufficient information about how to measure the effect of using probiotics and insufficient comparative effectiveness research between different probiotics and between probiotics and non-probiotic treatments.
3. There are insufficient large safety trials to pick up adverse events, identify rare events, and develop safety issues for further study.
4. Colonization studies are currently too limited. More information is needed regarding the long-term effects of using probiotics, especially in children and neonates.
5. The effect of probiotics on antibiotic resistance should be researched.
6. Researchers need to study the impact of ethnicity, diet, culture, and genetics on the microbiome and consider those issues in development, safety testing and marketing of probiotic products.
7. There are no diagnostic tools to determine the appropriate probiotics to use in a particular situation.
8. There are gaps in our understanding of the interaction between the host, its genome, and the microbiome in human beings, as well as the impact of probiotics on this balanced system.
9. There is insufficient evidence about particular microbial strains and their importance in developing probiotics.
10. There are insufficient post-marketing surveillance studies (including cohort studies).

Probiotic research-related concerns:

1. There is confusion about when an IND is necessary to study probiotic products and this is a burden to researchers. NIH funding is often dependent on obtaining an IND and the rules in this area are not clear or consistent across FDA Centers.
2. Probiotic research should have the rigor of the IND process without the ‘baggage,” i.e. the administrative burdens which may not be necessary. An abbreviated IND process for certain probiotics might make sense. In some instances, researchers should not have to do a Phase 1 safety study for a product that is already on the market
3. In order to study probiotics in healthy populations, we need to develop appropriate metrics and study end points to measure benefits and/or adverse outcomes.
4. Attention should be given to “master files” and who should have access to them for research purposes.
5. Attention should be given to whether probiotic researchers and manufacturers have in place a “rescue therapy” in case of an adverse event during research.

Ethical issues:

1. Scientists need to integrate ethical safeguards into future studies and ensure adequate informed consent.
2. Along with ethical concerns relating to safety and efficacy, adequate access to probiotics should be considered.
3. Given that an individual’s microbial community might be associated with race, culture, sexual habits, and diet -- if a diagnostic tool is developed to determine a person’s microbial community, consideration should be given to the manner in which that information is transmitted to the patient or research subject.
4. What do we need to tell patients about their microbiome?
5. What should be included in informed consent for research or clinical use of probiotics?
6. Is it appropriate to use probiotics for neonates or immune-compromised patients (which is not allowed in the US but is permitted overseas)?

Consumer and claims issues:

1. Regulation of probiotics should be “consumer friendly” so that consumers know which probiotic to choose.
2. There is currently a lack of government enforcement of misleading claims.
3. We need to be aware of consumer issues, such as the affordability of probiotics.
4. Given the current FAO/WHO definition of probiotics, attention should be given to whether there may be an embedded health claim in the word “probiotic.”
5. Substantiation claims should be strain (or combination of strains) specific. Labels should be specific about the strain(s) in the product, proper dosage, and range limits.

Issues for future consideration of the working group:

1. How probiotics are categorized – as a food, drug, or supplement – influences research, regulation and marketing. A new category might make sense. An alternative framework that integrates a unique non-drug, non-food category for some probiotics would be useful.
2. A statutory “functional foods” category would be useful in the area of probiotics. It could allow for rigor in research without the burdensome regulatory complications of the drug category.
3. FDA needs to broaden its concept of disease to include “syndromes” and symptoms that do not represent a disease process but rather “unwellness.” This requires a new conceptual framework.
4. Agreed upon standards (by FDA, FTC, industry, researchers, health care providers) and FDA guidance would be very useful in the following areas:
   a. A single definition of probiotics and consistent terminology
   b. Clear regulatory categories for probiotics
   c. Manufacturing standards (quality, shelf-life, purity, efficacy)
   d. Accurate strain characterization (i.e., genomics)
   e. Shelf life, claims, purity
   f. Certification process for safety
   g. Strain and product registries
5. Initial regulations could focus on creation of incentives to generate information (product characterization, standardization of product claims, registration of studies/study designs).
6. Safety studies (rather than mechanism studies) should be the focus of future research.
7. In considering a regulatory framework, all forms of administration of probiotics should be looked at, i.e., oral, nasal, vaginal, skin, and should include devices as well as foods and drugs.
8. Probiotics should not be treated as a single product – some have higher risks than others – and they should be regulated differently. Probiotics that are genetically modified may need a higher level of regulatory scrutiny than non-modified probiotics as their potential risks need to be identified.
9. We may want to look at lessons learned from genetically modified organisms and nanotechnology. With regard to nanotechnology, the FDA has begun a process of gathering data and creating a database of nanotechnology products with basic, standardized information about each product. This might be a useful model for probiotics.
10. Regulators need to be cognizant of potential environmental concerns if we are introducing bacteria into the environment.
11. If probiotics are defined as drugs, could generic probiotics exist and how would they be defined?
12. It might be useful to look to industries – such as the beer industry – that work with live bacteria and learn from them about how to maintain strain/product quality over time.
13. IRB members should have specific expertise in probiotics.
14. Front line physicians do not know how to use or prescribe probiotics. Education is necessary so that physicians know how to use probiotics and to prevent adverse experience reporting when it might not be justified.

In the afternoon, Dr. Frank Palumbo, Director of the UMB School of Pharmacy’s Center on Drugs and Public Policy, provided meeting participants with an introduction to the current categories of FDA regulated products. To give a concrete example of the impact of public perception and regulation on a class of commercial products, Jack Schwartz, Visiting Professor and Health Law & Policy Fellow at University of Maryland School of Law, presented a case study on the regulatory history of genetically modified food in the United States and Europe. After these talks, the participants again broke into small groups to discuss whether there is anything intrinsically different about probiotic products that make them different from other regulated health-related products. There were several common themes – listed below - that emerged from the small group discussions.

1. Probiotics are live organisms, not inert chemicals that have defined biomarkers and endpoints to measure efficacy.
2. Drug -- and even human genome -- research involves fewer variables than probiotic research. Microbiome and probiotic research is full of variables, e.g., the effect of the environment, the interaction of the human genome and the human microbiota, triggers, etc.
3. Probiotics promote a healthy balance in the body which requires a shift in how we think about drugs, treatments and supplements from the current “antagonistic” paradigm in which we fight disease to a “symbiotic” paradigm in which we create products that create/maintain a healthy balance in the body.
4. Animal models may be of limited utility in probiotics research because of the complexity of the human microbiome and the major differences between human microbiomes and animal microbiomes. They can be useful in the area of translocation, virulence, and toxicity but not for safety and efficacy in humans.
5. Scientists cannot do traditional pharmacodynamic and pharmacokinetic studies on probiotics.
6. Probiotics replicate and are therefore dynamic. Given these differences, dosing of probiotics is more problematic.
7. Probiotics could fit into all of FDA’s current categories but do not fit cleanly into any of them. Because probiotics are live, they raise unique safety concerns and challenges of quality assurance and quality control.
8. Probiotics are often derived from microbes living in human bodies.
9. Similar to botanicals, there are differences that appear from batch to batch when manufacturing probiotics.
10. Most probiotics are different from new drugs and should be treated differently by FDA in that they: (a) have already been on the market for a number of years: (b) are consumed daily or routinely; (c) have been subject to clinical studies indicating safety.
11. It might be helpful to think of FDA regulating products on a continuum based on stringency of FDA regulations as shown in the chart below. Probiotic products could be added as a new category/pathway (although other probiotic products would fall into existing categories).
Recommendations for Further Consideration

Following the second small group discussion, the Working Group met as a whole. The purpose of this first meeting was to engage in critical issue spotting and therefore no firm conclusions or recommendations were reached by the group. However, a general consensus emerged that the following issues should be considered by the Working Group:

1. Creation of an authoritative entity within the FDA Commissioner’s Office that would determine if an IND is necessary to perform probiotic research.

2. Creation of a new regulatory pathway for probiotics within FDA. This new category would fall within a dedicated Center or Office that would make initial determinations about the product and then, depending on the type of probiotic product either assign the product to the new pathway or another FDA Center for oversight. Probiotics in this new pathway would be regulated differently. For instance, they might be subject to an abbreviated IND process and Phase 1 clinical trials might be formulated differently or waived. In addition, research on probiotics in this category could be conducted on a non-disease endpoint. Probiotics that fall into this new category would have certain similar characteristics that distinguish them from drugs.
Appendix A

Participant List for June 14th Meeting

Investigators and Meeting Organizers

- Diane E. Hoffmann, MS, JD, Associate Dean for Academic Programs and Director, Law and Health Care Program, University of Maryland School of Law (Principal Investigator)
- Claire M. Fraser-Liggett, Ph.D, Professor of Medicine and Director, Institute for Genome Sciences, University of Maryland School of Medicine
- Frank Palumbo, Ph.D, JD, Professor and Executive Director, University of Maryland School of Pharmacy Center on Drugs and Public Policy
- Jacques Ravel, Ph.D, Associate Professor, Institute for Genome Sciences, University of Maryland School of Medicine
- Virginia Rowthorn, JD, Managing Director, Law & Health Care Program, University of Maryland School of Law
- Jack Schwartz, JD, Visiting Professor and Health Law & Policy Fellow, University of Maryland School of Law

Working Group Participants

Food and Drug Attorneys and Regulators

- A. Wes Siegner, Jr. MA, JD, Partner, Hyman Phelps & McNamara, Washington, DC
- Barbara A. Binzak, JD, Ph.D, Buchanan Ingersoll, P.C., Washington, DC
- Richard L. Cleland, JD, Federal Trade Commission

Academics

- Rena Steinzor, JD, Professor of Law, University of Maryland School of Law
- Karen Rothenberg, JD, MPA, University of Maryland School of Law
- Jordan K. Paradise, JD, Seton Hall Law School
- Gary Marchant, JD, MPP, Ph.D, Arizona State University Law School
- James T. O’Reilly, JD, University of Cincinnati Law School
- Rebecca M. Bratspies, JD, CUNY School of Law

Consumer Advocate

- David Schardt, MS, Senior Nutritionist, Center for Science in the Public Interest

Bioethicist

- Rosamond Rhodes, PhD, Associate Program Director & Professor of Bioethics, Professor of Medical Education, Mount Sinai School of Medicine
Industry and Consultants

- Qiang Xu, Ph.D., Vice President, Research, Osel Inc.
- Nora L. Zorich, MD., PhD., Vice President, Corporate Research and Development, Procter & Gamble
- June Austin, Research Fellow, Product Safety and Regulatory Affairs, Procter & Gamble
- Mary-Ellen Sanders, Ph.D, Dairy & Food Culture Technologies
- James T. Heimbach, Ph.D, FACN, JHeimbach LLC

Scientists and Researchers

Gastrointestinal tract

- Patricia L. Hibberd, MD, Ph.D, Chief, Division of Global Health, Massachusetts General Hospital for Children
- Pinaki Panigrahi, M.B.B.S., Ph.D, Associate Professor, Pediatrics, University of Nebraska Medical Center
- Alessio Fasano, MD, Professor, Pediatrics, University of Maryland Baltimore Medical School

Female Reproductive System

- Gregor Reid, Ph.D, MBA, Professor of Microbiology and Immunology, University of Western Ontario

Skin

- Julie Segre, Ph.D, Senior Investigator, Genetics and Molecular Biology Branch, Head Epithelial Biology Section, National Human Genome Research Institute, NIH

Nutrition

- Elaine Leonard Puppa, RN, M.Ed, MSN, Nurse Research Coordinator, Mucosal Biology Research Center, University of Maryland Baltimore Medical School

Dietary Supplements

- Marguerite Klein, MS, Health Science Administrator, Office of Dietary Supplements, NIH

Complementary and Alternative Medicine

- Linda C. Duffy, Ph.D, Program Officer, DER, Natural Products Branch, National Center for Complementary and Alternative Medicine, NIH
- Brian M. Berman, MD, Professor of Family and Community Medicine, Director, The Center for Integrative Medicine, University of Maryland School of Medicine
Appendix B

Agenda June 14th Meeting

8:30-9:00 Registration and Continental Breakfast
9:00-9:15 Introduction and Welcome
   Diane Hoffmann
9:15 – 9:45 Introduction of Meeting Participants
9:45 – 10:15 History of Probiotics
   Mary Ellen Sanders
10:15-10:30 Break
10:30-11:00 The Human Microbiome Project
   Claire Fraser-Liggett
11:00-11:15 The Current State of Probiotic Research
   Pat Hibberd

11:15-12:30 Small Group Discussions
   • What concerns relating to probiotics do participants have that they hope this project will address?
   • From each participant’s professional vantage point - what are the gaps in the science relating to the risks and benefits of probiotics?
   • Is there anything we should consider regarding risks and benefits that is not addressed in the literature, e.g., family, community, environmental concerns?

12:30-1:30 Lunch/Open Session

1:30 - 2:15 Report on Small Group Discussions

2:15-2:45 Introduction to Categories of FDA Regulated Products
   Frank Palumbo

2:45-3:00 Case Study - Genetically Modified Food
   Jack Schwartz

3:00-4:00 Small Group Discussions
   • Is there anything intrinsically different about probiotic products that make them different from other regulated health-related products?

4:00-4:30 Report on Small Group Discussions

4:30-4:45 Closing Remarks
Appendix C

Small Discussion Groups

Group #1 – Facilitator – Diane E. Hoffmann, MS, JD, Associate Dean for Academic Programs and Director, Law and Health Care Program, University of Maryland School of Law (Principal Investigator)

Group Members

- Patricia L. Hibberd, MD, Ph.D, Chief, Division of Global Health, Massachusetts General Hospital for Children
- Marguerite Klein, MS, Health Science Administrator, Office of Dietary Supplements, NIH
- Qiang Xu, Ph.D., Vice President, Research, Osel Inc.
- A. Wes Siegner, Jr. MA, JD, Partner, Hyman Phelps & McNamara, Washington, DC
- Rebecca M. Bratspies, JD, CUNY School of Law

Group #2 – Facilitator – Claire M. Fraser-Liggett, Ph.D, Professor of Medicine and Director, Institute for Genome Sciences, University of Maryland School of Medicine

Group Members

- Pinaki Panigrahi, M.B.B.S., Ph.D, Associate Professor, Pediatrics, University of Nebraska Medical Center
- Nora L. Zorich, MD., PhD, Vice President, Corporate Research and Development, Procter & Gamble
- Barbara A. Binzak, JD, Ph.D., Buchanan Ingersoll, P.C., Washington, DC
- Rosamond Rhodes, PhD, Associate Program Director & Professor of Bioethics, Professor of Medical Education, Mount Sinai School of Medicine
- Jordan K. Paradise, JD, Seton Hall Law School

Group #3 – Facilitator – Jacques Ravel, Ph.D, Associate Professor, Institute for Genome Sciences, University of Maryland School of Medicine

Group Members

- Elaine Leonard Puppa, RN, M.Ed, MSN, Nurse Research Coordinator, Mucosal Biology Research Center, University of Maryland Baltimore Medical School
- Mary-Ellen Sanders, Ph.D, Dairy & Food Culture Technologies
- Karen Rothenberg, JD, MPA, University of Maryland School of Law
- James T. O’Reilly, JD, University of Cincinnati Law School

Group #4 – Facilitator – Jack Schwartz, JD, Visiting Professor and Health Law & Policy Fellow, University of Maryland School of Law

Group Members
• Julie Segre, Ph.D, Senior Investigator, Genetics and Molecular Biology Branch, Head Epithelial Biology Section, National Human Genome Research Institute, NIH (only there for morning)
• Linda C. Duffy, Ph.D, Program Officer, DER, Natural Products Branch, National Center for Complementary and Alternative Medicine, NIH
• James T. Heimbach, Ph.D, FACN, JHeimbach LLC
• Richard L. Cleland, JD, Federal Trade Commission
• Gary Marchant, JD, MPP, Ph.D, Arizona State University Law School
• Alessio Fasano, MD, Professor, Pediatrics, University of Maryland Baltimore Medical School NIH

**Group #5 – Facilitator** – Frank Palumbo, Ph.D, JD, Professor and Executive Director, University of Maryland School of Pharmacy Center on Drugs and Public Policy

**Group Members**

• June Austin, Research Fellow, Product Safety and Regulatory Affairs, Procter & Gamble
• Gregor Reid, Ph.D, MBA, Professor of Microbiology and Immunology, University of Western Ontario
• Brian M. Berman, MD, Professor of Family and Community Medicine, Director, The Center for Integrative Medicine, University of Maryland School of Medicine
• David Schardt, MS, Senior Nutritionist, Center for Science in the Public Interest
• Rena Steinzor, JD, Professor of Law, University of Maryland School of Law (only there for morning)