Third Meeting Summary

Federal Regulation of Probiotics: An Analysis of the Existing Regulatory Framework and Recommendations for Alternative Frameworks – Meeting #3

February 16 and 17, 2012

University of Maryland Baltimore

On February 16th and 17th, 2012, researchers at the University of Maryland Baltimore (UMB) held the third and final meeting under a project that is 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 HMP’s scientific goals. The UMB probiotics project is an interdisciplinary collaboration between faculty members from the University of Maryland Schools of Law, Pharmacy and Medicine. The NIH grant funded the three meetings to explore regulation of probiotics with a selected group of stakeholders and experts (the “Working Group”). 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 and other materials relating to the project appear on the project website.

The goal of the multi-disciplinary collaborative project is to examine the legal and regulatory issues raised by probiotics and to determine whether the current regulatory framework is a good fit for the range of probiotics that are on the market, under development, or that may be developed in the future as a result of the HMP. During the meetings and now, in the analysis phase, we are looking at the field of probiotic products and the current regulatory structure to create a written record of the thoughts, concerns, and broad recommendations of the leading stakeholders in the field. We are also studying discrete regulatory changes that may improve the way that probiotics are currently regulated in order to ensure that probiotic products are made available to the general public in an appropriate manner.

At the first meeting (June 4, 2010), the Working Group focused primarily on the science of probiotics. After a number of preliminary talks by experts in the field, Working Group

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2 The UMB investigators are Diane E. Hoffmann, MS, JD, Associate Dean for Academic Programs and Director, Law and Health Care Program, University of Maryland Francis King Carey School of Law (Principal Investigator); Claire M. Fraser-Liggett, Ph.D, Professor of Medicine and Director, Institute for Genomic 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; and Jack Schwartz, JD, Visiting Professor and Health Law & Policy Fellow, University of Maryland School of Law.
3 http://www.law.umaryland.edu/programs/health/events/probiotics/meeting1.html
members were asked to reflect on any gaps in probiotic science and policy from their professional vantage points and to share their thoughts on what they hope the probiotics project will accomplish. A detailed summary of the first meeting appears on the projects website but, briefly, the issues raised at the first meeting were roughly grouped into the following categories – concerns with current Food and Drug Administration (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. In addition, one of the conclusions of the first meeting was that the Working Group should recommend an abbreviated approval process for certain probiotics. Based on this conclusion, meeting organizers formed an Abbreviated IND Process subgroup that has met a number of times to make recommendations in this area.

At the second meeting (February 3-4, 2011), the Working Group focused on the safety and characterization of probiotics and product claims. One of the conclusions that the UMB investigators drew from the first Working Group meeting was that probiotic product claims may be both under-regulated, especially in terms of what claims influence the consumer, and over-regulated in terms of applying a framework to claims that may not be appropriate for probiotics. To address these issues, at the second meeting, the Working Group considered recommendations to address both under- and over-regulation of claims, including a private right of action (a statutorily created right of a private individual to sue a business for engaging in deceptive practices, misrepresentation, or failing to disclose material facts), industry self-regulation, and creation of a probiotics monograph (or “recipe book” that covers acceptable ingredients, doses, formulations, and labeling for the product covered by the monograph).

At the most recent meeting, the Working Group looked at international models for regulation of probiotics – with a specific focus on Canada and the European Union. The group also went “outside the box” of current regulations and discussed the future of probiotics and whether future clinical and consumer applications might impact how probiotics should be regulated. The group also considered the recent Agency for Healthcare Research and Quality (AHRQ) report on the safety of probiotics and the implications it had for any recommendations the group might make at the conclusion of the project. Finally, Working Group members made brief presentations about short essays they had written at the request of the Investigators setting forth the three changes that they would make to the current regulatory framework in the United States to ensure that probiotics can be researched and marketed in a way that is both safe and equitable. A summary of the third meeting follows.

International Models for Regulation of Probiotics

The Working Group heard three presentations on international regulation. Daniel Buijs, a regulator with the Natural Health Products Directorate of Health Canada who has spoken to the Working Group before, provided details regarding Health Canada’s probiotics monograph that

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4 All materials from the first meeting (including a summary of the meeting) are available at the project’s website: [http://www.law.umaryland.edu/programs/health/events/probiotics/meeting1.html](http://www.law.umaryland.edu/programs/health/events/probiotics/meeting1.html).

James Heimbach, a specialist in food regulation who has worked at FDA, gave an overview of how the European Union regulates probiotics through the European Food Safety Authority. Finally, Kevin Gillies, Vice President of Regulatory Affairs at Danisco, gave an overview of how other countries, particularly Australia/New Zealand and Asia, regulate probiotics. After the presentations, the Working Group broke into small groups to discuss the following questions:

1. Are there things we can learn from the experiences of other countries/regions in their efforts to regulate probiotics?
2. Are there elements from the laws and regulations of other countries/regions that we should incorporate into our regulatory framework?
3. Are there elements from the laws and regulations of other countries/regions that we should definitely NOT incorporate into our regulatory framework?

Small Group Discussion Themes

Generally, with the exception of Canada’s probiotic monograph and Australia’s registration system, Working Group participants do not think that the regulatory structures in other countries and regions provide much guidance (either negatively or positively) in terms of how the United States should regulate probiotics. For the most part, Working Group members noted that other national and regional regulatory schemes are too culturally-specific (China, Japan), too restrictive (EU), or are too untested (India) to be very instructive. In fact, many noted that the United States is in the position to provide guidance in this area to other countries given the size of the probiotics market in this country and the desire on the part of stakeholders (such as the members of the Working Group) to create an appropriate regulatory structure.

As to Canada’s probiotic monograph (which the Working Group has been looking at since its second meeting), there was both interest and concern shown for the idea of a probiotic monograph but general agreement that a monograph could be a valuable vehicle for regulating some products. Discussions about Canada’s probiotic monograph have been held in conjunction with consideration of a proposal developed by Working Group member Professor Jim O’Reilly for an FDA probiotics monograph. See the second meeting report for details about the Working Group’s discussion on the pros and cons of a probiotics monograph.

Discussion of a registration system such as that used to regulate probiotics in Australia appears below.

The Future of Probiotics and Implications for Regulation

The Working Group also discussed the future of probiotics and whether future clinical and consumer applications might impact how probiotics should be regulated. To this end, John Huss, a faculty member in the Philosophy Department at University of Akron and an expert in the philosophy of science, presented on the issue of “The Human Microbiome Project – A New Paradigm?” In his talk, he challenged the Working Group to think about whether the HMP and
metagenomics\textsuperscript{6} generally create a new paradigm in the way we think about (and regulate) disease and health. He argued that, under the old paradigm of disease and health, we look for specific causes of disease in a “good bugs vs. bad bugs” framework. He believes that the HMP will create a new paradigm of a superorganism in which we view disease and health from a balance perspective – with homeostasis being a primary goal rather than killing “the bad bugs.”

Dr. Huss’s talk was followed a presentation from Dr. Pat Hibberd, an infectious disease specialist and Chief of the Division of Global Health at Massachusetts General Hospital. Her talk focused on what probiotics may become available in the future and how they might be used in both the consumer and clinical settings. Dr. Hibberd theorized that, in the future, there may be interest in combining probiotics to leverage their different properties, perhaps with personalized probiotics for a healthy microbiome. She also expects that there will be more interest in genetic engineering of probiotics for specific medical purposes as more is known about probiotic mechanisms of action.

After these talks, the Working Group broke into small groups to discuss the following questions:

1. Is there an opportunity with probiotics to develop a new regulatory paradigm based on wellness or health maintenance? What would some features of such a regulatory framework look like?
2. Are there new probiotic products that may come on the market in the next decade as a result of the HMP or other developments that may require changes to the regulatory framework?

Small Group Discussion Themes

The small group discussions in this area were wide ranging but focused primarily on two alternative regulatory schemes proposed by working group members. The first concept that generated interest among a number of Working Group members was one proposed by Gregor Reid, a probiotic researcher at University of Western Ontario. Dr. Reid’s proposal involves categorizing microorganisms in consumer and clinical products into levels depending on the safety, efficacy, and characterization of the microorganism.\textsuperscript{7} His proposed categories are as follows from least regulated (level 1) to most regulated (level 5):

- **Level 1 (Basic Level – may not be a probiotic depending on definition)**

\textsuperscript{6} Metagenomics refers to the genomic study of uncultured microorganisms. The advent of metagenomics is the availability of faster, cheaper sequencing technologies and the ability to sequence uncultured microbes sampled directly from their habitats. The goal of metagenomics is to distill meaningful information from the millions of new genomic sequences from heterogeneous microbial communities.

\textsuperscript{7} Since the meeting, an abbreviated 3-category version of Dr. Reid’s concept appeared in *Nature* (446 *Nature* Vol. 485 May 2012).
Microorganisms used as starter cultures in preparations, such as yogurt, kefir, or sauerkraut, whose role is to ferment a food, and which then die in the stomach or upon exposure to bile.

- **Level 2 (Safe But Not Clinically Proven Probiotic)**
  - Products which themselves (or the microbial species they contain) have a long history of safe use, but have not specifically been clinically tested. Or, the evidence is only of increased numbers of those species in stool. These and all strains at Levels 2-5 must be genetically identified and meet safety standards of the regulatory agency in the country of use.

- **Level 3 (Clinically Documented Probiotic)**
  - Microorganisms whose utilization (by mouth, skin, vaginal or other target site), and delivery (dairy, powder, food, cream, medical device, other) confer a basic effect that benefits health, as shown in human studies, e.g., production of compounds that help create, restore or maintain homeostatic pH or host cell barrier function, or benefit general immunity, and thereby may provide a benefit to all consumers.

- **Level 4 (Specific Probiotic Health Benefit)**
  - Microbial strain(s) that have an additional specific function not conveyed by all organisms that can be safely used by all consumers, but may or may not benefit everyone, and for which mechanisms of action are somewhat understood and proven.

- **Level 5 (Narrow Use)**
  - Microbial strain(s) with very targeted usage (e.g., elevating certain neurochemical levels in the brain to relieve stress). Not for all consumers but not in the drug category.

Although no consensus was reached by Working Group members regarding categorizing probiotics as Dr. Reid suggests, Working Group members agreed that the concept provided a useful framework for dividing the world of probiotic products and thinking about how probiotic products should be regulated depending on what data is available about a specific strain or product. Working Group members also noted that dividing probiotics into categories might also be useful in determining when an IND is required; which center at FDA should review a product; and what claims could be made about a product.

Another concept that gained traction among some Working Group members during small group and large group discussion was that of a registration system for certain probiotic products. Countries that use a registration system require manufacturers to inform the regulatory authority of the intention to introduce a product to the market. Registration does not signify “approval” or “authorization” but puts authorities on notice of so that they can monitor products. A registration system makes it difficult for “fly-by-night” manufacturers with little substantiation for their product claims to place their products on the market. Registration systems require advance notice before the manufacturer can place a product on the market (as opposed to a notification system that allows immediate access to the market). If the time period elapses without action on the part of the regulating entity, the product can be placed in commerce (although the regulatory authority does not forfeit the right to regulate the product at a later time). Not all products qualify
for a registration system and it is most often used with dietary supplements. A manufacturer is still required to follow regulations regarding acceptable ingredients, good manufacturing processes (GMPSs), labeling, transportation, storage, etc.

Australia has a registration system for dietary supplements that uses a convenient electronic application system and validation process. Products eligible for registration contain ingredients that have been evaluated and accepted by the regulatory authority and manufactured under GMPs. A manufacturer must submit qualitative formulation/ingredient information and finished good specifications. The manufacturer must also certify that, according to the applicable guidelines, it holds substantiation for claims and shelf-life. The government reviews the registration in 2-4 weeks, after which time the product can appear on the market with an “Aust L” number that must be included on the label.8

AHRQ Report on Safety of Probiotics

Linda Duffy of the Natural Products Branch of the National Center for Complementary and Alternative Medicine (which co-sponsored the AHRQ report) gave an overview of the report’s findings. Taylor C. Wallace, Senior Director of Scientific & Regulatory Affairs at the Council for Responsible Nutrition also provided insights about the report. The study concluded that despite the substantial number of publications, the lack of assessment and systematic reporting of adverse events in probiotic intervention studies make it difficult to answer questions on the safety of probiotic interventions with confidence. Wallace’s view is that the report should not put the safety of these microorganisms into question. He further argued that the report provides further evidence to advance the notion that the six genera included in the study have minimal safety concerns.

Working Group Member Essays

Finally, Working Group members made brief presentations about short essays they had written regarding three changes that they would make to the current regulatory framework in the United States to ensure that probiotics can be researched and marketed in a way that is both safe and equitable. The suggestions in the essays were wide-ranging but most focused on themes that have emerged repeatedly throughout the course of the project – concerns regarding research on probiotics, lack of clear guidance regarding research and marketing of probiotics, and lack of enforcement for misleading probiotic claims.

For more information about the project, visit the project’s webpage: http://www.law.umaryland.edu/programs/health/events/probiotics/

8 Aust L products are what we would consider dietary supplements in the United States. They do not include foods.