Final Report

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

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1 NIH Grant Number: 5R01HG005171-02, PD/PI Name: Diane E. Hoffmann. The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the National Human Genome Research Institute or the National Institutes of Health.
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1) Introduction

In 2010, researchers at the University of Maryland Baltimore (UMB) were awarded a grant from NIH’s Human Microbiome Project (HMP) to examine and make recommendations regarding the regulation of probiotics. The HMP, a $150 million NIH initiative to characterize the microbial communities found at several different sites on the human body and to analyze the role of these microbes in human health and disease, funded the “Healthy Cohort Study,” an effort to create a reference catalogue of microbial DNA in healthy adults as well as fifteen scientific demonstration projects. In addition, 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 grant was one of the ELSI projects funded under the HMP. The project was an interdisciplinary collaboration between faculty members from the University of Maryland Schools of Law, Pharmacy and Medicine. The NIH grant funded a number of meetings to explore the regulation of probiotics with a selected group of stakeholders and experts (the “Working Group”). The Working Group included NIH-funded researchers and administrators, legal academics, food and drug law attorneys, government regulators, consumer advocates, bioethicists, and industry representatives. A list of Working Group members appears in Appendix A.

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2 See NIH Press Release, NIH Human Microbiome Project Defines Normal Bacterial Makeup of the Body (June 13, 2013), http://www.genome.gov/27549144. Over 240 subjects participated in the Healthy Cohort Study. Subjects contributed samples from multiple body sites (skin, mouth, throat, nostrils, feces (to obtain microbial samples from the lower gastrointestinal tract) and the vagina, in women). 16S rRNA gene analyses were performed on bacteria from the samples. See D.A. Relman, Learning About Who We Are, 486 Nature 194 (2012).


4 FDA was invited to participate in the Working Group but declined to do so. Two individuals, one from the Office of Policy and the other from the Office of Chief Counsel, attended the first Working Group meeting as observers. They declined to participate in subsequent meetings, however, stating that the agency’s role in regulating probiotics presented a potential for conflicts of interest arising from actively participating in a project that might result in recommendations to change the current regulatory framework. Although they elected not to participate in the Working Group, after the first Working Group Meeting, three of the co-investigators on this project submitted a series of questions to staff at FDA’s Office of Policy and met with the
One of the most significant implications of the HMP is a potential expansion of the number of probiotic products available on the commercial market. 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 well-being and there is some uncertainty and debate about how these products should be regulated. The goal of this multidisciplinary collaborative project was 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. The project was designed to look 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. The Working Group also considered discrete regulatory changes that may improve the way that probiotics are currently regulated in order to ensure that beneficial probiotic products are made available to the general public in a way that is both safe and effective.

This white paper summarizes the discussions and recommendations that emerged from the three stakeholder meetings. The paper, however, is not a consensus document—it represents numerous viewpoints and perspectives on the issue of the current and ideal regulation of probiotics. As a result, we have included the range of suggestions and recommendations that emerged on a particular topic. Where ideas and recommendations emerged from the Working Group, we identify them as such. The report is written, however, from the perspective of the co-Director and a Regulatory Policy Analyst in the Office of Policy. The set of questions we submitted and a draft of our contemporaneous notes taken during the meeting in response to the questions are attached at Appendix C. Prior to finalizing the White Paper, a copy was sent to eight officials at FDA including one Center Director, offering to make a presentation of our findings and requesting feedback on the paper. Five of the co-investigators met with approximately a dozen FDA staff to present our findings. We did not receive written comments on the report.

5 All materials from the three meetings (including summaries of the meetings) are available at the project’s website. Federal Regulation of Probiotics, UNIV. OF MARYLAND FRANCIS KING CAREY SCHOOL OF LAW, http://www.law.umaryland.edu/programs/health/events/probiotics/ (last visited Aug. 26, 2013).
investigators and reflects the current literature on probiotics as well as the views of the Working Group.

2) Project Background

As mentioned above, UMB’s probiotics project is part of NIH’s HMP and provides a regulatory evaluation of one important spinoff of the HMP—probiotics. Scientists associated with the HMP are studying microbial communities (or the “microbiota”) and their influence upon human development, physiology, immunity, and nutrition. As researchers are increasingly understanding through the HMP, a huge and diverse range of bacterial species colonize the human body. Microbial communities exist in the digestive passage from the mouth to the anus and into the vaginal tract of women. They also reside on the skin. Many lines of research have demonstrated the significant role of the microbiota in human physiology. The microbiota are involved in the healthy development of the immune system, prevention of infection from pathogenic or opportunistic microbes, and maintenance of intestinal barrier function. For a variety of reasons, normal native bacteria may not always perform these functions optimally. Research has shown that it is possible to categorize the microbiota components on the basis of whether they exert potentially pathogenic or health promoting properties. For example, lactic acid-producing genera such as bifidobacteria or lactobacilli have a long-standing association with health. These bacteria can be increased in the human body (at least for a period of time) either by feeding individuals appropriate strains as a probiotic or through the provision of prebiotic growth substrates. Research in this area is leading to a better understanding of the resident microbiota in health and disease, and one of the outcomes will be the development of evidence-based probiotic products.

There is no statutory or regulatory definition of probiotics in the United States. The most widely used definition of probiotics and the one used during the course of our project is the definition proposed in the 2001 report of a Joint FAO/WHO Expert Consultation on “Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live
In that document, probiotics are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” In a 2005 presentation, Commander Julienne Vaillancourt of the FDA Center for Biologics Evaluation and Research (CBER) confirmed that there is no single, standard definition of the term. She also stated, however, that the working definition of live biotherapeutics used by CBER’s Office of Vaccines Research and Review, i.e., “live microorganisms with an intended therapeutic effect in humans” includes “probiotics for clinical use.”

Probiotics are available commercially in many products but primarily as foods and dietary supplements. Probiotics in the form of clinical therapeutics and diagnostics are currently under development. Dr. Patricia Hibberd, an infectious disease specialist and Chief of the Division of Global Health at Massachusetts General Hospital and member of the Working Group, 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.

As with any health-related product, it is important that probiotics be safe and effective (if a claim of effectiveness is made). Moreover, probiotics must be prepared in such a way that the beneficial effects persist throughout the supply chain to the consumer and through the expiration date of the product. Probiotics must also be able to survive in the intestinal ecosystem until the desired effect is achieved.

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7 Julienne Vaillancourt, U.S. Food & Drug Administration, Regulating Pre- and Pro-biotics: A US FDA Perspective (PowerPoint presentation, Mar. 17, 2005), available at http://www.iom.edu/~/media/Files/Activity%20Files/PublicHealth/MicrobialThreats/Vaillancourt17Mar05ProbioticsRegulation.pdf.
8 A list of numerous commercial strains sold as probiotics appears in Appendix B.
9 See Bernat Olle, Medicines from Microbiota, 31 Nature Biotechnology 309 (2013).
As we noted in our grant proposal, “as probiotics begin to proliferate in the market, there is a need to critically consider the regulatory structure that is most appropriate” for them. This consideration must incorporate the wide range of probiotic products that are and may become commercially available, e.g., food, food additives, drugs, dietary supplements, and cosmetics. At the time we applied for the grant in 2008, there was already great interest among scientists and consumers in the use of probiotics to improve human health and, as any supermarket and health food store shopper can readily see, this interest has continued to grow during the three-year grant period. We undertook this project because we believed that a regulatory structure which adequately accounts for the risks of probiotics as well as the accuracy of claims of effectiveness is necessary to protect and guide consumers and health care providers who may use or recommend their use. In addition, the regulatory structure needs to be flexible enough to allow for (or at least not discourage) research on new probiotic products that may have therapeutic benefits. Our goal was to work with scientists, academics, government regulators, industry and consumer representatives, bioethicists, food and drug lawyers, and health policymakers to develop regulatory recommendations that conform to this delicate balance of interests.

3) Summary of Working Group Meetings

The Working Group met three times at the UM Carey School of Law in Baltimore, Maryland. These meetings involved presentations by both Working Group members and outside experts. In addition to presentations, each meeting included multiple small group facilitated discussions in which Working Group members were assigned to mixed-discipline groups to discuss specific issues relating to the theme of the meeting. A summary of the three meetings appears below. Agendas for each of the meetings appear in Appendix D.

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 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 hoped the probiotics project would accomplish. The issues raised at the first meeting can be roughly grouped into the
following categories: concerns with current Food and Drug Administration (FDA) regulation of probiotics; gaps in the current research on probiotics; concerns about the quality of the research on probiotics that has been conducted; ethical and consumer issues related to product claims; and issues for future consideration of the Working Group. One of the conclusions of the first meeting was that the Working Group should recommend an abbreviated Investigational New Drug (IND) application process for certain probiotics. Based on this conclusion, meeting organizers formed an Abbreviated IND Process subgroup that met a number of times to make recommendations in this area. Those recommendations are discussed on pages 31-34.

At the second meeting (February 3-4, 2011), the Working Group focused on the safety and characterization of probiotics and on product claims. One of the conclusions that the UMB investigators drew from the first Working Group meeting was that probiotic product claims of effectiveness may be under-regulated and that existing regulations may be under-enforced, especially claims that influence consumer purchases. But many Working Group members also believed that claims may be over-regulated in that the current regulatory framework for health claims may not be appropriate for some probiotic products. To address these issues, at the second meeting, the Working Group considered recommendations to address over- and under-regulation of claims as well as under-enforcement. These recommendations included a modified private right of action (a statutorily created right of a private individual or organization to step into the shoes of a regulatory agency and enforce existing regulations relating to 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 third and final meeting, (February 16-17, 2012), the Working Group considered the 2011 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. The Group also looked at international models for regulation of probiotics.

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probiotics—with a specific focus on Canada and the European Union—and 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. Finally, Working Group members made brief presentations about short essays they had written at the request of the Investigators, setting forth three changes they would like to see made to the current regulatory framework in the United States to ensure that probiotics can be researched and marketed in a way that is safe, reasonable, and helpful to consumers. Many suggestions from those essays are incorporated in this report.

During the term of the grant and at the three Working Group meetings, the Investigators studied how probiotics and, more generally, health-related products are regulated in the United States. Some products are heavily regulated throughout every stage of the product’s existence—through research and development, to production, sale, and consumption. Others may be subject to government regulation in some phases of the product’s development and marketing, but not others. In addition, private organizations or trade groups often set forth guidelines for manufacturers as a form of self-regulation. We studied each step of this continuum and asked whether probiotics raise unique concerns or questions that require regulatory consideration. This White Paper is structured to reflect the background, discussion, and recommendations developed by the Working Group and the investigators as we reviewed various aspects of the regulatory framework.

4) Regulation of Probiotics in the United States—Are Probiotics Different?

Before addressing specific regulatory concerns, we addressed a foundational issue: whether probiotics have intrinsic and distinct characteristics that are important in considering how they should be regulated. We determined that while probiotics share characteristics with other regulated products, as a group, probiotics have a clearly defined set of characteristics that should be taken into consideration in the regulatory process. By their very nature, probiotics are live organisms that are dynamic and thus unlike chemicals. Probiotics may degrade and lose their viability under certain circumstances. As a result, probiotic research and production involves a greater number of variables than research with many other substances, including the influence of
the environment on the effectiveness and viability of the probiotic; the interaction with the human genome and human microbiota; and triggers within the human body that may activate or deactivate the probiotic. Thus, without quality control, certain probiotics may lose the properties that once formed their selection and isolation criteria. Animal models may be of limited use in probiotic research because the human microbiome is highly complex and differs in significant ways from animal microbiomes. As with botanicals, there are differences that appear from batch to batch when manufacturing probiotics. Also, many probiotics are consumed daily as foods. Finally, unlike other products regulated by the FDA, probiotics are often derived from microbes living in human bodies. Given these differences, probiotics raise some unique, and potentially problematic, questions of dosing for therapeutic purposes, manufacture, storage, and shelf life. While the import of these intrinsic characteristics may be difficult to translate into regulatory processes, they should be the base from which we contemplate how probiotics are regulated.

In addition to the intrinsic characteristics of probiotics as live microorganisms that differentiate them from most other health-related products, another unique feature of probiotics is that they are intended to promote wellness and balance. Although the HMP and related research are likely to lead to clinical therapeutic (i.e., drug) uses for certain probiotics, most stakeholders in the world of probiotics understand that most probiotics play a role that is unlike that of drugs. As a result, the large majority of probiotics now are sold as foods and dietary supplements. As demonstrated by the HMP, the human body is a finely balanced ecosystem in which the microbiota respond to external and internal perturbations of the body to maintain a healthy balance. However, various systems in the body, such as the gut, can be thrown out of balance by a number of factors, including antibiotic use. Probiotics are designed to restore the balance of the microflora in the gut, vagina, and other body sites where microbial communities exist. Probiotics, to some extent, contemplate the role of foods in preventing or reducing disease and illness.

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This concept of promoting “balance” in various bodily systems is not part of the disease paradigm that has governed regulation of health-related products in this country for years. Broadly speaking, under the disease paradigm, humans are healthy unless they have an illness that must be diagnosed and treated. Under current law, any article that is used for “diagnosis, cure, mitigation, treatment, or prevention” of disease or “intended to affect the structure or any function of the body of man or other animals”\(^{12}\) is a drug. This definition sweeps into it any products, including foods, that have a role in treating or preventing disease (except in the case of foods and dietary supplements that make claims regarding the effect of the product on the structure or function of the body or disease reduction claims). Many in the Working Group noted that the traditional definition of “drug” does not consider the use of products to promote a healthy balance of microflora, the role of such products in generally healthy individuals, or the role of food in promoting health. Some agreed that an alternative “wellness paradigm” would be a useful response to the promise of current probiotic research that is revealing the role of probiotics in keeping healthy people healthy and preventing or reducing the risk of illness in sub-healthy individuals.

Another unique feature of probiotics is their potential effect on the environment. The effects of probiotics released into the environment, their ability to multiply, and the possibility that they may have adverse environmental effects, have not been studied adequately. The need for such research is particularly important in the case of genetically engineered bacteria.\(^{13}\)

### 5) Current Regulation of Probiotics by the FDA

In any regulatory analysis, the initial question that must be asked is what regulatory structure is already in place and does the new product fit within that existing regulatory structure, or does it raise concerns that require a new or revised regulatory framework.

#### i. Background- FDA Product Regulation


\(^{13}\) See essay submitted by Working Group Member John Huss (on file with the investigators).
In this project, we primarily focused on the regulation of probiotics by the FDA, which is the agency within the US Department of Health and Human Services tasked with oversight and regulation of foods, dietary supplements, prescription and over-the-counter drugs, vaccines, biopharmaceuticals, blood transfusions, medical devices, cosmetics, tobacco products, and veterinary products. While other agencies may have a role in the regulation of probiotics—such as the FTC, which regulates certain aspects of product advertising and marketing and will be discussed later, the FDA is the primary regulator of probiotics and was therefore the primary focus of the Working Group meetings.

The FDA regulates products by category. Each category is regulated by a center that evaluates and monitors many aspects of the life cycle of a product. These may include research, manufacture, safety, efficacy, transportation, labeling, and claims. Products within each category are subject to different rules and regulations. Table 1, on page 15, indicates the different products regulated by the FDA and the center within the FDA that regulates that product category.
<table>
<thead>
<tr>
<th>Product Category</th>
<th>Foods</th>
<th>Dietary Supplements</th>
<th>Cosmetics</th>
<th>Drugs</th>
<th>Biologics (a category of drugs)</th>
<th>Medical Devices</th>
<th>Veterinary Products</th>
<th>Tobacco Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included in category</td>
<td>All food products, bottled water, food additives, infant formula, medical foods.</td>
<td>Vitamins, minerals, herbs or other botanicals, amino acids, or dietary substances used to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent or extract of the above</td>
<td>Products used to cleanse or beautify the body.</td>
<td>Over the counter and prescription drugs.</td>
<td>Vaccines, blood products, and other biologics.*</td>
<td>Instruments, machines, or other articles which do not achieve their primary intended purposes through chemical action within the body. This encompasses electronic products including any product that gives off radiation.</td>
<td>Livestock feeds, pet foods, veterinary drugs and devices, veterinary biologics.</td>
<td>All tobacco, including smokeless tobacco products.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regulating Center</th>
<th>Safety and labeling</th>
<th>Safety and labeling</th>
<th>Safety and labeling</th>
<th>Premarket approvals, safety, labeling, and drug manufacturing standards</th>
<th>Premarket approvals, manufacturing and performance standards, tracking of malfunctions and adverse events</th>
<th>Safety, effectiveness, labeling, and distribution</th>
<th>Performance standards, premarket applications for new and modified risk tobacco products, labeling and advertising</th>
</tr>
</thead>
</table>

* Biological products, like other drugs, are used for the treatment, prevention or cure of diseases in humans. In contrast to chemically synthesized small molecular weight drugs, which have a well-defined structure and can be thoroughly characterized, biological products are generally derived from living material—human, animal, or microorganism—are complex in structure, and thus are usually not fully characterized. Frequently Asked Questions About Therapeutic Biological Products, U.S. FOOD & DRUG ADMINISTRATION, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm (last visited Aug. 26, 2013).
In addition to these centers, the FDA’s Office of Combination Products (“OCP”) responds both formally and informally to industry inquiries about which FDA center should regulate a particular product. The OCP was established in 2002, dividing regulatory responsibilities for products combining elements of drugs, devices, and biologics among the relevant Centers—CDER, CDRH, and CBER. Where a product contains a drug and a medical device, a drug and a biologic, a medical device and a biologic, or all three, it is termed a “combination product” and regulated according to the primary mode of action.\(^{14}\) Industry or FDA centers can seek the guidance of the OCP to determine (1) which center should regulate a non-combination product when jurisdiction is unclear; and (2) which center should have primary jurisdiction in the case of a proposed combination product.

The FDA places products in categories by their intended use. Because the intended use of a product is based on the claims made about it by the manufacturer rather than its ingredients or other characteristics, the statutory definitions of the FDA product categories are important to note, as they relate to the category into which a probiotic product might fit and which FDA center will regulate it. Particularly relevant to the regulation of probiotics are the definitions of food, components of food, dietary supplements, cosmetics, and drugs:

- Conventional foods are articles used for food or drink for man or animals; chewing gum; and articles used for components of food.\(^{15}\) Within this broad category are subcategories of food that CFSAN regulates and that are defined below:
  - **Food additive** – any substance the intended use of which results or can reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of food unless the substance is generally recognized as safe (GRAS).
  - **Substances Generally Recognized as Safe** (GRAS) – substances added to food that are generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of their intended use. A food


\(^{15}\) FDCA, Sec. 201(f) (codified at 21 U.S.C. § 321(f)).
substance may be established as GRAS either through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food.  

- **Medical food** – a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.

- **Foods for special dietary use** - a narrow category of foods that FDA defines as “foods that are specially formulated to meet a special dietary need, such as a food allergy or difficulty in swallowing, but that provide nutrients intended to meet ordinary nutritional requirements.” By regulation, FDA has approved label statements for three categories of foods for special dietary use – hypoallergenic foods, infant foods and food “that purports to be or is represented for special dietary use because of usefulness in reducing or maintaining body weight.”

- **Cosmetic** – a product, except soap, intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance.

- **Dietary supplement** – a product that is intended to supplement the diet and contains any of the following dietary ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; or a concentrate, metabolite, constituent, or extract; or combination of any of the above. The product must be a substance historically used by man to supplement the diet; intended for ingestion in pill, capsule, tablet, powder or liquid form; not represented for use as a conventional food or as the sole item of a meal or diet; and labeled as a “dietary supplement.”

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16 FDCA, Secs. 201(s), 409; 21 C.F.R. § 170.30.
17 Section 5(b) of the Orphan Drug Act, 21 U.S.C. § 360ee(b)(3).
19 FDCA, Sec. 201(i) (codified at 21 U.S.C. § 321(h)(3)(i)).
• **Drug** – an article that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans or in other animals.\(^{21}\)
  
  o **Cosmetic drugs** – a product can be *both* a “cosmetic” and a “drug” depending on the nature of the claims. There is no statutory category for, or definition of, cosmetic drugs. A product can be both if it claims to both cleanse or beautify (a cosmetic) *and* makes a drug claim. For regulatory purposes, the FDA treats such dual status products as drugs and subjects them to drug safety, efficacy, labeling, and manufacturing requirements.

Probiotics have traditionally appeared in foods, which, along with cosmetics, are the least regulated products consumers use in or on their bodies. The earliest probiotic products—although they were not labeled as such—were fermented products such as kefir (a fermented milk drink) and yogurts. To this day, the most well-known probiotic products are yogurts. However, in the last decade, probiotics have appeared in an increasing number of non-food products such as dietary supplements and cosmetics,\(^{22}\) including Align, a daily probiotic supplement containing Bifantis bacteria made by Procter and Gamble, and Redness Solutions Makeup SPF 15 with Probiotic Technology made by Clinique. There are also probiotic products that could fall into the medical device category, such as the Saforelle Florgynal Probiotic Tampon.\(^{23}\) Finally, although no probiotic drugs have been approved by the FDA, several clinical trials are under way that are studying the safety and efficacy of probiotic formulas.\(^{24}\)

ii. **Current Regulation of Probiotics – Issues of Concern**

While probiotics fall (or will fall) into virtually every product category regulated by the FDA, to date, the FDA does not have a central office or pathway that deals specifically with probiotics. Nor does the agency have a regulatory definition of probiotics. Probiotics are regulated based on the product category into which they fall, i.e., food, food additive, cosmetic,

\(^{21}\) 21 U.S.C. § 321(g).
\(^{22}\) Although probiotics can be cosmetics, the Working Group did not focus on this product category.
\(^{23}\) Tampons have traditionally been regulated as medical devices.
\(^{24}\) *See* Olle, *supra* note 9, at 314 Tbl.3.
dietary supplement, or drug. When questions arise regarding into which category a probiotic belongs, the answer is determined on a case-by-case basis. Moreover, although many are sold as dietary supplements, probiotics are not specifically listed under the definition of dietary supplements, which specifically lists vitamins, minerals, herbs or other botanicals, and amino acids, or a concentrate, metabolite, constituent or extract of any of these listed substances.

Many Working Group members expressed concern that, because probiotics fall into multiple categories, expertise about them is spread unevenly across multiple centers at the FDA without a single authoritative agency voice on the issue. Working Group members noted that this has led to inter-center inconsistencies in interpretation and application of regulations, data requirements, and the content of potentially relevant guidance documents. Furthermore, some believe, in the absence of a clear FDA position on regulation of probiotics, CBER may be the default center to review any probiotic where there is a question about whether the product requires an IND given that recent CBER guidance implies that probiotics are live biotherapeutics—a category of products considered drugs. This concerned many Working Group members, who noted that CBER may not be the most appropriate center to regulate probiotics traditionally considered food or dietary supplements with added microorganisms.

In another set of concerns, many members of the Working Group pointed out that the current regulatory framework does not properly address the role of foods in preventing disease, improving health, or possibly treating disease. For example, although there is a statutory category for medical foods, the FDA has not promulgated regulations or issued guidance clarifying that the category could include probiotics. Probiotic foods and dietary supplements that attempt to take on the role of improving health or treating disease by making health-related claims are automatically placed in the drug category.

A related concern is that once a manufacturer pursues an IND for a probiotic product, it will get “locked into” the drug category. Section 912 of the FDA Amendments Act of 2007 added subsection 301(ll) to the FDCA, which prohibits the sale of food to which a drug, licensed

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25 See 21 C.F.R. § 101.9(j)(8).
biological product, or biological product for which “substantial clinical investigations” have been instituted, has been added.\textsuperscript{26} From a historical perspective, this marks a significant change in the regulation of food and drugs.\textsuperscript{27} Prior to the advent of subsection 301(ll), there was considerable flexibility in the regulatory categorization of a substance as a food, a drug, or both. Some Working Group members fear that this “lock in” provision inhibits manufacturers and researchers from pursuing research that studies the role of foods in preventing disease, improving health, or treating disease because, given that the FDA considers probiotics to be biological products,\textsuperscript{28} the provision seems to indicate that a probiotic product for which research has been conducted cannot be added to food. Commentators note that adding a drug or biological product to food contrary to this paragraph will cause the food to be forever considered a drug (hence the “lock in”). This is problematic if probiotic manufacturers prefer to market their product as a food for general consumption rather than as a drug with a more limited distribution.

While some Working Group members expressed the opinion that probiotics should be regulated separately from other products, others disagreed and thought that the current FDA regulatory structure provides a comprehensive and potentially flexible framework for regulating probiotic products and is able to incorporate probiotics as it has incorporated other new types of products. Those who viewed the current structure more positively noted that the intended use of a probiotic product should govern the regulatory category into which the product will fall and, accordingly, the regulatory requirements the product must meet. They considered that this regulatory framework offers numerous product pathways for marketing. They also expressed the view that many of the research concerns identified by other members of the Working Group (see infra page 25) can be addressed by carefully crafting study protocols to ensure that a product is placed in a particular regulatory pathway.

\textsuperscript{26} See Fred H. Degnan, \textit{Clinical Studies Involving Probiotics: When FDA’s Investigational New Drug Rubric Applies—and When It May Not}, 3 GUT MICROBES 1, 5 n.38 (2012), available at http://www.landesbioscience.com/journals/gutmicrobes/article/22158/ (stating that the scope of this prohibition is not clear and that FDA has not issued definitive guidance on how it intends to interpret the provision).


\textsuperscript{28} See infra text accompanying notes 45-47.
iii. Recommendations

To address the lack of a central office or pathway that deals with probiotics and the resulting inconsistencies that result, Working Group members suggested a number of ways the FDA could create a more targeted and streamlined process, including:

- Creation of an authoritative entity within the FDA Commissioner’s Office that would determine if an IND is necessary to perform probiotic research.
- Creation of a new regulatory pathway for probiotics within the 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, assign the product either to the new pathway or another FDA center for oversight. Probiotics in this new pathway would be regulated differently from other regulated products. For instance, certain probiotics might be subject to an abbreviated IND process. In addition, research on probiotics in this category could be conducted on a disease endpoint. Probiotics that fall into this new category would have certain similar characteristics that distinguish them from drugs. As a graphic example, some probiotics might be regulated along the continuum of regulated products falling between foods and drugs as indicated below:

<table>
<thead>
<tr>
<th>Foods and Cosmetics</th>
<th>Medical Foods</th>
<th>Dietary Supplements</th>
<th>Probiotics (meeting specific criteria)</th>
<th>Medical Devices</th>
<th>Drugs (including Biologics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Least regulated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potential new category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most regulated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Some suggested creating a single office to regulate probiotics within CFSAN. CFSAN regulates the greatest number of probiotic products on the market and likely has developed greater technical capability and broader experience in community structures/therapeutic microbiology products than the other FDA centers. Furthermore, CFSAN is in the best position to assess the additional nutritional component that many
probiotics offer above their specific efficacy benefit. A similar model for the regulation of cosmetics and colors already exists under CFSAN.29

- Alternatively, others suggested the FDA should use the existing FDA Office of Combination Products30 (OCP) to make initial determinations as to which center should evaluate a probiotic product. This office has experience evaluating products that do not neatly fit into a single product category. One Working Group member suggested that in order to facilitate a productive industry/OCP interaction: (1) industry should be encouraged to utilize OCP’s request for designation (“RFD”) process; and (2) the FDA should be encouraged to streamline the RFD process. She said, “[t]he keys to effectively utilizing the existing OCP for probiotics jurisdictional questions will be to both make industry comfortable with the timeline for RFDs and alleviate industry concerns about the answers they may receive from OCP. For example, companies inquiring whether a product will be regulated as a dietary supplement or a drug may not want to spend the time or resources preparing an RFD and waiting for a response—particularly when there is a risk that the FDA will determine that the new product is a drug that requires a large quantity of data and information to support marketing. OCP should be prepared to answer questions about probiotics regulation in an efficient, timely, and useful way. The RFD process can currently require several rounds of dialogue, leading to delay in the FDA’s recommendation. . . . This process will require some patience and education for both industry and the FDA.”31

Other suggestions and recommendations in this area included the following:

- The FDA should establish collaborative pathways for products that may not fit within traditional categories. The public and relevant stakeholders should have input into establishing these pathways using the notice for public comment procedure, public

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29 See essay submitted by Working Group Members June Austin and Nora L. Zorich (on file with the project investigators).
31 See essay submitted by Working Group Member Barbara Binzak Blumenfeld (on file with the investigators).
meetings, and educational outreach to gather information about these products. The FDA should also take advantage of scientific and technical advisory boards with experience with probiotics.³²

- Congress should reevaluate the “lock in” provision in section 301(ll) of the FDCA that prohibits the addition to a food of an approved drug, a licensed biological product, or a drug or biological product for which substantial clinical investigations have been instituted. This would allow substances that are not going to be marketed as drugs or biologics (although they have gone through some clinical testing) to be marketed as foods and made more widely available.

- The category of products that are considered foods should be clarified/expanded to include substances that are used for:
  - dietary management of health conditions or diseases, i.e., foods should be able to be studied to determine how they might impact disease and marketed based on that information;
  - reduction of risk of acute disease (such as colds, flu, antibiotic-associated diarrhea);
  - reduction of side effects or increasing the efficacy of drugs.³³

- Congress should add “probiotic” to the list of dietary supplements in DSHEA, so it would be listed specifically with other articles noted in the statute such as vitamins, minerals, herbs and other botanicals.

6) Research on Probiotics  

i. Background  

³² See essay submitted by Working Group Member Jordan Paradise (on file with the investigators).
³³ See essay submitted by Working Group Member Mary Ellen Sanders (on file with the investigators).
With the advent of the HMP, research relating to probiotics has skyrocketed in the last decade. In terms of clinical studies, a search of PubMed conducted in 2013 under the search term “probiotics” revealed no studies prior to 1991; 5 studies from 1995 to 1997; 384 from 2007-2009, and 430 from 2010 to 2012. Notwithstanding the enormous growth in probiotic research—or maybe because of it—a number of research concerns were specified by Working Group members, particularly those involved in research. At the root of these concerns is that researchers and manufacturers would like to conduct research on probiotics in a manner that is safe and appropriate but not be subject to the research regulations for drugs as they may not be applicable to certain commonly used probiotics, in particular, foods.

Much of the Working Group discussion regarding research was related to investigational new drug applications (INDs). An IND is a request for authorization from the FDA to administer an investigational drug or biological product to humans. Such authorization must be sought prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application. An IND is required for a clinical study if it is intended to support a new indication for a drug, a change in the approved route of administration or dosage level, a change in the approved patient population or a population at increased risk of harms associated with the drug, or a significant change in the promotion of an approved drug. There are two main categories of IND: investigator-initiated and sponsor-initiated. Investigator-initiated INDs are used when an academic researcher or physician wishes to perform a clinical trial to study an unapproved drug treatment, for example, a new indication for an existing drug. Sponsor-initiated INDs are filed by pharmaceutical companies studying new drugs or new uses for existing drugs. Both of these types of studies require approval by an institutional review board (IRB),

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34 An IND goes into effect 30 days after the FDA receives it. Interstate shipment and administration of the product may begin at that time without additional FDA authorization or before the 30 days if the FDA sends notice to the manufacturer prior to the 30 day time period. See 21 C.F.R. § 312.40.
35 21 C.F.R. § 312.2.
an independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a clinical trial. The IRB must review, approve, and provide continuing review of the trials, protocols and amendments, and of the methods and materials to be used in obtaining and documenting informed consent of the trial subjects.

ii. Research on Probiotics – Issues of Concern

As noted above, the statutory definition of a drug in the FDCA is “an article intended to diagnose, cure, mitigate, treat or prevent disease.” This definition is used, among other things, to define how and when a research study can be used to make claims about a product. If a clinical research trial measures an outcome that indicates a substance’s ability to diagnose, cure, mitigate, treat, or prevent disease, and the study is used to make claims about the substance (e.g., substance X lowers blood pressure), the FDA will consider the substance a drug. The measured outcomes are considered “endpoints,” and if an endpoint measures the way a substance diagnoses, cures, mitigates, treats, or prevents a disease, it is a drug or disease endpoint. Use of a disease endpoint has two important consequences: First, the research becomes drug research and is therefore subject to higher levels of scrutiny and human subjects protection than research on non-drug substances. Second, the research cannot be used to support product claims for foods and dietary supplements (which are not permitted to make drug claims).

The example of a yogurt currently available on a supermarket shelf illustrates the problem. If a properly conducted research study found that yogurt reduced the incidence of diarrhea in the elderly, the manufacturer could not lawfully add that claim to the product label, because the claim relates to mitigation of a disease and is therefore a drug claim. If a product

37 FDCA, Pub. L. No. 75-717, 52 Stat. 1040 (codified at 21 U.S.C. § 321(g)).
38 See Degnan, supra note 26.
makes a drug claim, it must be regulated as a drug.\textsuperscript{39} Most manufacturers would not want their yogurt regulated as a drug, only available to consumers through drug distribution channels.

Because probiotics generally promote wellness and balance, many of the studies that have been undertaken on probiotics have been conducted using endpoints that would be viewed by the FDA as disease endpoints. For example, a 2010 study tested a fermented milk’s ability to reduce the incidence of common infectious diseases in healthy children in day care centers. Even though the study documented a decreased incidence rate for common infectious diseases (CIDs) in the active group by 19 percent compared to a control group, use of the product in this study to prevent CIDs in day care children would be considered a drug use. Under the current FDA framework for claims, this study could only be used to substantiate a drug claim, therefore making fermented milk a drug according to the FDA. This perspective was troubling to many members of the Working Group who believe that the ability to conduct research with disease endpoints would provide greater opportunities to conduct basic research on probiotics. However, researchers and manufacturers are concerned that studies with disease endpoints will take their products out of the food and dietary supplement market where they believe most of these products belong.

Compounding this problem is the paucity of endpoints that are not disease endpoints. It is challenging to measure health improvement and/or health maintenance in a healthy person. Some researchers have suggested that the focus of probiotic studies could be in measurement of homeostasis. From a statistical point of view, if a study were able to minimize the variation around the mean for a specific measure (even in the absence of changing the mean), it could be a reflection of improved health. This notion, proposed by Dr. Daniel Tancredi, emphasizes the importance of homeostasis as a focus of studies on health (as opposed to disease), and provides a rationale based in solid statistical theory as a way to measure wellness or health maintenance.\textsuperscript{40}

\textsuperscript{39} As discussed on pages 64-66, in certain cases, both medical foods and foods bearing \textit{health claims} may lawfully mention a disease or disease endpoint in a product claim without being regulated as drugs.
\textsuperscript{40} Mary Ellen Sanders et al., \textit{Health Claims Substantiation for Probiotic and Prebiotic Products}, 2 GUT MICROBES 127 (2011), \textit{available at}
One challenge to demonstrating the value of this approach is to identify appropriate biomarkers that can be studied. The article notes the following properties would be important in a biomarker:

- maintaining moderate levels of the biomarker would be associated with good health;
- high or low values would be associated with ill health;
- biomarker levels in the same person would fluctuate over time; and
- reducing the magnitude or duration of such fluctuations in healthy people would be considered desirable.  

Such a biomarker could be an individual endpoint or be formed as a ratio of two other biomarkers, when maintaining the same relative amounts of the two component biomarkers would be desirable. Assuming a biomarker with the above properties is available, it could be used as the outcome measure in a randomized controlled trial to provide evidence that the experimental food is able to improve the maintenance of health in humans. As an example, in pediatric nutrition, the measurement of metabolic homeostasis is the standard approach when developing infant formulas.

Working Group members voiced concern that NIH and the FDA often require an IND for studies relating to probiotics even in cases where an IND may not be required or appropriate, such as studies with probiotics that have a history of safe use in the target population. In some cases, this has been a significant problem for investigator-initiated INDs. Under the investigator-initiated IND process, academic or independent researchers must depend on the cooperation of the product manufacturer. For example, if a researcher wants to determine if the product might have a therapeutic benefit and has independent funding to conduct a study to determine this, the need for an IND would require the researcher to work with the company to obtain the required


41 Id.
42 Id.
43 Id.
information. If the company does not want the study conducted, it can essentially block it by refusing to provide the necessary background data required for an IND.

A number of Working Group members believe that the cost and time required to complete an IND may be having a chilling effect on probiotic research.

One Working Group member noted that the need for an IND should be based on the intended use of the researched product, and the safety of the research. The value of an IND is that it starts the essential process of documentation needed to prepare a drug file and permit distribution of the drug across state lines. If there is no intent to submit a drug file and pursue the development of a product that will be used as a drug, then there is no need for an IND. Further, the Working Group member argued that the question of safety of a particular study should be left up to IRBs, and based on scientific, not regulatory, considerations. If the rules regarding INDs are not clarified, she stated, researchers will submit INDs, not because of the need to do so, but because they are unclear about the rules and fear loss of funding opportunities if they do not.44

A key concern of the IND Subcommittee was draft FDA guidance45 and regulatory activity that appeared to define all probiotics as live biotherapeutic products (which are drugs) and therefore require all probiotics—even ones being marketed as foods or dietary supplements—to go through the IND process. This would have been the case even if the product

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44 See essay submitted by Working Group Member Mary Ellen Sanders (on file with the investigators).
45 U.S. FDA, GUIDANCE FOR INDUSTRY INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS)—DETERMINING WHETHER HUMAN RESEARCH STUDIES CAN BE CONDUCTED WITHOUT AN IND, DRAFT GUIDANCE (Oct. 2010), available at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM229175.pdf. **Subsequent to finalization of this white paper, FDA published the guidance in final form. Footnote 14 of the final guidance did not appear in the draft guidance and states, “[T]wo provisions [of the Food, Drug and Cosmetic Act] indicate that a live organism that is a constituent of an article that is commonly used as human food or drink (e.g., a probiotic in yogurt) may be used as a dietary ingredient in a dietary supplement.” Id. at 10. The Working Group did not convene to discuss the import of this clarification.
manufacturer intended the research to test claims that are legal for foods (i.e., structure/function, risk reduction, or medical food claims). The IND Subcommittee viewed this articulation of the law as inappropriate and inaccurate because under current law, assignment of a particular use of a substance or microorganism to a product category is properly based on the claims made, rather than on the nature of the research supporting those claims.

In February 2012, this concern appeared to have been addressed to a certain degree by the FDA. In final guidance relating to clinical trials with live biotherapeutic products (LBPs), the FDA stated that “[t]his guidance . . . does not apply to products lawfully marketed as conventional foods or dietary supplements that are proposed for investigation solely to evaluate an LBP’s use in affecting the structure or any function of the body.”\(^{46}\) As such, it appears that an IND would not be required for studies of foods and dietary supplements that are conducted to make structure/function claims. However, other language in the February 2012 guidance states that “if a clinical investigation is intended to evaluate a product’s ability to diagnose, cure, mitigate, treat or prevent a disease, an IND is required under 21 C.F.R. Part 312.”\(^{47}\) The IND Subcommittee expressed concern that, even with the new guidance in place, the FDA will interpret any study with clinical endpoints as one in which the intent is to diagnose, cure, mitigate, treat or prevent a disease, even if the sponsor asserts that the intent of the study is to be able to make a structure/function or reduction of risk of disease claim. Further, the IND Subcommittee expressed the view that the new guidance is not broad enough, as it does not mention investigations related to medical foods or foods for special dietary use.

A final concern regarding probiotic research expressed by some Working Group members was inconsistency across institutes at NIH and IRBs about when an IND opinion from the FDA is required and inconsistency across centers at the FDA about when an IND is required. While Working Group members were able to provide examples of inconsistencies in treatment of similar probiotic research proposals across NIH Institutes that occurred in the mid-2000s, at


\(^{47}\) Id.
about that time NIH established a trans-agency working group on prebiotics and probiotics that has attempted to ensure uniformity of treatment across the Institutes for probiotic research. As regards the FDA, differences in treatment as to when an IND is required appear to be based on whether a product manufacturer deals initially with CSFAN or CBER.

**iii. Recommendations**

Concerns relating to research endpoints lead to several conclusions. First, research with disease endpoints should be allowed to substantiate non-drug claims without designating the product as a drug, as long as the effect of the product on healthy individuals is known. Moving forward, validated biomarkers for disease prevention in healthy populations are necessary, especially in the gut and immune system. Without these acceptable endpoints, companies may not be able to conduct useful clinical trials for non-drug claims. This is a problem in research generally, not just probiotics research, but one that is particularly difficult for probiotics because many endpoints tested for probiotics do not have validated biomarkers. Furthermore, the FDA or other scientific agencies should also recognize acceptable ways to 1) demonstrate modulation of a condition—for example cholesterol level—in healthy individuals without making a disease claim and 2) measure homeostasis.

The majority of Working Group members expressed the view that the FDA should adopt clear guidelines for when an IND is or is not required and for an abbreviated IND process that would allow researchers, in certain situations, to bypass Phase 1 clinical safety studies. If proposed research is to support the development of a new drug, then an IND should be required.

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48 Prebiotics are non-digestible food ingredients that stimulate the growth and/or activity of bacteria in the digestive system in ways claimed to be beneficial to health.

49 *See The Probiotic and Prebiotic Working Group (PPWG), NIH Division of Nutrition Research Coordination, [http://sigs.nih.gov/PPWG/Pages/default.aspx](http://sigs.nih.gov/PPWG/Pages/default.aspx) (last visited Aug. 26, 2013). The PPWG’s goals include promoting “trans-agency collaborations in advancing the evidence base of probiotics and prebiotics” and to “promote constructive interactions across all NIH Institutes, Centers and Offices.” Id.*
If proposed research is to investigate non-drug claims for a food or dietary supplement, an IND should not be required even if the researchers use a disease endpoint.

Consistent with the recommendation above, many Working Group members expressed the view that all FDA guidance documents on this topic should be compiled into a single source and that the FDA should revise the guidance to reflect the need for the agency to allow research without INDs when legitimate claims for foods are being studied (such as for structure/function, reduction of risk of disease, and medical food claims).

The Working Group IND subcommittee developed the proposal set out in Box 1 specifying both when an IND should not be required and when an abbreviated IND process would be appropriate.

Box 1: IND requirements for Probiotic Studies

Human Studies Conducted with a Probiotic When No IND Should Be Required
1. Consistent with current law, no IND should be required for research on probiotic products to evaluate the following claims: structure/function claims, food for special dietary use claims, disease management claims for “medical foods” pursuant to the Orphan Drug Act Amendments of 1988, or health claims (disease risk reduction claims) as provided for in the Nutrition Labeling and Education Act (NLEA) of 1990. This should include studies being conducted with disease endpoints to support any of these types of claims. As an example, no INDs were required for calcium/osteoporosis studies conducted in the past that supported an FDA-approved health claim that calcium reduces the risk of osteoporosis although osteoporosis is a disease endpoint.  

50 For a detailed discussion of when an IND is not required under current law, see Degnan, supra note 26.
51 The Nutrition Labeling & Education Act of 1990 (NLEA), Pub. L. No. 101-535, 104 Stat. 2353, required FDA to determine whether claims respecting 10 specific substance/disease relationships met the requirements for a health claim. NLEA § 3(b)(1)(A)(vi) and (x). The relationship between calcium and a reduced risk of osteoporosis was one of those 10
foods and dietary supplements making reduced risk claims based on studies that used disease endpoints should be treated the same way as calcium was in relation to reduced risk of osteoporosis.\textsuperscript{52}

2. The structure/function effects of a probiotic should be able to be investigated in a diseased population without an IND if: a) the probiotic is marketed or intended to be marketed as a food (including medical foods and foods for special dietary use) or dietary supplement, and b) the study is being conducted to support a structure/function or other non-drug claim. This paragraph assumes that the study will be conducted pursuant to the usual protections for study participants such as IRB approval and informed consent.

3. An IND should not routinely be required for safety studies being conducted to support a Generally Recognized as Safe (GRAS) determination or “new dietary ingredient” (NDI)\textsuperscript{53} submission.

4. If a study meets the existing IND Exemption,\textsuperscript{54} no IND should be required.

**Proposed Abbreviated IND Process**

The FDA should adopt an abbreviated IND process that allows research on probiotics being undertaken to make a drug claim (i.e., a claim that the product is useful for the cure, mitigation, treatment, prevention, or diagnosis of disease) to proceed without a Phase 1 clinical safety study in certain cases. Probiotics would be eligible for the

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\textsuperscript{52} See Nutrition Labeling and Education Act of 1990, Pub. L. No. 101-535, 104 Stat. 2353 (codified in part at 21 U.S.C. § 343(i), (q), (r)).


\textsuperscript{54} 21 C.F.R. § 312.2.
abbreviated IND process only if adequate evidence of safety in the target population at the desired use levels is available. FDA authorizations of probiotics in foods or dietary supplements (food additive approvals, GRAS regulations, GRAS Notifications subject to a “no questions” letter, NDI Notifications subject to a “no questions” letter, among other things) may serve as a basis for establishing safety for a given use to be investigated in human studies.

For probiotics in this category:

a. The probiotic that is the subject of the abbreviated IND must be researched in the same dose and delivery system as the probiotic previously deemed to be safe (via the GRAS process or other approved process) so as not to raise a safety concern.

b. If the sponsor wishes to conduct a study to support a therapeutic benefit for an at-risk population, then FDA must make a determination if the available information on safety is suitable for this new target population.

c. To determine if a probiotic has adequate evidence of safety in the target population, the following databases, guidance, and/or determinations may be useful: GRAS\textsuperscript{55} or NDI-notified substances;\textsuperscript{56} food additive status; material time and extent status;\textsuperscript{57} Qualified Presumption of Safety (QPS) status established by the European Food Safety Authority (EFSA);\textsuperscript{58} or other international databases.


\textsuperscript{56} The FDA does not maintain a list of NDI-notified substances but there are a number of subscription-only databases of NDI-notified substances maintained by private organizations such as the American Herbal Products Association. See, e.g., NDI Database, AHPA, http://ndi.npicenter.com/ (last visited Aug. 26, 2013).

\textsuperscript{57} The FDA uses “material time and extent” data to determine whether a drug can be included in the over-the-counter (OTC) drug monograph based on an analysis of whether the drug (or component of the drug) has been on the market to a sufficient extent over a sufficient period of time to meet the statutory test set forth in the guidance noted in this footnote. The regulations establish a two-part process. First, to determine whether a drug product is eligible to be considered for the OTC monograph system, certain information must be submitted in a time and extent application to show that a drug product (or component of the product) has been marketed as an OTC to a material extent and for a material time. Second, if the drug product is found eligible, FDA publishes a notice of eligibility in the Federal Register that requests that interested persons submit data to demonstrate the safety and effectiveness of the drug product for its OTC

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The abbreviated IND process application would include:

- An introductory statement and general investigational plan (per 21 C.F.R. 312.23 (a)(3)).
- A clinical study protocol for which IRB approval would be required.
- A summary of clinical safety data and/or in-market exposure data (material time and extent).\(^{59}\)
- Reference to GRAS specifications or a copy of the NDI notification as appropriate.
- Documentation that the strain being investigated is GRAS or the subject of an NDI.

7) Safety of Probiotics

i. Background

Working Group members agreed that safety of probiotics should be a primary focus of regulatory efforts in order to ensure that the field can develop with the full confidence of regulators and consumers. As part of this project, we examined the FDA’s existing safety standards for all regulated products. A summary of the safety standards for each category is presented below in Box 2:

\(^{58}\) The QPS is an ongoing annual assessment that is updated annually by the Panel on Biological Hazards within EFSA. See Qualified Presumption of Safety, EUROPEAN FOOD SAFETY AUTHORITY, http://www.efsa.europa.eu/en/topics/topic/qps.htm (last visited Aug. 26, 2013).

\(^{59}\) See supra note 57 regarding “material time and extent” determinations.
Box 2: Product Safety Standards

**Drugs**

Safety Standards

- The drug must be safe and effective for the product’s indication.\(^6^0\)
- A drug manufacturer/sponsor must file an Investigational New Drug Application (IND) with the FDA. An initial filing of an IND contains:
  - Results of pharmacological and toxicological evaluations
  - Chemistry and pharmaceutical manufacturing and controls data
  - A clinical plan for the development of the new drug product and a specific protocol for the initial clinical trial proposed to be conducted
- Safety data, i.e., data on morbidity and mortality, must be compiled throughout the clinical trials process which is conducted in three phases prior to marketing.
- Results of premarketing studies must be submitted to the FDA in the form of a New Drug Application.
- Post market safety data must be collected via Medwatch and entered into the FDA’s Adverse Event Reporting System (AERS).
- Safety is continually evaluated.

**Conventional Foods**

Regulation

- Unlike drugs and medical devices, foods do not require approval by the FDA prior to marketing and therefore the FDA has much less regulatory authority over this category of products.

Safety Standards

- Food must not be “ordinarily injurious to health” and must not be adulterated. The standard for adulteration of food caused by naturally occurring substances is less rigorous than the standard for added substances.

- Food is considered adulterated if it:
  - bears or contains any poisonous or deleterious substance which may render it injurious to health, but if the substance is a naturally occurring substance, the food is not considered adulterated if the quantity of the substance does not ordinarily render it injurious to health.
  - bears or contains:

\(^6^0\) For drugs, safety is a separate determination from the ultimate approval decision, which includes a risk/benefit analysis that takes into consideration, among other things, the condition being treated and other available treatments.
• any added poisonous or deleterious substance that is unsafe within the meaning of section 406 of the Food Drug & Cosmetic Act (FDCA), i.e., tolerances for poisonous ingredients;
• Pesticide residue; and/or
• An unsafe food additive or unsafe new animal drug.
  – consists in whole or in part of any filthy, putrid, or decomposed substances, or is otherwise unfit for food.
  – is prepared, packed or held under unsanitary conditions.
• Food manufacturers must adhere to Good Manufacturing Practices (GMPs)
  – The FDA does not have explicit statutory authority to promulgate legally binding GMP regulations for food but established them under the general authority of section 402(a) of the FDCA, which outlines general standards for food processing and handling deemed necessary to prevent/avoid contamination of food (21 C.F.R. § 110).
  – In enforcement actions, the FDA usually does not rely on the food GMP regulations as creating legally binding requirements against the food industry but instead uses evidence gathered during factory inspections to prove a direct violation of the FDCA.
• Food must meet Hazard Analysis & Critical Control Points and Principles (HACCP). HACCP is a management system for use in all areas of the food industry in which food safety is targeted through review and control of biological, chemical, and physical hazards from raw material production, procurement and handling to manufacturing, distribution and consumption of the end product. Section 418 of the Food Safety Modernization Act (2011) expanded the HACCP system and vested the FDA with broad authority to manage and enforce HACCP. The FDA promulgated proposed rules establishing “science-based minimum standards” for HACCP compliance on January 16, 2013.\textsuperscript{61}

\textit{Food Additives}

\textbf{Safety}

• A manufacturer wishing to market a new ingredient in a conventional food can
  – Make a self-determination that the ingredient is Generally Recognized as Safe (GRAS); and/or
  – File a GRAS notification with the FDA; OR
  – File a food additive petition supported by extensive toxicology testing.
• A Food Additive Petition must include the following:
  – Information about the chemical composition and substances used in the additive’s preparation.
  – The amount of additive in the food and its proposed use in the food.
  – Methods to determine the amount of the additive in the food.

• Data that it will have its intended effect.
• Required safety data (See below).

• Food Additive-Safety Standard
  • There is a two-part food additives safety standard: 1) history indicating that the substance is not hazardous to the health of man or animal; and 2) “reasonable certainty” that no harm will result from use of the additive.
  • The Delaney Clause (in the FDCA) requires that “no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal.”

• Tests Showing Safety of Food Additives
  • The FDA has summarized in its Redbook the various types of testing that may be required to show that a particular use of a food additive is safe.
  • Depending on the food additive and its intended use, the data required to demonstrate safety varies depending on the additive’s chemical structure, projected human exposure, and current knowledge about its safety.
  • As long as the tests conducted do not show that the additive “induce[s] cancer” (thereby invoking the Delaney Clause), the FDA will review the data and then determine the level at which the additive does not cause an adverse effect. Then, the FDA will apply a safety factor to that number (21 C.F.R. § 170.22).
  • Food Additives must also undergo toxicity testing and meet a “safety factor” to account for differences between humans and animals.

GRAS (Generally Recognized as Safe) Substances

• GRAS substances are substances added to food for which a manufacturer either
  • Makes a self-determination that the ingredient is GRAS and/or
  • files a GRAS notification with the FDA.

• GRAS Self-Determination
  • Any interested person may make a self-determination that a substance is GRAS for a particular use. Prior to 1997, a manufacturer could submit a petition to the FDA requesting GRAS affirmation. This process is no longer available.

• GRAS Notification
  • Since 1997, manufacturers have been allowed to notify the FDA of their GRAS self-determination and provide evidence supporting their decision. After

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63 The Redbook is the common name for an FDA guidance document, GUIDANCE FOR INDUSTRY AND OTHER STAKEHOLDERS; TOXICOLOGICAL PRINCIPLES FOR THE SAFETY ASSESSMENT OF FOOD INGREDIENTS (rev. ed. July 2007).
evaluating the notification, the FDA is to respond to the manufacturer, conveying the agency’s disposition within 90 days. The FDA may either “have no questions at this time” regarding the notice or indicate that the notice does not provide adequate basis for GRAS. If the FDA responds that the notice is inadequate, the submitter makes its own decision, although it would be inadvisable for a manufacturer to proceed under these circumstances.

- Contents of a GRAS notification
  - A GRAS notification must include information about the identity and properties of the substance and a discussion of the notifier’s reasons for considering the substance GRAS. Information is generally chemical, toxicological and, if applicable, microbiological in nature.
- GRAS Safety Standard
  - The same safety standards that apply to food additives (see above) apply to GRAS substances. The Redbook provides guidance for GRAS determinations as well as for food additives.

**Genetically Modified Organisms (GMO) in Food and Food Ingredients**

- Bioengineered foods and food ingredients (including food additives) must adhere to the same standards of food safety and adulteration provisions under the FDCA as traditional foods and food ingredients.

**Dietary Supplements**

Safety Standards

- Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), a manufacturer is responsible for ensuring that a dietary supplement is safe before it is marketed although it does not require premarket approval by the FDA.
- The FDA can take action if the product is adulterated or misbranded.
- A dietary supplement is adulterated if
  - it fails the general food safety standard in that the product bears any poisonous or deleterious substance which may render it injurious to health;
  - it presents a significant or unreasonable risk of illness or injury under conditions of use recommended or suggested in the labeling or, under ordinary conditions of use, if no conditions of use are suggested or recommended in the labeling;
  - the Secretary of the Department of Health and Human Services declares it to pose an imminent hazard to public health;
  - it contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury;
  - it contains a food additive (not a dietary ingredient) that is unapproved for such use, is not generally recognized as safe, or is otherwise adulterated or fails to meet current GMPs for dietary supplements.

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64 FDCA Section 413(c) (codified at 21 U.S.C. § 350(b)).
• As of 2007, manufacturers, packers, and distributors of dietary supplements were required to report information about serious adverse effects associated with the use of dietary supplements to the FDA.

**New Dietary Ingredients**

• A new dietary ingredient (NDI) is an ingredient in a dietary supplement that was *not* marketed in the United States in a dietary supplement before Congressional passage of DSHEA on October 15, 1994.\(^{65}\)

• Dietary ingredients marketed after October 15, 1994 are NDIs and therefore require the manufacturer to notify the FDA of its plan to use the NDI in a dietary supplement.

• The NDI notification must include supporting data that the dietary supplement containing the NDI will reasonably be expected to be safe under the supplement’s labeled conditions of use (21 U.S.C. § 350b(a)(2)). The manufacturer should include evidence regarding an adequate history of safe use, safety studies, or both.\(^{66}\)

**Good Manufacturing Practices**

• The FDA also regulates the safety of products through good manufacturing practices (GMPs), which are production and testing practices that help to ensure a quality product. The FDA has a number of GMP procedures for all product categories. For example, as noted above, a drug may be deemed adulterated if it passes all of the specifications tests but is found to be manufactured in a condition that violates current GMP guidelines. Therefore, complying with GMPs is a mandatory aspect of pharmaceutical manufacturing.

The available literature indicates that safety evaluations of probiotics should consider “pathogenicity, infectivity, virulence factors, toxicity, metabolic activity and intrinsic properties of the microbes.”\(^{67}\) While some strains of probiotics are safe for human use, for others there is limited data on safety. One issue of concern relating to the safety of probiotics is the potential for lateral gene transfer, or horizontal gene transfer, which refers to the transfer of genetic material between organisms other than from vertical gene transfer, i.e., gene exchange from the parental generation to the offspring. Lateral gene transfer is a mechanism of gene exchange that happens independently of reproduction and is one of the mechanisms for bacterial antibiotic

\(^{65}\) Id.

\(^{66}\) Draft Guidance for Industry, supra note 53.

Genes that are responsible for antibiotic resistance in one species of bacteria can be transferred to another species of bacteria through various mechanisms. In an ever-changing environment such as the gastrointestinal tract, some members of the Working Group speculated that the introduction of new organisms such as probiotics may eventually lead to lateral gene transfer but at least one review of the literature in this area noted that studies to date “indicate that . . . [d]espite the necessity for microbial genomes to adapt and maintain themselves in an environment where they are challenged by horizontal gene transfer, these genomes remain stable.”

Traditionally, the gold standard for determining the safety and efficacy of new drugs is the randomized placebo-controlled double blind clinical trial, i.e., randomized clinical trials or “RCTs”. Such trials, however, present some challenges for research on food safety. The RCT is designed primarily to address efficacy, although it may also provide an opportunity to provide safety information via very large studies or by post-marketing collection of adverse event reports. The safety of foods and food components are generally not studied via RCTs. Many of the studies on probiotic safety in foods have been non-controlled randomized studies; non-randomized controlled studies; or observational studies including cohort studies, case-control studies, cross-sectional studies, and case reports. These studies are also based on healthy populations rather than diseased populations.

Safety has also been determined in some cases by history of safe use where a food has been consumed for decades without significant adverse events. The concept of historical usage is employed by the FDA and other international regulatory bodies. For instance, a food substance may be established as GRAS (generally recognized as safe) if it is a substance used in food

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69 Carol A. van Reenen & Leon M.T. Dicks, Horizontal Gene Transfer Amongst Probiotic Lactic Acid Bacteria and Other Intestinal Microbiota: What Are the Possibilities? A Review, 193 ARCHIVES MICROBIOLOGY 157 (2011) (citing Tone Tønjum et al., Transformation and DNA Repair: Linkage by DNA Recombination, 12 TRENDS IN MICROBIOLOGY 1 (2004)).

before 1958. Under 21 C.F.R. § 170.30(c) and § 170.3(f), general recognition of safety through experience based on common use in foods requires, among other things, a substantial history of consumption of a substance for food use by a significant number of consumers. The FDA has approved a number of microorganisms and microbial-derived ingredients that are used in foods as GRAS.\(^71\) The agency has also taken no action against several GRAS notifications from manufacturers relating to probiotic ingredients, including a probiotic for use in food and beverages,\(^72\) and at least four probiotics for use in infant formula.\(^73\)

The FDA also considers “material time and extent” data in relation to approval of over-the-counter (OTC) drugs.\(^74\) For those wishing to establish the safety of an OTC drug, they may submit a time and extent application to establish safety and effectiveness data. In addition,

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\(^{71}\) See Partial List of Microorganisms and Microbial-Derived Ingredients that are Used in Foods, U.S. FOOD & DRUG ADMINISTRATION (July 2001), http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/MicroorganismsMicrobialDerivedIngredients/default.htm.

\(^{72}\) Ganeden Biotech received notice from the FDA in August 2012 that the agency had no questions or objections to the GRAS notification of GanedenBC30 (Bacillus coagulans GBI-30, 6086) for use as an ingredient in a range of foods and beverages. In April 2012, the Japanese company Yakult announced that an independent panel of scientists had evaluated Lactobacillus casei strain Shirota and determined that the strain is safe for use as a food ingredient. Yakult submitted this GRAS self-determination to the FDA in March 2012. See Letter from James T. Heimbach (for Yakult) to Paulette Gaynor, Supervisory Consumer Safety Advisor, U.S. F.D.A. (Mar. 20, 2012), available at http://www.accessdata.fda.gov/scripts/fcn/gras_notices/GRN000429.pdf (attaching a copy of determination report by Jheimbach LLC to letter). FDA responded in December 2012 stating that it had no questions regarding Yakult’s self-determination of GRAS status. See Letter to James T. Heimbach from Dennis M. Keefe, Dir., Office of Food Additive Safety (Dec. 10, 2012), available at http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm335746.htm.

\(^{73}\) These include: Lactobacillus casei subsp. Rhamnosus strain GG (Mead Johnson, GRAS Notification 231), Lactobacillus reuteri strain DSM 17938 (Nestle Nutrition, US, GRAS notification 410), Lactobacillus rhamnosus strain HN001 produced in milk-based medium (Fonterra Co-operative Group, New Zealand, GRAS Notification 281), Bifidobacterium lactis strain Bb12 and Streptococcus thermophilus (Nestle USA, GRAS notification 49). See Generally Recognized as Safe (GRAS), U.S. FOOD & DRUG ADMINISTRATION, http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/ (last visited Aug. 27, 2013).

\(^{74}\) See supra note 57 regarding “material time and extent” determinations.
EFSA uses a Qualified Presumption of Safety (QPS) index that includes microorganisms presumed to be safe for use in foods for the general population based, among other things, on history of safe use.  

The challenge of conducting clinical food safety studies had a major impact on the most extensive review of probiotic safety to date. In 2009, “[t]he Agency for Healthcare Research and Quality (AHRQ) commissioned the Southern California Evidence-based Practice Center based at [the RAND Institute] to carry out a systematic review on the safety of probiotics used in research to reduce the risk of, prevent, or treat disease. The evidence report was jointly sponsored by the NIH Office of Dietary Supplements, the NIH National Center for Complementary and Alternative Medicine (NCCAM), and the FDA’s CFSAN.” In April 2011, AHRQ published a report based on this review. The report, “Safety of Probiotics Used to Reduce Risk and Prevent or Treat Disease,” cataloged “what is known about the safety of interventions containing Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, and/or Bacillus strains used as probiotic agents in research to reduce the risk of, prevent, or treat disease.” Linda Duffy, Ph.D., M.P.H., the Program Officer at the Division of Extramural Research within NCCAM, presented the findings of the report to the Working Group.

The researchers identified 622 intervention studies on probiotics that reported the presence or absence of adverse health outcomes in human participants, without restriction by study design, participant type, or clinical field. The investigators were unable to make broad conclusions about the safety of probiotics because “[t]here is a lack of assessment and systematic reporting of adverse events in probiotic intervention studies and interventions are poorly documented.” In 235 studies, only nonspecific safety statements were made (e.g., the product is “well tolerated”); “[t]he remaining 387 studies reported the presence or absence of specific adverse health outcomes.”

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75 See European Food Safety Authority, supra note 58.
76 AHRQ, supra note 10, at ES-1.
77 Id. at vi.
adverse events.” The AHRQ study was hindered by the lack of well-documented studies and could only conclude that

the available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence.

More specifically, they noted that, based on reported adverse events, RCTs showed no statistically significant increased risk of adverse events, including serious adverse events, associated with short-term probiotic use compared to control group participants. However, the report stated that “long-term effects are largely unknown. Existing studies primarily examined Lactobacillus alone or in combination with other genera, often Bifidobacterium.” Moreover,

[f]ew studies directly compared the safety among different intervention[s] or participant [characteristics]. Indirect comparisons indicated that effects of delivery vehicles (e.g., yogurt, [other] dairy) should be investigated further. Case studies suggested that participants with compromised health are most likely to experience adverse events associated with probiotics. However, RCTs in medium-risk and critically ill participants did not report a statistically significant increased risk of adverse events compared to control group participants.

At least one organization expressed concern regarding the import of the findings of the AHRQ report. Taylor Wallace, Ph.D., and Douglas MacKay, N.D., with the Council for Responsible Nutrition, noted in a paper in the Journal of Nutrition that the report provided “little guidance to the healthcare and nutrition communities” because it relied primarily on a drug-oriented, evidence-based medicine paradigm instead of an evidence-based evaluation of other forms of data and practical information.

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78 Id. at ES-2.
79 Id. at 117.
80 Id. at vi.
The safety of food and dietary supplements is frequently discussed in relation to the regulation of new dietary ingredients or NDIs. As noted earlier in this section, the term “new dietary ingredient” means a dietary ingredient that was not marketed in the United States in a dietary supplement before Congress passed DSHEA on October 15, 1994. Ingredients appearing in a dietary supplement prior to this date are “grandfathered in” and no notification to the FDA is required if the ingredient is added to a new product. There is no authoritative, FDA-approved list of dietary ingredients that were marketed in dietary supplements before this date, but trade associations have created a number of such lists, including the probiotics listed in Box 3 below:


83 Section 413(c) of the FDCA (codified at 21 U.S.C. § 350(b)).
Box 3: Probiotics Marketed before 1994

Bifidobacterium bifidum  
Bifidobacterium infantis  
Bifidobacterium longum  
Bifidus adolescentis  
Lactobacillus acidophilus  
Lactobacillus casei  
Lactobacillus jugurtlدلbrueckii (bulgaricus)  
Lactobacillus plantarum  
Lactobacillus rhamnosus  
Saccharomyces boulardii  
Streptococcus faecium (Enierococcus faecium)  
Streptococcus salivarius  
Streptococcus thermophilus

The burden of proof is on manufacturers and distributors to determine if an ingredient is a “new dietary ingredient” and, if not, for documenting that a dietary supplement that contained the dietary ingredient was marketed before October 15, 1994. If an ingredient is an NDI, manufacturers and distributors are required to notify the FDA and make assurances as to why consumption of the new dietary ingredient is reasonably expected to be safe under the conditions recommended or suggested in the labeling. According to 2011 FDA guidance relating to NDIs, the safety of an NDI can be established based on history of safe use. According to the guidance,

An important component of reliability [of data relating to safe use] is the length of an ingredient’s history of use. A description of the population and the ways in which they use the food is also important. The frequency of food consumption and the number of consumers who used the food are at least as important as the number of years over which the product was available. Because there is little scientific literature addressing this topic,

85 See supra note 53.
FDA cannot make specific recommendations at this time, although the agency considers 25 years of widespread use to be the minimum to establish a history of safe use.\textsuperscript{86}

Over the last few years, Congress and FDA have increased their oversight of food safety and, of particular relevance to probiotics, have made changes to the NDI approval process. In 2010, Congress passed the FDA Food Safety Modernization Act, which required the FDA to publish guidance that clarified when a dietary supplement ingredient is an NDI, when information should be provided to the FDA on the ingredient and its safety, and appropriate methods for establishing the identity of an NDI. Some have argued that Congress did this to counter the impact of DSHEA, which treats herbal and non-botanical dietary supplements as foods and not drugs and allowed the supplement industry to remain largely immune to requirements of prospective demonstration of safety and efficacy.\textsuperscript{87} In July 2011, the FDA released draft guidance in this area that was “intended to assist industry in deciding when a premarket safety notification for a dietary supplement containing a new dietary ingredient is necessary and in preparing premarket safety notifications.”\textsuperscript{88} In July 2013, FDA released additional NDI guidance for industry that does not supersede the 2011 guidance but rather attempts to simplify the complex NDI notification rules.\textsuperscript{89}

ii. Safety of Probiotics – Issues of Concern

We asked the Working Group whether current FDA safety standards are appropriate for probiotics. For the most part, Working Group members agreed that current FDA safety standards for foods, food additives, and drugs are adequate for probiotics, although they noted that improvements should be made in the areas of (1) guidance as to how to apply safety standards specifically to probiotics and (2) oversight and enforcement of safety standards. On

\textsuperscript{86} Draft Guidance for Industry, supra note 53.  
\textsuperscript{88} See Draft Guidance for Industry, supra note 53.  
the other hand, although they considered safety standards for probiotic food adequate, some Working Group members were of the opinion that safety standards for probiotic dietary supplements are not sufficient. This is particularly an issue for dietary supplements sold prior to 1994, which were “grandfathered” in by the DSHEA and for which manufacturers need not submit any safety data to the FDA.⁹⁰

A particular area of concern among Working Group members related to the safety of GRAS substances and NDIs – both of which require manufacturers to conduct their own safety assessments with, in the case of GRAS substances and some dietary ingredients, no requirement to notify FDA of their determination. In terms of GRAS substances, the FDCA provides a mechanism for notification of the FDA of marketing of GRAS substances but does not require such notification.⁹¹ Leaving this responsibility primarily to manufacturers, especially in a time of limited resources for oversight and enforcement, was criticized by members of the Working Group. It should be noted that this criticism of the GRAS process is not unique to probiotics.⁹²

Similarly the notification process for NDIs was criticized by some members of the Working Group. The first concern identified with the NDI process was how manufacturers should determine if a probiotic was present in the food supply prior to 1994 or whether it is an NDI. Clearly it is easier for a manufacturer if an ingredient is grandfathered in and not subject to FDA notification requirements. Because probiotics can be characterized at different levels (i.e., strain, species, etc.), some in the probiotics industry have argued that use of a new strain within a microbial species that was present in the food supply before 1994 should not constitute a new ingredient. In a position paper issued in May 2011, the International Probiotics Association and other trade organizations argued that “individual strains belonging to microbial species with a

⁹⁰ Section 413(c) of the FDCA (codified at 21 U.S.C. § 350(b)).
⁹² The American Heart Association, for example, has challenged the GRAS process with regard to salt. The Association questioned the fundamentals of the GRAS process, including the wisdom of allowing food manufacturers to make their own GRAS determinations. See Letter from Gordon F. Tomaselli, Pres., American Heart Ass’n to the FDA and USDA Food Safety & Inspection Service (Jan. 26, 2012), available at http://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_437039.pdf (regarding approaches to reducing sodium consumption).
history of safe use as starter culture used for food fermentation or as a probiotic in food” should not be considered NDIs but rather considered as having existed in the food chain prior to 1994.93

Another issue related to NDI regulation was raised by recent guidance documents issued by the FDA. As noted earlier, pursuant to the 2010 FDA Food Safety Modernization Act, in July 2011, the FDA released draft guidance in this area.94 The guidance was met with widespread concern by the probiotic industry, because—although it does not refer to probiotics specifically—it used the term “microorganism” and notes that “not all microorganisms are dietary ingredients.” As noted above, probiotic manufacturers and researchers usually do not want their products placed in the drug category because of the additional regulatory burdens and the prohibitive cost of development for most drugs. Therefore, manufacturers and researchers who are contemplating adding new or different probiotics to a dietary supplement want the new addition to be considered a dietary ingredient rather than a non-dietary microorganism that might require the product be regulated as a drug or biologic. At least one commentator stated that “a bacteria that has not been used as food is not likely to be considered a dietary ingredient [by FDA].”95 It is possible that microbes not traditionally added to foods or to supplements will be identified through research on the HMP as promoting a microbiome environment beneficial to human health. The draft guidance issued by the FDA appears to preclude the use of such microorganisms as dietary supplements. However, in June 2012, FDA officials indicated after a meeting between FDA Commissioner Hamburg and Senators Hatch and Harkin that the FDA would revisit the controversial new NDI guidance.96 At the time of submission of this white

95 See Myers, supra note 84, at 3 (citing Anthony Young).
paper, FDA had not given a timeframe for revision of the NDI guidance but did publish additional “Q&A” for industry regarding the guidance in July 2013.97

Finally, several Working Group members raised the issue of lateral gene transfer. One member stated that there is now ample evidence that lateral gene transfer among bacteria is common.98 As noted earlier, although there is no evidence of this having happened with probiotics to date, this issue remains a concern especially if probiotic therapy is increasingly used in conjunction with antibiotics.

iii. Recommendations

Many in the Working Group believed that historical usage should be used to establish safety in probiotics as it is for other foods and dietary supplements via the GRAS and NDI process, but with several caveats. History of safe use should be considered only if the same target population and essentially the same dose and delivery system are used. The more the proposed use of the probiotic departs from historical usage in terms of the target population, dose or delivery system, the more persuasive the argument that additional safety analysis should be required. While many probiotics do have a long history of safe use, new probiotics that have not been on the market or those belonging to a species for which safety cannot be presumed should be required to go through more rigorous safety assessment, with appropriately designed study methods.

With regard to lateral gene transfer, several Working Group members suggested that before introducing new probiotic strains into an organism, the potential for lateral transfer of genes conferring resistance to antimicrobials must be addressed.99 To that end, two industry representatives in our Working Group advocated for mandatory testing to determine the antibiotic resistance patterns of probiotics at the strain level and to eliminate the possibility of the

97 See New Dietary Ingredients in Dietary Supplements supra note 89.
98 See essay submitted by Working Group Member John Huss (on file with the investigators).
99 Working Group Member John Huss essay (on file with the investigators) (citing M. Rauch & S.V. Lynch, The Potential for Probiotic Manipulation of the Gastrointestinal Microbiome, 23 CURRENT OPINION IN BIOTECHNOLOGY 192 (2012)).
probiotic strain(s) carrying transmissible antibiotic resistance genes. They suggested that antimicrobial susceptibility testing currently conducted by the EFSA be conducted initially given that it is standardized and established for probiotics.\textsuperscript{100} If a strain is significantly above the breakpoint (or the level at which a bacterium is deemed either susceptible or resistant to an antibiotic), then the probiotic strain should be evaluated for the presence of transposable antibiotic resistance elements such as plasmids or transposons.

Safety is clearly an overarching concern among all probiotic stakeholders, from government regulatory agencies, to consumer advocacy organizations, to manufacturers. In order for the potential of probiotics to be realized, probiotics must be safe in both practice and perception. While no consensus emerged on how the safety of probiotics can be assured, several other suggestions regarding how safety of probiotics can be better addressed emerged from Working Group discussions. These included the following:

- The FDA should clarify guidance relating to NDIs to allow newly discovered probiotics to be used as dietary supplements but only with thorough safety assessment (since history of safe use data will not be available).\textsuperscript{101}
- The FDA should use the same approach for safety of NDIs as is used for food additives and GRAS substances, which focus on the safety of the ingredient for an intended use. These approaches do not require a separate safety assessment for every product and every manufacturer.\textsuperscript{102}
- The EFSA approach to safety, i.e., the Qualified Presumption of Safety (QPS) list, should be adopted in the United States.\textsuperscript{103}

\textsuperscript{100} See essay submitted by Working Group Members June Austin and Nora L. Zorich (on file with the investigators).
\textsuperscript{101} See essay submitted by Working Group Member Mary Ellen Sanders (on file with the investigators).
\textsuperscript{102} Id.
\textsuperscript{103} The QPS list applies to “biological agents such as bacterial and fungal species or viruses used . . . in the food and feed chain.” See Qualified Presumption of Safety, supra note 58.
• The FDA or an industry consortium should establish recommended procedures for establishing the safety of probiotics, similar to the Redbook guidelines for assessing the safety of chemicals intended for addition to food, or USP standards.

• The FDA should require companies to report serious adverse events to the FDA of probiotic foods, as is required for drugs and dietary supplements. 104

• The FDA or another government agency could categorize safety risks and create “classes” of probiotic products based on safety risk. The FDA could look to the Cosmetic, Toiletry, and Fragrance Association (CTFA) safety review process as a model. CTFA established the Cosmetic Ingredient Review (CIR), an independent nonprofit organization comprised of a group of scientists, to review the safety of cosmetic product ingredients. Although CIR is financed by the cosmetic industry, it is composed of academics who are prohibited from working for any cosmetic company while serving on the CIR. 105

• The FDA or another agency or nongovernmental organization might consider creating something similar to the American Academy of Pediatrics Red Book 106 which lists “bad bugs” but that would list “beneficial bugs” instead.

• The FDA should improve GMPs for probiotic dietary supplements. Although GMPs do not relate to safety beyond the issue of contaminants, some in the Working Group noted that GMP standards could be enhanced to ensure product safety.

8) Characterization of Probiotics

104 The Working Group members felt that this would be beneficial although establishing causality for adverse events in a non-controlled setting is problematic.

105 While the FDCA does not require premarket approval of cosmetics, it prohibits the marketing of adulterated or misbranded cosmetics in interstate commerce. Violations of the Act involving product composition—whether they result from ingredients, contaminants, processing, packaging, or shipping and handling—cause cosmetics to be adulterated and subject to regulatory action.

106 The Red Book is a guide published by the American Academy of Pediatrics Committee on Infectious Diseases that sets forth the latest findings and clinical guidelines on the manifestations, etiology, epidemiology, diagnosis, and treatment of more than 200 common childhood conditions. It is not the same Redbook referred to in footnote 63.
i. Background

Characterization refers to the use of external techniques to probe into the internal structure and properties of a material and document those structures and materials. Characterization is used to identify products and to ensure that a product is what it claims to be—“[r]eliable identification by adequate methods confirms the identity of the strain in commercial use and is also necessary for proper labeling of products containing them.”107 The issue of characterization is particularly important in relation to probiotics because, unlike most other regulated products, probiotics are living organisms and therefore change over time, making it more challenging to be certain of the characteristics of the product post-manufacture. Therefore, any recommendations relating to characterization must address this inherent fact as well as the degree to which it matters in terms of assessing the effects of consumption.

A specific and unique application of probiotics—faecal microbiota transplantation (FMT) or fecal transplant—is useful to understand the complexity of characterizing probiotics. FMT is an existing treatment that involves the process of transplantation of faecal flora from a healthy individual into a recipient as a treatment for patients suffering from various severe intestinal disorders such as Clostridium difficile infection. If the stool contents could be made into pill form for oral ingestion, it would raise the question of whether it would, or could, meet FDA standards for characterization. The Working Group concluded that current standards would be difficult to meet because it would be impossible to identify all the microbes in the pill, therefore causing the “microbial limit” test in the guidance to be exceeded. Further, the chemical and microbiological components of the pill formulation would clearly vary from batch to batch and therefore run afoul of the requirement for consistency in product composition. While FMT is a unique and unusual application of probiotics and should not necessarily be categorized with other probiotic products, the concept highlights the concern that a potentially life-saving

treatment might not be approved by the FDA under current standards.\textsuperscript{108} Despite the lack of standards or guidelines specific to FMT, FDA recently reiterated that it would accept IND submissions for fecal transplants.\textsuperscript{109}

In January 2012, the U.S. Pharmacopoeia (USP) released new draft standards—\textit{Microbial Food Cultures Including Probiotics}—that detail the essential quality specifications, intended uses in food, safety considerations, regulatory status, and purity of probiotics. The standards will be incorporated into the \textit{Food Chemicals Codex} (FCC). While still untested, these new standards may be helpful in the characterization of probiotics.

\textit{ii. Characterization of Probiotics – Issues of Concern}

The FDA uses different characterization standards for the different categories of regulated products. It has not set forth characterization requirements specifically for probiotics either at the research or manufacturing stage.\textsuperscript{110} However, in 2010 the agency published guidance that sets forth requirements for chemistry, manufacturing, and controls (CMC) for early clinical trials using live biotherapeutic products (LBP).\textsuperscript{111} Without using the term “probiotic,”

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\textsuperscript{108} See E. Allen-Vercoe et al., \textit{A Canadian Working Group Report on Fecal Microbial Therapy: Microbial Ecosystems Therapeutics}, 26 CAN. J. GASTROENTEROLOGY 457 (2012). This group report also noted the challenge of creating a consistent therapeutic product that would satisfy Heath Canada’s requirements for a new biological drug product. \textit{See also} Olle, \textit{supra} note 9, at 310 (“Although CBER’s guidelines seem clear for products based on defined compositions of live organisms, it is still unclear how these guidelines will be applied to FT [fecal transplants].”).
\textsuperscript{109} See \textit{Guidance for Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies}, U.S. FOOD & DRUG ADMINISTRATION (July 2013), http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm361379.htm. This guidance document also made clear that FDA would exercise its discretion not to enforce IND requirements for certain uses of FMT in clinical care.\textsuperscript{110} All NIH-funded live biotherapeutic studies currently under an IND approval from CDER have passed through the FDA characterization product quality testing protocol prior to the IND being approved.
\textsuperscript{111} See \textit{U.S. FOOD & DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY, EARLY CLINICAL TRIALS WITH LIVE BIOTHERAPEUTIC PRODUCTS: CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION} (2010), \textit{available at}
\end{flushright}
the language used in the guidance and its definition of LBP indicate that the FDA believes that probiotics fit within the LBP category.\textsuperscript{112} The Working Group noted two concerns with the guidance. First, the guidance is designed for researchers conducting early clinical trials as part of the IND process and should therefore only apply to LBPs in drugs and to products making drug claims (such as a food which manufacturers want to market with a drug claim). This guidance should be clarified to exclude products lawfully marketed as conventional foods or dietary supplements, i.e., those wanting to make structure/function or health claims. Presumably these latter categories of products are not included within the guidance, although clarification by the agency would be useful in this area, especially given that its broad language seems to include probiotic products. To date, the FDA has not specified characterization requirements for probiotic foods and dietary supplements not making drug claims.

A second concern is that the characterization requirements in the LBP guidance are inappropriate for probiotics, even if the probiotic meets the definition of a drug and falls squarely within the parameters of the guidance. The guidance provides the following:

(1) A description of the LBP’s drug substance, including its physical, chemical, or biological characteristics, must be included in the IND. A description of the drug substance should include:

- Biological name and strain designations;
- Original source of cells from which the drug substance was derived;
- Culture/passage history of the strains;
- If cells were obtained from a clinical specimen, a description of the clinical health of the donor(s), if known (merely noting procurement from a commercial provider is not adequate);
- Summary of the phenotype and genotype of the product strains, with special attention to biological activity or genetic loci that may indicate activity or potency; and

\textsuperscript{112} According to the guidance, “[a] live biotherapeutic product (LBP) . . . is a biological product that: 1) contains live microorganisms, such as bacteria or yeast; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine.” \textit{Id.}
• Documentation and summary of modifications, if any, to the LBP, e.g., intentional introduction of foreign genes or mutations, along with details of the genetic construction.

Characterization of an LBP must include a description of the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance (21 C.F.R. § 312.23(a)(7)(iv)(a)). Test results should contain actual laboratory data in tabulated form rather than summaries. Results for quantitative assays should be presented as actual data and not simply as “Pass,” “Satisfactory,” or “Within Specification.”

Many in the Working Group agreed that these requirements are not adequately customized for probiotics. Specifically, the current LBP guidance requires a description of the phenotype or genotype of the strain with particular attention to biological activity or the genetic loci that may signal potency or activity. It is often challenging to identify the genetic loci for probiotics, most notably in early clinical trials. Further, the guidance refers to genotypic methods that are inadequate and outdated. Perreira et al. described the evolution of characterization techniques:

During the last few years molecular techniques have replaced or complemented traditional phenotypic methods. DNA-DNA hybridization is the current gold standard for determination of bacterial identification, with two strains being considered to belong to the same species if their DNA-DNA relatedness is 70% or more. However, due to the difficulties associated with this technique, and the need of expertise not normally present in the food industry, phylogenetically based approaches such as sequence analysis of the 16S rRNA gene are currently the most commonly used methods for bacterial species identification. In general, microorganisms sharing a 16S rRNA gene homology higher than 97% are considered members of the same species.

iii. Recommendations

In terms of the test for microbial burden, guidance relating to probiotics should specify what kind of assay is required. Recently, “the development of high-throughput sequencing technologies has enormously increased sequencing capability, significantly reducing sequencing costs.” Given these new techniques and the reduction in their costs, current genome

113 Id.
114 Perreira et al., supra note 107, at 79.
115 Id. at 81.
sequencing technology should be required, as it allows for whole genome analysis and could serve as the standard for characterization.

Some Working Group members noted that, while use of germ-free mice in research would likely allow probiotics to meet characterization standards, using such mice does not make a great deal of sense given that probiotics are designed to work in complex microbial environments. Moreover, LBP characterization standards are focused on the product; this may be inappropriate for probiotics because safety and effectiveness may be dependent on both the characteristics of the product and the microbiome of the consumer. While the interaction between an introduced agent and the consumer is not unique to probiotics, probiotics may present unique questions of host/agent interaction that should be taken into account with regard to characterization of probiotics.

In terms of developing characterization requirements for probiotics, several suggestions emerged from the Working Group:

- Characterization requirements should be developed for probiotics in foods and dietary supplements, as well as probiotics in drugs. Overlaps and differences between the requirements for both groups should be clearly set forth by the FDA.
- The FDA should specifically address the seminal bacterial features that determine whether the resulting probiotic is the same or different from previous products. The FDA will also need to consider whether these key features should be different for probiotics used for oral use versus non-oral use (e.g., dietary supplement, food, medical food, or drug use, versus use of a probiotic in conjunction with a medical device).
- Characterization standards must be flexible enough to encompass new technology and must be specific enough to allow for proper/precise identification of strains.
- An organization outside of the FDA, such as the American National Standards Institute (ANSI), could develop characterization standards for probiotics.
- The microorganism added to make a probiotic should be deposited in an independent reference culture collection as a means of assuring consistency between the product taken by consumers and the product as marketed.
• The USP draft standards for products containing probiotics could be the basis of a broader standard focused on probiotic ingredients in general, versus solely those in foods.
• All products should have a certificate of analysis on file for each lot produced, done by a reputable company, certifying what organisms are present, in what quantity and include testing for potential contaminants.116
• Regulators should clarify the degree to which probiotics must be characterized in different contexts, i.e., in labeling, NDI notification, or development of good manufacturing practices (GMPs).117

9) Probiotic Product Claims and Labeling

i. Background – FDA and FTC Regulation of Product Claims and Labeling

A major focus of the probiotics project was product claims, i.e., what probiotic product manufacturers can claim about their products on the product labels and in advertisements. This focus on product claims flows from two contrasting concerns—that probiotic product claims may be both under-regulated (or non-compliance may be under-enforced) AND over-regulated in terms of the evidentiary requirements for certain types of statements that can be made about probiotic foods and dietary supplements.

Definition of Probiotics

Before addressing how the FDA regulates claims and labeling, the Working Group discussed the foundational issue of how probiotics should be defined and how the definition of probiotics relates to product claims. As mentioned earlier, the definition used during the project and the definition most commonly used in the field comes from the 2001 report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria.118 In that document, probiotics

116 See essay submitted by Working Group Member Patricia Hibberd (on file with the investigators).
117 Note that some of these recommendations are already in place for certain NIH-funded studies.
118 JOINT FAO/WHO EXPERT CONSULTATION, supra note 6.
are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” Some members of the Working Group queried whether simply labeling a product a probiotic constitutes a health claim, given that the definition states that a probiotic confers a “health benefit.”

Two members of the Working Group recommended that the FDA adopt a definition of probiotics that is different from the FAO/WHO definition. They recommend doing so to clarify the term “health benefit” and to reflect potential new uses beyond the current use of probiotics as foods or dietary supplements. Under this proposal, a probiotic would be defined as:

[a] live microorganism to include spores when germinated (if demonstrated these would be expected to metabolize in the intended environment) which when administered directly to/on the host either orally or topically in adequate amounts, confers a measureable/quantifiable and meaningful physical, mental and/or social well-being benefit on the host (human or animal).

This definition builds upon the currently accepted World Health Organization (WHO) definition of a probiotic in the following ways:

- It substitutes the word “health” with “physical, mental and social well-being.” This is based upon WHO’s own definition of health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (Official Records of the World Health Organization, no 2, p.100, 1946). This change reflects the position that it is reasonable to assume that when WHO used the word “health” to describe the benefit a probiotic conferred on a host, the agency intended it to extend beyond traditional therapeutic benefits to include meaningful physical (e.g., immunological, microflora modulation, serum cholesterol lowering, etc.), as well as mental or social well-being benefits. Examples of physical benefits (which are not intended to treat disease) could be skin barrier changes; improvement in skin texture, fine lines and wrinkles; mitigation of abdominal discomfort, or improved mobility. Some examples of social benefits could be reduction of body, vaginal or oral odor, gas and bloating, or improvement of appetite.
- It clarifies that a probiotic may be administered either orally or topically.
• It adds a requirement that the probiotic effect be one that can be measured or quantified and requires that this effect be a meaningful effect to the host.119

While the Working Group members who support this new definition argue that a definitional change would support a category for probiotics that wish to make beneficial claims outside of the drug category, other Working Group members believe there is no compelling justification to move from the FAO/WHO definition. They argue that the proposed modified definition is much more complicated and, while it provides examples of what the definition should cover, in fact it does not change it. For example, the proposed definition narrows “administered” to “topically or orally.” The word “administered” includes any conceivable administration route including for example, intra-vaginal and rectal administrations. In a similar fashion, the original definition says any “host,” while the revised definition says “human or animal” host. This raises the question of whether the probiotic could be given to a plant, perhaps to help defend against a plant pathogen, and why the definition needs to be limited to humans or animals. Finally, critics of the modified definition disagree that it clarifies the concept of “health benefit,” as the FAO/WHO definition implicitly includes mental health and social benefits.

Jurisdiction over Health Claims

For health-related products, both the FDA and the FTC regulate what manufacturers can say about a product.120 Furthermore, the claims a manufacturer makes about a product also relate to how that product is regulated by the FDA, e.g., products making what the FDA considers to be drug claims are required to go through the drug approval process.121 Because

119 See essay submitted by Working Group Members June Austin and Nora L. Zorich (on file with the investigators).
121 The intended use of an article for FDA regulatory purposes is not based upon the manufacturer’s subjective intent. Rather, the determinant is “objective intent” based upon
different FDA regulatory categories require vastly different degrees of scientific substantiation (and therefore investment), the issue of how claims are regulated is complex and controversial. As some probiotics arguably do not squarely fit into current FDA product categories, the issue of claims is further complicated and unclear.

While the FDA regulates advertising of prescription drugs and labeling of prescription and OTC drugs, dietary supplements, medical devices, cosmetics, and food, FTC regulates advertising of OTC drugs, foods, dietary supplements, medical devices, and cosmetics (including TV, radio, internet and print ads).

**Labeling Requirements**

The FDA has the responsibility for administering federal food labeling requirements in accordance with the FDCA. The Act prohibits labeling that, among other things, is false or misleading or that fails to list the amounts of certain ingredients. Within the FDA, CFSAN’s Office of Nutrition, Labeling and Dietary Supplements publishes regulations and guidance on food labeling (including conventional food, dietary supplements, infant formula and medical foods) and provides policy interpretations for overseeing compliance with the relevant statutes.
and regulations. The Nutrition Labeling and Education Act (NLEA) of 1990 requires most foods to bear nutrition labeling and requires food labels that bear nutrient content claims and some health messages (as noted in the guidance) to comply with specific requirements. The FDA stipulates that all food products must have a principal display panel (PDP) that contains the statement of identity (name of the food) and the net quantity statement (amount of product). The statement of identity is the name of the product by law or regulation. Ingredients must be listed in descending order by predominance and weight. The nutrition facts must appear on each product, including total calories, fat, carbohydrates, protein and fiber. “Trace ingredients” must be listed if the trace ingredient is present in a significant amount and has a function in the finished food. If a substance is an incidental additive and has no function or technical effect in the finished product, it need not be declared on the label. Food labels must meet FDA standards but do not require preapproval.

130 Id.
131 Id. and 21 CFR 101.3.
132 Id. and 21 CFR 101.4.
133 Id. and 21 CFR 101.9 (C).
134 FDA does not define “trace amounts”; however, there are some exemptions for declaring ingredients present in “incidental” amounts in a finished food. If an ingredient is present at an incidental level and has no functional or technical effect in the finished product, then it need not be declared on the label. An incidental additive is usually present because it is an ingredient of another ingredient. Id.
135 Id.
136 However, to determine the nutrient levels in foods, companies may develop or use databases, and these may be submitted voluntarily to the FDA for review. Id.
The DSHEA amended the FDCA by defining “dietary supplements” and adding specific labeling requirements for them, as well as optional labeling statements.\textsuperscript{137} Labeling requirements for dietary supplements include: 1) a statement of the product’s identity, i.e., the name of the supplement; 2) a net quantity of contents statement (or the amount of the dietary supplement); 3) nutrition labeling; 4) an ingredient list, and 5) the name and place of business of the manufacturer, packer, or distributor.\textsuperscript{138}

A 2008 GAO report summarized the tools the FDA has to respond to food (including dietary supplement) labeling violations:

It may ask companies to voluntarily recall any food that has already entered the distribution chain. FDA may also send a warning letter to a firm, which is a notice that enforcement actions may be forthcoming if corrections are not made; according to FDA guidance, warning letters are used for serious violations. For less serious violations, FDA may send an untitled letter, which is an informal communication that corrective actions are needed. At any point, FDA may hold a regulatory meeting with the firm to resolve a labeling violation or work with a firm to obtain voluntary compliance. When violations are not corrected, FDA may initiate actions to seize and remove the food from the marketplace (a seizure) or enjoin a firm from continuing a practice that violates food labeling statutes and regulations (an injunction).\textsuperscript{139}

Labeling for drugs differs from that for food and dietary supplements, the most important difference being that drug labels require preapproval by the FDA.\textsuperscript{140} This preapproval mechanism gives the FDA greater control over drug labeling than it has for foods. Under the FDA’s prescription drug labeling guidelines, specific information must be included on the label

\textsuperscript{137} See supra note 83.
\textsuperscript{138} See GUIDANCE FOR INDUSTRY: A DIETARY SUPPLEMENT LABELING GUIDE (April 2005).
\textsuperscript{139} See U.S. GOV’T ACCOUNTABILITY OFFICE, FOOD LABELING: FDA NEEDS TO BETTER LEVERAGE RESOURCES (2008) supra note 127.
\textsuperscript{140} See GUIDANCE FOR INDUSTRY: LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS – IMPLEMENTING THE PLR CONTENT AND FORMAT REQUIREMENTS (February 2013) In the case of products subject to an OTC monograph, because the monograph includes approved claims, these products can enter the market without preapproval by the FDA if the claims are allowed by the monograph. See also GUIDANCE FOR INDUSTRY: LABELING OTC HUMAN DRUG PRODUCTS — QUESTIONS AND ANSWERS (December 2008).
or a package insert.\(^{141}\) A drug label must provide information about the safe and effective use of the drug that is informative and accurate.\(^{142}\) No promotional, false, or misleading claims and no implied claims or suggestions are permitted for use if evidence of safety or effectiveness is lacking.\(^{143}\)

Currently, probiotic manufacturers do not have to specify on their product labels the strains they use in probiotic products or specify the number of live microbes of each strain that the products deliver through the end of shelf life. One member of the Working Group noted that some manufacturers refuse to divulge this information by claiming that it is proprietary information. He likened this to “a manufacturer boasting it adds vitamins to its food while refusing to disclose which vitamins.”\(^{144}\)

**Claims Regulation**

Under current law, as stated above, FDA regulation of claims differs based on which category the product falls within.\(^{145}\) For example, a drug claim describes the effect of a substance on the diagnosis, treatment, mitigation, cure or prevention of disease.\(^{146}\) With the exception of health claims, i.e., claims for reduction of risk of disease (which are a category of prevention claims), this type of claim may only be used for drugs, and the claim requires pre-approval by the FDA.\(^{147}\) An example of a drug claim is that a product “reduces the pain and

\(^{141}\) GUIDANCE FOR INDUSTRY: LABELING FOR HUMAN PRESCRIPTION DRUGS AND BIOLOGICAL PRODUCTS *supra* note 140.

\(^{142}\) *Id.*

\(^{143}\) *Id.*

\(^{144}\) See essay submitted by Working Group Member David Schardt (on file with the investigators).

\(^{145}\) See *supra* note 121.

\(^{146}\) 21 U.S.C. § 321(g) and see text accompanying note 21.

\(^{147}\) See FDA information page, “Is It a Cosmetic, a Drug, or Both? (Or Is It Soap?)” available at [http://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074201.htm](http://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074201.htm). As stated *supra*, OTC drugs, however, are regulated under a monograph system and no preapproval of claims is required as long as the claim is approved under the appropriate monograph.
stiffness associated with arthritis.” 148 There are a number of claims that the FDA allows manufacturers to make about foods and dietary supplements, and each type of claim has its own substantiation requirements:

**Structure/Function claims** describe the role of a nutrient or dietary ingredient intended to affect normal structure or function of the body in humans. There is no pre-approval required for these claims; however, the manufacturer is responsible for ensuring the accuracy and truthfulness of these claims, and a dietary supplement manufacturer must notify FDA within 30 days of marketing a dietary supplement with a structure/function claim. In addition, structure/function claims made by dietary supplement manufacturers must bear the following disclaimer: “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.” An example of a structure/function claim is: “Helps maintain normal cholesterol levels.”

**Nutritional content claims** characterize nutrient levels. An example is “this product contains 40% omega-3 fatty acids, 10 mg. per cap.”

**Health claims** describe the effect of a product on the reduction of risk of disease in a healthy or at-risk population. Although “reduction of risk of disease” might also be considered a prevention claim (which would otherwise be considered a drug claim), Congress carved out an allowance for foods and dietary supplements wishing to make reduction of risk of disease claims when it passed the NLEA. These claims require pre-approval by the FDA based on significant scientific agreement. 151 The Food and Drug Administration Modernization Act of 1997 (FDAMA) provided a second way for the use of a health claim on foods (but not dietary supplements) to be authorized as a result of a successful notification to FDA of a health claim based on an "authoritative statement" from a scientific body of the U.S.

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148 Example provided in FDA GUIDANCE FOR INDUSTRY: STRUCTURE/FUNCTION CLAIMS, SMALL ENTITY COMPLIANCE GUIDE (Jan. 9, 2002).
150 For a full description of nutritional content claims, see Claims that Can be Made for Conventional Foods and Dietary Supplements, U.S. FOOD & DRUG ADMINISTRATION (Sept. 2003), http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm111447.htm.
151 A finding of significant scientific agreement by the FDA requires the agency’s best judgment as to whether qualified experts would likely agree that the scientific evidence supports the substance/disease relationship that is the subject of the proposed health claim. See Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims, U.S. FOOD & DRUG ADMINISTRATION (Jan. 2009), http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Labe lingNutrition/ucm073332.htm.
Government or the National Academy of Sciences.\textsuperscript{152} An example of an approved health claim is “Use of calcium in the diet on a regular basis may help to reduce the risk of osteoporosis.” The FDA has approved very few health claims; none have been approved for probiotics.\textsuperscript{153}

Qualified health claims are an additional category of health claims created by judicial rulings over the past decade and a half. In \textit{Pearson v. Shalala},\textsuperscript{154} the plaintiffs challenged FDA’s general health claims regulations for dietary supplements and the FDA’s decision not to authorize health claims for four specific substance/disease relationships. The U.S. Court of Appeals for the D.C. Circuit held that the First Amendment does not permit the FDA to reject health claims that the agency determines to be potentially misleading, unless the agency also reasonably determines that no disclaimer would eliminate the potential deception.\textsuperscript{155} Based on this ruling, the FDA created the qualified health claim. This food and dietary supplement claim requires less than significant scientific agreement and must be accompanied by a disclaimer or qualifier explaining the level of scientific evidence supporting the claim. Manufacturers wishing to use a qualified health claim must file a petition with the FDA within 30 days of marketing a product,\textsuperscript{156} and the FDA may issue a letter of enforcement discretion.\textsuperscript{157} An example of a qualified health claim is the following: “One small study suggests that chromium picolinate may reduce the risk of insulin resistance . . . FDA


\textsuperscript{154} 164 F.3d 650 (D.C. Cir. 1999).

\textsuperscript{155} \textit{Id}.

\textsuperscript{156} 21 U.S.C. § 343(r)(6)(c).

\textsuperscript{157} The FDA has broad regulatory authority and enforcement discretion in the area of qualified health claims. Although premarket approval of these claims is not required, a manufacturer may file a petition in advance of making a qualified health claim. In response to a petition, the agency may choose to exercise its enforcement authority in this area. One available measure is a “letter of enforcement discretion,” in which the FDA informs a manufacturer of what it can and cannot do in relation to a specific claim. \textit{See, e.g., Qualified Health Claims: Letter of Enforcement Discretion – Chromium Picolinate and Insulin Resistance}, U.S. FOOD & DRUG ADMINISTRATION (Aug. 25, 2005), http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm073017.htm.
concludes, however, that the existence of such a relationship . . . is highly uncertain.”

There are currently no qualified health claims for any probiotic product.

Medical Food Claims are exempt from the requirement to bear nutrition labeling (21 C.F.R. § 101.9(j)(14)) and from the health claim and drug requirements that attend the mention of a disease relationship on a product label (see 21 C.F.R. § 101.14(f)) if the product is specially formulated and processed for partial or exclusive feeding of a patient orally or by enteral tube; and intended for dietary management of a patient when it cannot be achieved by modifying the normal diet (e.g., chronic medical needs; limited/impaired capacity to ingest, digest, etc.; other special medically determined nutrient needs); and providing nutritional support to manage unique nutrient needs resulting from a specific disease/condition (per medical evaluation); and intended for use only under medical supervision; and intended only for patients receiving active/ongoing medical supervision. Examples of medical food claims include the following: “A phenylalanine-free food to aid in the nutritional management of hyperphenylalaninemia including PKU” and “a nutritionally complete formula that provides a concentrated source of calories for patients with restricted fluid allowance or increased energy needs…useful in the dietary management of volume-restricted patients, oncology patients, hypermetabolic conditions, trauma, sepsis, and post major surgery.”

**FTC Regulation**

The FTC has rules regarding substantiation for health-related product claims that are different from those of the FDA. The basis of all FTC product claims is Section 5 of the FTC

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160 For more information about FDA regulation of health claims, see online webinar by Working Group Member Barbara Binzak Blumenfeld (Buchanan Ingersoll & Rooney PC) prepared for the Working Group at http://www.law.umaryland.edu/programs/health/events/probiotics/claims_webinars.html.
Act, which prohibits “unfair or deceptive acts or practices in or affecting commerce”\(^\text{161}\) and Section 12 of the FTC Act, which prohibits disseminating or causing the dissemination of a false advertisement in commerce for the purpose of inducing, or that is likely to induce, the purchase of any food, drug, device, service, or cosmetic.\(^\text{162}\)

In terms of advertising, an advertisement is deceptive if it contains a representation or omission of fact that is likely to mislead a consumer acting reasonably under the circumstances, and that representation is material to a consumer’s purchasing decision.\(^\text{163}\) Deceptive advertisements are those that include false claims, fail to disclose material facts, or make unsubstantiated claims.\(^\text{164}\) In determining if an advertisement meets FTC requirements, the FTC takes the perspective of a reasonable consumer who is likely to hear or see the ad.\(^\text{165}\) As advertisements may have more than one reasonable interpretation, where an ad conveys more than one meaning a seller is liable for the misleading meaning interpretation even if it can be interpreted in a way that is not misleading.\(^\text{166}\) An advertisement will be considered misleading if a significant number of reasonable consumers believe the misleading claim.\(^\text{167}\)

To determine if an advertisement is deceptive, the primary evidence of what representations an advertisement conveys is the advertisement itself.\(^\text{168}\) An express claim directly states the representation at issue and the representation itself establishes the meaning of the ad claim.\(^\text{169}\) However, the FTC can look beyond the express claim in determining what claim

\(^{164}\) Id.
\(^{166}\) See FTC Policy Statement on Deception, supra note 163.
\(^{167}\) Id.
\(^{169}\) Id. at 24.
or claims an ad communicates to reasonable consumers. The agency also looks at the interaction between and among the constituent elements of the ad to determine the “net impression” that is conveyed by the ad as a whole. The agency may rely on the ad itself and need not resort to extrinsic evidence if the text or depictions are clear enough that the agency can conclude with confidence that the claim is conveyed to reasonable consumers. The agency can also look to extrinsic evidence to determine the impact of an advertisement including common usage of terms, expert opinion as to how an advertisement might reasonably be interpreted, generally accepted principles of consumer behavior, surveys, or any other reliable evidence of consumer interpretation.

Manufacturers must have substantiation for objective product claims they make in advertisements. Under FTC law, making objective claims without a reasonable basis is a deceptive practice, and advertising claims made for a food, dietary supplement, drug, cosmetic or service without a reasonable basis for the claim constitutes false advertising.

Determining the level of substantiation required to establish a reasonable basis for a claim is a complicated process requiring consideration of a number of relevant factors, including:

- the type of claim (health or safety claim)
- the type of product
- the consequences of a false claim

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170 Id. at 24. Such claims are referred to as “implied claims” which are defined in the guide as “any claims that are not express and range on a continuum from language virtually synonymous with an express claim to language that literally says one thing but strongly suggests something else to language that relatively few consumers would interpret as making the claim.”

171 Id. at 25.

172 Id.


175 Id.
• the benefits of a truthful claim
• the cost of developing substantiation for the claim
• the amount of substantiation experts in the field believe is reasonable.\textsuperscript{176}

These principles apply to foods, dietary supplements, and drugs and claims that would be considered by the FDA to be structure/function, health claims, qualified health claims or drug claims. For all of these health-related claims, the FTC requires substantiation by competent and reliable scientific evidence that is sufficient to satisfy the relevant scientific community that the claim is true.\textsuperscript{177} The evidence can consist of “tests, analyses, research, or studies that have been conducted and evaluated in an objective manner by qualified persons and are generally accepted in the profession to yield accurate and reliable results.”\textsuperscript{178} The supporting evidence must be sufficient in quality and quantity, when considered in light of the entire body of relevant and reliable scientific evidence to substantiate that the representation is true.\textsuperscript{179} It appears from recent FTC enforcement activity that, for claims that the FTC considers therapeutic (claims that a drug, food, or dietary supplement will treat, cure, or mitigate a health-related problem) at least two randomized clinical trials are required to meet this standard.\textsuperscript{180} For claims that relate to prevention or reduction of risk of a health-related problem, the FTC has allowed evidence other

\textsuperscript{176} Id.
\textsuperscript{179} See Cleland Power point presentation \textit{supra} note 173.
\textsuperscript{180} Note that structure/function claims are not considered therapeutic claims by the FTC but rather fall into the category of health-related claims that require substantiation by competent and reliable scientific evidence that is sufficient to satisfy the relevant scientific community that the claim is true. See Dietary Supplements: An Advertising Guide for Industry, \textit{supra} note 178.
than randomized clinical trials to support such a claim, depending on the claim and the level of substantiation that experts in the field would generally require for such a claim.¹⁸¹

As noted earlier, both the FTC and FDA have a role in regulating health product claims and labeling. Although the FTC gives “great deference to an FDA determination of whether there is adequate support for a health claim,”¹⁸² as stated in FTC guidance on the issue, the FTC and the FDA will generally arrive at the same conclusion when evaluating unqualified health claims.¹⁸³ Nonetheless, the FTC’s Enforcement Policy Statement on Food Advertising notes that there may be certain limited instances when a carefully qualified health claim in advertising may be permissible under FTC law, in circumstances where it has not been authorized for labeling by the FDA.¹⁸⁴

Manufacturers have sometimes run into trouble with FTC regulators for using studies that the FTC considers inadequate to support the claim at issue because the study related to a different product, different dosage, different target population, or inappropriate endpoint for the claim.¹⁸⁵

ii. Background – International Models for Regulation of Non-drug claims for Probiotics

In order to have the broadest possible perspective on the most effective way to regulate probiotics, the Co-Investigators and the Working Group examined probiotic regulation in other nations and regions, particularly with regard to product claims. Below are brief descriptions of the other probiotic regulatory frameworks that we studied as part of this project.

Canada

¹⁸¹ See Randal Shaheen & Amy Ralph Mudge, Has the FTC Changed the Game on Advertising Substantiation?, ANTITRUST, Fall 2010, at 65 (quoting Novartis Corp., 127 F.T.C. 580, 725 (1999)).
¹⁸³ Id.
¹⁸⁵ See Cleland Power point presentation supra note 173.
Canada has taken a proactive role in regulating probiotic products. Probiotic product classes in Canada do not correspond exactly with those in the United States. Probiotic foods in Canada are typically restricted to products where dose is not really a concern (e.g., yogurt, drinks, etc.). The Canadian probiotic monograph covers “natural health products,” most of which would be regulated in the United States as dietary supplements.186 Daniel Buijs, a regulator with the Natural Health Products Directorate of Health Canada and a member of the Working Group, provided detailed information about Health Canada’s probiotics monograph. The monograph was written based on the FAO/WHO 2006 Guidelines187 and a targeted review of the scientific literature. Under the Canadian probiotics monograph, all probiotic natural health products are subject to pre-market assessment and licensing which requires the manufacturer to provide evidence of safety and efficacy under the product’s recommended conditions of use. If a product complies with the monograph requirements, it is eligible for expedited review of its marketing application. The Canadian probiotics monograph allows four specific claims for four specific strains of live microorganisms and limited generalized claims for combinations of strains that meet all additional requirements. (See Table 2 below). 188

The monograph allows additional claims not specified in the monograph, but a manufacturer wishing to use such claims must provide additional evidence to Health Canada to support the product’s safety and efficacy. To market a product under the monograph, manufacturers must attest to strain-specific evidence regarding identity, safety and efficacy. The monograph also requires that label quantity must be present at the product’s expiration date. As of January 31, 2011, Health Canada had received approximately 53,000 applications for pre-market approval of natural health products. Specific to probiotics, at that date, 315 probiotic products had been

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licensed through the monograph process, 24 probiotic products had been licensed outside of the monograph process, and 290 probiotic submissions were in queue.

Since it was developed, the Canadian probiotics monograph has received and responded to feedback from manufacturers, consumers and scientists. In terms of scientific challenges, Health Canada noted the following concerns:

- Challenges with regard to lactic acid bacteria taxonomy.
- Exclusion of transferrable antibiotic resistance.
- Scientific basis for extrapolation from strain to species.
- Validated biomarkers/surrogate endpoints for gut health/immunity.
- Validated methods for quality assurance—despite significant scientific progress, data gaps remain.\(^{190}\)

To deal with these concerns, Health Canada created interim solutions to allow market access for products with a recognized history of safe use and long term goals that will require additional research and/or policy to resolve. In June 2013, in an email to the Investigators, a representative of Health Canada noted that comprehensive revisions would likely be made to the probiotics monograph “within the next year.”

**European Union**

In addition to Canada, another region that has addressed the regulation of probiotics directly is the European Union. The agency charged with regulation of probiotic foods and food supplements—the large majority of probiotics—is the European Food Safety Authority (EFSA). As a first step, EFSA developed a list of safe microbial cultures called the Qualified Presumption of Safety (QPS) list that was designed to be used for pre-market safety assessment of certain

biological agents—many of which are microbial cultures.\textsuperscript{191} Following publication of this list, EFSA set January 2010 as the deadline to scientifically assess claims which would then return to the European Commission either for rejection or final publication.\textsuperscript{192} In October of 2010, the agency posted its formal assessment of the merit of more than 800 health claims, including widely used assertions that probiotic products boost the immune system.\textsuperscript{193} The claims were submitted to EFSA by the food industry and member states. The panel rejected all the probiotic claims with the exception of a generic claim that yogurt cultures containing the microorganisms \textit{Lactobacillus delbrueckii}, \textit{Lactobacillus bulgaricus} and \textit{Lactobacillus Streptococcus} promote better lactose digestion.\textsuperscript{194} According to the panel, claims that various food additives could strengthen the body’s defenses, improve immune function and reduce gut problems were either so general as to be inadmissible or could not be shown to have the claimed effect. Many of the rejected claims had been on product packages for years. In a separate ruling, the panel examined a dossier of 12 studies submitted by Yakult for its proprietary strain of probiotic bacteria, \textit{Lactobacillus casei shirota}. It found that all were inadequate to support the company’s claim that its products maintained immune defenses against the common cold.

Danone, the European market leader in probiotic products, withdrew from the EFSA process its claims that its products Actimel and Activia boosted the immune system and aided digestive health, after EFSA rejected similar claims made by other manufacturers. The company has since dropped most of its immune health claims from its advertising.

\textsuperscript{191} See text accompanying note 58; \textit{Qualified Presumption of Safety, supra} note 58.
\textsuperscript{194} However, in approving this claim in 2010, EFSA states in its ruling that research provided by the manufacturer that related to probiotic use of the bacterium was “non-pertinent” to the agency’s ruling. \textit{See Scientific Opinion on the Substantiation of Health Claims Related to Live Yoghurt Cultures and Improved Lactose Digestion (ID 1143, 2976), pursuant to Article 13(1) of Regulation (EC) No 1924/2006, 8 EFSA J. 1763 (2010, rev. Jan. 12, 2011), available at http://www.efsa.europa.eu/en/efsajournal/doc/1763.pdf.}
In 2012, EFSA rejected 74 probiotic dossiers submitted to EFSA for reconsideration. EFSA’s rulings have been a serious blow to the food industry, which has invested heavily in probiotics. The industry has complained that EFSA is applying excessively rigorous scientific standards when assessing the new claims and has produced several letters and white papers asking for changes in how EFSA evaluates probiotic claims. Although EFSA has not approved any probiotic health claims to date, Switzerland’s Federal Office of Public Health granted Danone the right to place a health claim on an Activia yogurt package containing *B. animalis* CNCM-I_2494 that states “Activia contributes to digestive comfort by reducing transit time and bloating.” The claim is only allowed in the Swiss market.

**Japan**

Japan does not specifically regulate probiotics, but many probiotics fall into the Food for Specific Health Uses (FOSHU) category, which is a more closely regulated category than conventional foods. FOSHU products are foods that contain functional ingredients for which health claims must be approved. Unlike conventional foods, FOSHU products are specifically intended to be consumed for the maintenance and promotion of health. In order for a manufacturer to sell a food as FOSHU—and therefore be able to include the FOSHU label on a product—the Japanese Department of Health must first assess the safety of the food and its efficacy for its intended use.

To obtain FOSHU approval, a manufacturer must show:

- Effectiveness;
- Absence of any safety issues (via animal toxicity tests, confirmation of effects in the case of excess intake, etc.);

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- Use of nutritionally appropriate ingredients (e.g., no excessive use of salt);
- Guarantee of compatibility with product specifications by the time of consumption; and
- Established quality control methods, such as specifications of products and ingredients, processes, and methods of analysis.\(^{197}\)

In addition to standardized FOSHU for which standards and specifications are already established for foods based on scientific evidence, there are two other FOSHU categories—qualified FOSHU and reduction of disease risk FOSHU. Qualified FOSHU are food products with health functions which have not been substantiated to the same degree as standardized FOSHU. Reduction of disease risk FOSHU products are allowed to make reduction of risk claims when reduction of risk is clinically and nutritionally established in an ingredient.

FOSHU products that modify gastrointestinal conditions such as bifidobacteria and lactic acid bacteria are approved FOSHU products.

Australia

Australia regulates most health products through the Department of Health and Ageing’s Therapeutic Goods Administration. All drugs and products that would be considered dietary supplements in the United States are included in a register and contain a certification number on the label—either AUST R or AUST L. AUST R medicines are assessed for safety, quality and

effectiveness. They include all prescription medicines and many OTC products, such as those for pain relief, coughs and colds and antiseptic creams. AUST L medicines are much lower risk than self-medication products. They are used for minor health problems and are reviewed for safety and quality. They include sunscreens over SPF4 and many vitamin, mineral, herbal and homoeopathic products. Labels of AUST L products must include the product’s purpose on the label.

Australia has a registration system for these AUST L products (many of which would be considered dietary supplements in the United States) 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.

The Working Group also looked at other countries’ regulatory schemes but, with the exception of Canada’s probiotic monograph and Australia’s registration system, Working Group participants did 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, 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 to create an appropriate regulatory structure.

iii. FDA Regulation of Product and Labeling Claims: Issues of Concern

One major area of concern identified by the Working Group relates to what claims can be made about probiotic products and the substantiation required for each type of claim. This is particularly complicated in the area of probiotics because most probiotics appear in foods and dietary supplements and making health or disease claims for these products risks pushing them into the heavily regulated drug category. This is further complicated by the fact that approved health claims are not regarded by consumers as “better” than structure/function (S/F) claims. Thus, research into the health-promoting effects of probiotics may be stifled because there appears to be little return on investment for a food company to go through the costly and lengthy process to gain an approved health claim or even a qualified health claim. In fact, very few manufacturers have availed themselves of the process in place for approval of authorized and qualified health claims because of the amount of time and resources such a process takes and a lack of understanding of FDA’s guidance in this area.

Many Working Group members noted concerns about lack of clear FDA guidance relating to the S/F claim. S/F claims are currently used by a number of probiotic food and dietary supplement manufacturers because they require less evidence to substantiate than other types of claims and do not require preapproval by the FDA. However, when and how S/F claims can be made is very complicated and legally debatable. This confusion is in part a result of the way in which the claim was established. As noted earlier, the statutory definition of a drug in the FDCA includes an article intended to diagnose, cure, mitigate, treat or prevent disease. Also included in the FDCA definition is the concept that drugs are “articles (other than food) intended to affect the structure or any function of the body of man or other animals.” The phrase “other than a food” implicitly recognizes that a food or food ingredient can affect the structure or function of the body without thereby becoming a drug. This recognition is the basis for the S/F claim.

200 FDCA, sec. 201(g)(1) (codified at 21 U.S.C. § 321(g)).
Although the FDA has issued detailed regulations and guidance attempting to differentiate between S/F claims for foods and dietary supplements and drug claims that may not be made without prior FDA approval, the guidance has not always been helpful. It is often difficult to distinguish drug claims from S/F claims for dietary supplements and foods. Examples of the difficulty in discerning where a claim falls include the following:

<table>
<thead>
<tr>
<th>Structure Function Claim</th>
<th>Drug Claim</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Helps retain healthy cholesterol levels”</td>
<td>“Helps lower cholesterol levels”</td>
</tr>
<tr>
<td>“Promotes urinary tract health”</td>
<td>“Improves urine flow in men over 50”</td>
</tr>
</tbody>
</table>

Some industry representatives believe that it is increasingly difficult even to conduct research to make S/F claims due to the narrow range of acceptable endpoints for S/F claims. Under the definition of a drug in the FDCA, food labeling is permitted to include claims relating to the intended effect on the structure or function of the human body without classifying the product as a drug. Recognizing this, in DSHEA, Congress explicitly authorized claims for dietary supplements that “describe[] the role of a nutrient or dietary ingredient . . . to affect the structure or function in humans [and] characterize the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function.” In promulgating regulations under DSHEA, however, the FDA stated that an S/F claim will be considered a drug claim if it indirectly or impliedly relates to disease prevention or amelioration. Some have argued that in doing this, the FDA overreached its statutory authority under DSHEA. This is another area in which more clarity is required, especially given the fact that any prohibition on “implied” statements requires judgment calls that manufacturers may not be able or willing to make.

203 Dietary Supplement Health and Education Act of 1994 (DSHEA), FDCA Sec. 413(c), 21 U.S.C. § 350(b).
Scientists are also affected by the current regulatory framework for product claims. Many of the studies that have been conducted on probiotics were conducted using endpoints that would be viewed by the FDA to be disease endpoints. Probiotics in food are thought to be useful for, among other things, dietary management to reduce the risk of acute diseases (colds, flu, gastrointestinal infections); mitigation of symptoms in persons who are not fully healthy (irritable bowel syndrome); improvement of the therapeutic efficacy of a drug; and management of the side effects of a drug (such as the side effects of an antibiotic). However, the FDA would likely consider these to be disease claims and therefore consider the product creating these benefits to be drugs even if the probiotic has been on the market for years. This conundrum may inhibit research because studies evaluating the benefits of probiotics may require INDs and may not be useful to companies for substantiating claims on foods or supplements. Since many companies marketing probiotics are not interested in marketing a drug, research may not proceed, and research on the therapeutic benefits of probiotic foods and dietary supplements may be limited.

A complex area of the law that the Working Group discussed was the difference between a disease prevention claim and a risk reduction claim and how these claims may be handled differently by the FTC and FDA. The subtle difference between a disease prevention claim and a risk reduction claim is important because disease prevention claims are considered drug claims but risk reduction claims are permitted for foods and dietary supplements under the Nutrition Labeling and Education Act (NLEA) of 1990.

As the law stands now, a permissible health claim can suggest that a food reduces the risk of contracting a disease, but it becomes a drug claim if it suggests mitigation, cure or treatment of an existing disease. This distinction may allow food manufacturers to, in effect, make prevention claims but be subject to a lower standard of evidence than that imposed on drug manufacturers wishing to make prevention claims. Drug manufacturers must go through the IND process and through Phase I, II and III clinical trials and premarketing approval by the FDA. Food manufacturers wishing to make reduction of risk of disease claims or “health claims” must obtain prior approval from the FDA that is supported by “significant scientific agreement” or supported by a report of an authoritative body such as the National Academy of Sciences.
The Working Group also considered whether the medical foods category might be appropriate for certain probiotics and probiotic claims. However, the FDA advises in its guidance relating to medical foods that it considers the statutory definition of medical foods to narrowly constrain the types of products that fit within this category of food. FDA warning letters for purported medical foods have focused primarily on the absence of distinctive nutritional requirements for the disease or condition for which the product is marketed, as well as unlawful marketing practices and illegal drug claims. Given FDA’s narrow view of this category, without modification it is likely not a useful avenue for regulation of probiotics outside of those probiotics that currently fit into the regulations noted above. The “nutritional requirement” component of the statute is not well defined by the FDA, which indicates that the category may not be sufficiently flexible to incorporate a subset of probiotic products. Under the current language, a dietary need for probiotics would be required, and in many cases of probiotic use by individuals it is not clear if such a requirement is met. The original formulation of medical foods was the use of foods to help with a medical condition. Subsequently, the FDA added the “nutritional need” component, which makes the requirement less clear.

The Working Group also did not recommend making greater use of the Foods for Special Dietary Use category because, as it is currently used, it is a very narrow category that FDA has sought to narrow even further. As mentioned above, in an Advanced Notice of Proposed Rulemaking issued in 1996, FDA defined foods for special dietary use as “foods that are specially formulated to meet a special dietary need, such as a food allergy or difficulty in swallowing, but that provide nutrients intended to meet ordinary nutritional requirements.” Very few probiotics would fall into this restricted class of products, which is designed to support a narrow category of patients. Commentators have noted that FDA has not recently made use of this authority and has instead withdrawn regulations for some foods for special dietary use.

Different standards for claims and what claims mean is complicated for manufacturers but different types of claims also make it challenging for consumers to make educated choices at the supermarket. Several studies have noted that consumers have difficulty distinguishing among the many different types of claims on food labels and, further, cannot distinguish between
S/F claims and health claims. This difficulty is exacerbated by the fact that many S/F claims are based on small, preliminary unpublished studies or based on studies conducted on diseased populations rather than healthy individuals. Although the law requires claims to be truthful and based on sufficient evidence, inevitably some ambiguous or misleading claims reach the marketplace. Furthermore, many S/F claims are based on different formulations than what is actually in the product or on studies that look at biomarkers of unknown significance and often do not disclose that research shows the product does not work as claimed.

Dr. Ruth Farrell, an OB/GYN and bioethicist at the Cleveland Clinic, who is the Principal Investigator on another NIH-funded Human Microbiome Project grant, noted that even very knowledgeable consumers are confused by the various types of claims made about probiotics. Her research on patient attitudes to probiotic therapy indicates that medical patients are savvier than average consumers about probiotics but are still unsure about the meaning and import of various product claims. Although patients in search of some type of relief from a chronic illness may be more willing to accept a certain degree of risk in the hope of attaining a therapeutic benefit, they still find it difficult to make decisions under the current framework for claims.

In 2003, FDA’s Task Force on Consumer Health Information for Better Nutrition announced a process that was designed to help consumers assess the science behind product claims. The proposal would have allowed the FDA to give foods a “grade” of A (significant scientific agreement), B (evidence not conclusive), C (evidence is limited and not conclusive) or D (little scientific evidence supporting this claim). The proposal faced opposition from many sides, including the Center for Science in the Public Interest (CSPI) and the American Medical Association. These groups argued that the initiative bypassed labeling laws passed by Congress and would mislead consumers by allowing claims supported by questionable science. CSPI also opposed the initiative because the information it would have provided to consumers was similar to the information provided to consumers via qualified health claims.\footnote{204 See discussion of qualified health claims infra page 65.} CSPI believes that many consumers do not understand qualified health claims, and that even heavily qualified claims lead some people to think that a product has health benefits that it may not have.
While the FDA Task Force model did not gain acceptance, there is a somewhat similar nongovernmental grading framework for complementary and alternative medicines (including dietary supplements) called “Natural Standard.” Natural Standard is a research organization that supports an online database that provides evidence-based information about complementary and alternative medicines and gives grades to products that “reflect the level of available scientific data for or against the use of each therapy for a specific medical condition.” The grading system gives grades of “A” through “E” with “A” being “strong positive scientific evidence” and “E” being “strong negative scientific evidence” of effectiveness. The service, which was started by a pharmacist and a doctor, is not funded or supported by “any interest group, professional organization or product manufacturer” and charges a subscription fee for access to the database. This type of impartial, readily available online information might be a useful tool to provide consumers and health care providers with information about probiotics.

iv. FTC Regulation of Product and Labeling Claims: Issues of Concern

An area of concern noted by the Working Group in relation to FTC regulation of probiotics is the degree of substantiation required to make health-related claims. While the distinction between disease prevention and risk reduction claims has been largely settled in the context of FDA oversight of claims, the distinction between prevention and reduction of risk claims is less clear under the Federal Trade Commission Act. NLEA did not amend the FTC Act and therefore FTC does not make a distinction between reduction of risk of disease claims and prevention claims. Either claim must have a reasonable basis for substantiation, which as noted above on page 67, has typically been less than the evidence required for therapeutic claims. The FTC has stated in opinions that this requires objective tests and studies or other evidence considered valid by professionals with expertise in the relevant area, “using procedures generally accepted in the profession to yield accurate and reliable results.” The standard allows for much flexibility on the part of FTC and generally requires differing levels of evidence for different types of claims. According to FTC guidance, “[t]here is no fixed formula for the number or type

206 Id.
of studies required, sample size or study duration.” 207 Historically, FTC considered the costs and benefits of efforts at substantiating claims, e.g., clinical trials and other human studies. The agency frequently defers to experts for their opinion.

While the gold standard is the double blind RCT, the FTC has not historically followed the FDA’s approach to regulation of health claims.208 However, that practice may be changing. In an action instigated by FTC against Nestlé Healthcare Nutrition (HCN) in 2010, the FTC alleged that Nestlé HCN made false claims in television, magazine, and print ads about its probiotic product BOOST Kid Essentials when the company claimed that the product prevents “upper respiratory tract infections in children, protects against colds and flu by strengthening the immune system, and reduces absences from daycare or school due to illness.”209 These statements, according to FTC, went beyond simply claiming increased immunity to claiming that the product would prevent children from getting sick—a stronger claim that lacked substantiation.

Nestlé HCN and the FTC settled the case by agreeing to a consent order that was signed in 2010.210 The consent order prohibited Nestlé HCN from making claims that a product prevents or reduces the risk of upper respiratory tract infections “unless the FDA has issued a regulation authorizing the claim based on a finding that there is significant scientific agreement among experts qualified by scientific training and experience to evaluate such claims, considering the totality of publicly available scientific evidence.”211 (This language is based on regulations promulgated by the FDA under the NLEA.) The FTC considers this “significant scientific agreement” standard to be what “experts in the field of diet-disease relationships would

208 *See* Randal Shaheen & Amy Ralph Mudge, *Has the FTC Changed the Game on Advertising Substantiation?*, 25 ANTITRUST 65 (2010).
211 *Id.*
consider reasonable substantiation for an unqualified health claim.”212 In the Nestlé HCN settlement, the FTC required the company to obtain FDA pre-approval before it could make a URTI risk-reduction claim for its products because this would “facilitate compliance with the order” by demonstrating adherence to the “significant scientific agreement” standard.213 At least one commenter on this aspect of the consent order characterized it as an “unusual element of the settlement” and setting an “unusually high standard” for making claims.214

As to Nestlé HCN’s claims that BOOST reduces children’s absences from daycare and school due to illness, the FTC determined that “competent and reliable scientific evidence” means

at least two adequate and well-controlled human clinical studies of the product, or of an essentially equivalent product, conducted by different researchers, independently of each other, that conform to acceptable designs and protocols and whose results, when considered in light of the entire body of relevant and reliable scientific evidence are sufficient to substantiate that the representation is true.215

In further action, in 2010, FTC agreed to a settlement with the Dannon Company, Inc. in response to an FTC complaint that charged the company with deceptive advertising in relation to allegedly exaggerated health benefits of its Activia yogurt and DanActive dairy drink. According to the FTC’s complaint, Dannon claimed in nationwide advertising campaigns that DanActive helps prevent colds and flu, and that one daily serving of Activia relieves temporary irregularity and helps with “slow intestinal transit time” without sufficient evidence to back these claims.

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Dannon agreed not to make such claims on its Activia yogurt and DanActive dairy drink products. 216

These were FTC’s first probiotics claims cases and how the agency dealt with them is significant. These two cases make clear that manufacturers are correct to tread with caution into the area of probiotic claims and that clear guidance is required with regard to appropriate substantiation for health-related claims.

v. Product Claim and Labeling Recommendations

a. Labeling and Safe Use Recommendations

A number of Working Group members made the following recommendations regarding labeling of probiotic products:

- A probiotic product should be labeled with the names of the genus, species, and strain of all the probiotic microorganisms in it, as recommended by the International Scientific Association for Probiotics and Prebiotics.
- DSHEA requires dietary supplement manufacturers to have substantiation of label claims and to notify the FDA within 30 days after first marketing a product with a statement of nutritional support that such a statement is being made. In practice, the FDA has not requested this substantiation. The FDA should do so for both probiotic supplements and

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216 See Decision and Order, In the Matter of The Dannon Company, Inc., a corporation (2/4/11) available at https://www.ftc.gov/enforcement/cases-proceedings/0823158/dannon-company-inc. Prior to action by the FTC in this case, in 2009, the Dannon Co. settled a false advertising lawsuit and agreed to set up a $35-million fund to reimburse consumers who bought its Activia and DanActive yogurts. The class action lawsuit was filed in January 2008 and alleged that Dannon made misrepresentations when marketing its Activia and DanActive yogurts by claiming health benefits that did not exist. As part of the settlement, the company, although admitting no wrongdoing, agreed to make changes to the labeling and advertising of Activia and DanActive. DanActive labels that said the yogurt has “a positive effect on your digestive tract’s immune system” were reworded to say the yogurt will “interact with your digestive tract’s immune system.” Nathan Olivarez-Giles, Dannon Settles False Advertising Lawsuit over Activia, DanActive Yogurt, L.A. TIMES, Sept. 19, 2009, http://articles.latimes.com/2009/sep/19/business/la-fi-yogurt-settlement19.
probiotic foods and require companies to make this substantiation readily available, for example on company websites, so that consumers and healthcare professionals can see for themselves the basis of the product claims.\(^{217}\)

- Manufacturers of probiotic products should be required to specify the number of live microbes of each strain that the products deliver through the end of their shelf life, and these numbers should reflect the efficacious doses used in the trials that form the basis for any claims of health benefits.

- The FDA should adopt the voluntary guidelines developed by the Consumer Health Products Association for minimal information that should appear on the label of dietary supplements containing probiotics to assure safe use.\(^{218}\) These guidelines recommend the inclusion of the following information:

  o Colony Forming Units (CFU) count or other appropriate measure of live bacteria at the time of expiration (guaranteed minimum) of the product.
  o Storage conditions: Specific directions about the conditions under which the probiotic-containing product must be maintained in order to ensure viability and potency. (Storage conditions can vary depending on strain, temperature, humidity, and other factors. Storage conditions should be based on stability testing under various conditions. Each manufacturer should establish adequate storage directions based upon product-specific stability and/or test data.)
  o Lot number or production code on the point of purchase container for every package and as appropriate, on the immediate container.
  o A clear identification of the probiotic bacteria including the strain (unless there is scientific substantiation that the claimed health benefits are not strain specific) based on widely accepted nomenclature. If a trademarked name is used to identify the bacteria, the actual genus, species, and strain should also be

\(^{217}\) See essay submitted by Working Group Member David Schardt (on file with the investigators).
\(^{218}\) See essay submitted by Working Group Members June Austin and Nora L. Zorich (on file with the investigators).
included on the label. (This information gives consumers the knowledge and opportunity to research the strains.)

- Contact information for the manufacturer including an address or a telephone number that consumers can call if they have any questions or concerns. For products that do not have adequate space on the label, a company should list a website where the consumer can obtain contact information.

- Directions for suggested usage.

b. **Modified Private Right of Action**

Because under-regulation is primarily associated with limited enforcement resources available to the FDA and the FTC, a recommendation that gained traction among several Working Group members was a modified private right of action under the FDCA and/or the Federal Trade Commission Act.

As background, a private right of action is a statutorily created right of a private individual to sue a private actor (e.g., a business) for engaging in certain unlawful activities typically enforced by federal or state agencies, e.g., deceptive practices, unfair practices, misrepresentation, or failure to disclose material facts. While no federal-level private right of action exists for these types of consumer law violations,²¹⁹ most states have what are colloquially referred to as “mini-FTC” statutes or UDAP (Unfair or Deceptive Acts or Practices) laws.²²⁰ These laws vary from state to state but generally most state UDAP statutes provide Attorneys General with a broad variety of powerful remedies, including preliminary and permanent injunctive relief, restitution, civil penalties, attorney’s fees, and even the power to have a receiver appointed under certain circumstances.²²¹ UDAP statutes also are being used with increasing

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²²¹ *Id.*
frequency by private litigants pursuing class action relief for alleged unfair and deceptive business practices.\(^{222}\) This trend is based on the recognition in some jurisdictions that it is difficult to establish class action suits under traditional fraud laws. In these jurisdictions, there has been a trend towards “liberalizing the requirements for class litigation and recovery on UDAP claims.”\(^{223}\) According to a 2009 report by the National Consumer Law Center,

UDAP statutes are primarily civil statutes. Some allow criminal penalties for extreme violations, but almost all enforcement is through the civil courts. The typical UDAP statute allows a state enforcement agency, usually the Attorney General, to obtain an order prohibiting a seller from engaging in a particular unfair or deceptive practice. The Attorney General can also ask the court to impose civil penalties of a certain dollar amount for violations and to order the seller to return consumers’ payments. The typical statute also allows consumers to seek similar remedies—return of payments or compensation for other consumer loss (often with some sort of enhancement to account for intangible or hard-to-document losses), sometimes an injunction against repetition of the fraudulent practices, and, in most states, reimbursement for attorneys’ fees.\(^{224}\)

The study went on to note,

[b]efore the adoption of state UDAP statutes in the 1970s and 1980s, neither consumers nor state agencies had effective tools against fraud and abuse in the consumer marketplace. This was so, even though the Federal Trade Commission Act had prohibited unfair or deceptive acts or practices since 1938. In most states, there was no state agency with a mandate to root out consumer fraud and abuse, much less tools to pursue fraud artists.

Consumers had even fewer tools at their disposal. A consumer who was defrauded often found that fine print in the contract immunized the seller or creditor. Consumers could fall back only on claims such as common law fraud,


\(^{224}\) See Carter, Consumer Protection in the States, \textit{supra} note 220.
which requires rigorous and often insurmountable proof of numerous elements, including the seller’s state of mind. Even if a consumer could mount a claim, and even if the consumer won, few states had any provisions for reimbursing the consumer for attorney fees. As a result, even a consumer who won a case against a fraudulent seller or creditor was rarely made whole. Without the possibility of reimbursement from the seller, consumers could not even find an attorney in many cases. UDAP statutes were passed in recognition of these deficiencies. 225

However, according to the 2009 report,

. . . the effectiveness of UDAP laws varies widely from state to state. The holes are glaring. Legislation or court decisions in dozens of states have narrowed the scope of UDAP laws or granted sweeping exemptions to entire industries. Other states have placed substantial legal obstacles in the path of officials charged with UDAP enforcement, or imposed ceilings as low as $1,000 on civil penalties. And several states have stacked the financial deck against consumers who go to court to enforce the law themselves. 226

Many members of the Working Group agreed that a national law that created incentives for plaintiffs and lawyers to take smaller cases and/or go after smaller companies would be a useful regulatory tool, but they also agreed that such a tool would need appropriate checks and balances to discourage frivolous lawsuits, such as a provision that permitted the FTC and FDA to intervene and/or dismiss a case with prejudice under certain circumstances and creation of national standards for safety/effectiveness as a template for a case against a company to set forth what evidence would support a successful claim. Professor Jack Schwartz, one of the project co-investigators, has developed a concept for a private right of action that could be designed to increase policing of insufficiently substantiated structure/function or qualified health claims and yet reduce the downside risks of frivolous lawsuits or plaintiffs solely going after deep pockets. Under his suggestion, the private right of action would:

- enforce the FTC Act with equitable and compensatory damages remedies plus fee-shifting;
- be limited to State AG’s and tax-exempt organizations, so as to eliminate the specter of plaintiff lawyers bringing shakedown suits;

226 Id. at 3.
be available only for advertising to consumers of products under the jurisdiction of the FDA;
be subject to dismissal if the challenged advertising claim is substantially similar to a labeling claim specifically approved by the FDA; and
be subject to notice to the FTC and the FTC’s right to take over the suit, comparable to the procedure in a False Claims Act qui tam action.

A private right of action is not a cure-all for under-enforcement, and it may be politically unpalatable to create a targeted legal remedy for a single product category especially when existing state law, such as state UDAP laws and tort claims for fraud, might be sufficient to cover many unsubstantiated claims and misbranding cases. Furthermore, because most UDAP cases are removed to federal court, although cases are brought at the state level, settlements tend to be national in scope without a specific federal law. A further concern of critics is that a private right of action might have a chilling effect on innovation and would have limited effect on unscrupulous small companies that market products with little concern about either adequate substantiation for their claims or the risk of litigation.

c. **Probiotics Monograph**

Another concept suggested by Working Group members to streamline the number of claims that a manufacturer can make and provide for a more efficient oversight process of claims was a probiotics monograph. Generally, a monograph is a kind of “recipe book” that covers acceptable ingredients, doses, formulations, and labeling for the product covered by the monograph. Monographs are updated to add additional ingredients and allowable claims as needed. This idea came from our neighbors in Canada, who are using the monograph system to regulate certain probiotics on the Canadian market, as well as from FDA’s monograph for over-the-counter drugs under which products such as some sunscreens, laxatives, cough-cold and other products can be sold and marketed without premarket approval.

Working Group member and law professor James O’Reilly (Cincinnati College of Law) provided the Working Group with a concrete recommendation for using the FDA’s existing OTC drug monograph structure for probiotics. His proposal would be based on the concept that
probiotics are a functional class of products that are generally recognized as safe and effective for a similar particular benefit. Similar to current OTC monographs, a probiotics monograph would include the following components:

- a list of active ingredients necessary to achieve a specified benefit;
- levels of active ingredients necessary to achieve the benefit;
- product claims the FDA determines fairly communicate that benefit;
- mandatory warnings for this type of product;
- purity standards for actives;
- a listing of permissible excipient and/or inactive ingredients; and
- methods and standards of testing.

No probiotic products are currently approved under a monograph. In terms of monograph advisory committees, the FDA could use an existing one or create a new one. This would be relatively easy because it would involve amending an existing regulation.

Under Professor O’Reilly’s proposal, the essential elements of a probiotics monograph in the United States would be:

1. type and dose of live organism
2. manufacturing and packaging conditions
3. inactive ingredients
4. claims of benefit allowed, with levels of technical claim support data
5. warnings required
6. a standard statement that a marketer can vary from the monograph’s approved conditions by filing and receiving approval of a new drug application.

Professor O’Reilly suggested the following benefits to using the OTC drug monograph as an approach for regulating probiotics:

- An advisory committee process is already in place and chartered at the FDA for this type of process;
• A non-complying product is free to “opt out” and file a new drug application for a parallel approval;
• The monograph mechanism has been in place for 40 years at the FDA and is a well-established mechanism for drafting, review and finalization of certain products;
• An existing office within the FDA’s Center for Drug Evaluation & Research already handles monograph questions;
• The process would not require new offices, new regulatory models or pathways for probiotics;
• Monographs have generated a well-understood set of claims accepted by the FTC and useful in private enforcement claims;
• Monographs can preempt state labeling laws once the federal OTC drug rule is effective;
• The process is open and familiar to industry and NGOs. The FDA would gather submissions (including scientific input and industry views) leading to a final enforceable rule;
• Probiotic clinical trials would not necessarily require an IND if the study is confirmatory to meet an OTC monograph;
• A monograph would create a strong basis for active ingredient characterization and for use of specifications or production controls on key ingredients;
• A monograph would likely meet with success in court challenges because of the history of successfully overcoming past criticisms of the OTC drug monographs. Products already labeled as probiotics prior to the monograph would be subject to approval by the advisory committee, which could issue a temporary monograph for new products with the possibility of requiring new information.

A probiotics monograph could be a useful vehicle for regulating some probiotics. Arguments in favor of using a monograph include:

• A monograph would provide assurance to the FDA and FTC that a product approved under the monograph has met a certain standard and the FTC would likely defer to it.
• The process could be used as an avenue to assure safety.
• If user fees were an option for companies seeking approval under the monograph, the fees could be used to enhance FDA enforcement efforts.

• If a product is within the monograph, it does not require an IND or IRB approval.

• Statutory change may not be required to create a probiotic monograph.

• A monograph would address foods that want to make drug-like claims, by indicating which claims could be made about which ingredients.

• A monograph would be a useful resource for the field by setting standards from which the science can develop, especially in terms of properly designed clinical trials. For example, the monograph could capture good IND criteria and establish them as standards for the field.

• A monograph could also address characterization issues specific to probiotics.

• The monograph could be used to approve various kinds of claims. Disease prevention claims are currently allowed under the OTC monograph.

• The current rules relating to monographs allow for the inclusion of combination products which would be useful in the case of probiotics.

• Although not currently done, a product approved under the monograph could carry a seal or statement that it was approved under the monograph.

Despite these advantages, there are several reasons why a probiotics monograph is not a catch-all solution for all probiotic products. The main concern is that the FDA OTC monograph process is for drug products. If products that have been considered dietary supplements or foods were made part of the OTC monograph, this would place the supplement into the drug category. This is something that researchers and manufacturers would resist although they could remain in the food or dietary supplement category if they did not wish to make these generic drug claims or other drug claims. However, others noted that the FDA could create a probiotics monograph outside the current OTC drug monograph framework as Canada has done. Such a monograph would not force products into the OTC drug category. Further, many view the monograph process as rigid and stagnant and not designed to constantly reevaluate new ingredients or create new monographs. The monograph system is based on the concept of a product as stable and
unchanging over time, which may be different from probiotics that are dynamic and able to replicate.

In terms of process, before creating a monograph for probiotics, the FDA would have to decide the focus of the monograph—for example, the probiotic strain; a bodily function (i.e., gut health, vaginal health, skin health, etc.); specific product types (e.g., skin creams); or a class of products (e.g., health promotion products). Ideally a monograph would be created with a focus that was sufficiently flexible to incorporate new products or strains as they were developed.

An organization outside of the FDA could develop and oversee the monograph as is done in the case of homeopathy. Although there are important dissimilarities between homeopathic remedies and probiotics and some concerns were raised about the homeopathic model, the homeopathic monograph is an example of a monograph managed outside of the FDA and based on non-clinical studies.

d. Probiotic Categorization Framework

Dr. Gregor Reid, a probiotic researcher at Western University in Canada, proposed a framework for categorizing microorganisms in consumer and clinical products (including foods and drugs) into levels depending on the degree of safety, efficacy, and characterization of the microorganism. Although no consensus was reached by Working Group members regarding categorizing probiotics as Dr. Reid suggests, many 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 scientific evidence is available about a specific strain or product. Working Group members also noted that dividing probiotics into categories might be useful in determining when an IND is required, which center at the FDA should review a product, and what claims can be made about a product.

Under Dr. Reid’s proposal, the absolute necessity for all probiotics would be: (a) a requirement of strain(s) designation and speciation by acceptable molecular methodology preferably whole genome sequencing, (b) proof of safety through experimentation or long history of use in humans, (c) a minimal end-of-shelf life viable count that is suitable to confer a health benefit, (d) production by good manufacturing practices, (e) a clear description of how to use the product to acquire the stated health benefit (for example how many yogurts or slices of cheese are needed), (f) where the consumer can find scientific and/or clinical documentation on the product, preferably, or at least on the strain(s), (g) how to handle and store the product, and (h) a contact number or web site to report suspected adverse events. Such requirements would rule out many currently marketed products. Dr. Reid’s proposed categories distinguish between live microorganisms on the basis of evidence of safety and efficacy. A summary of his proposal was published in *Nature*\textsuperscript{228} in 2012 and the categories range from least regulated (level 1) to most regulated (level 3).

**Level 1** includes products that have basic functional activity that is relatively easy to measure, affordable to perform and result in effects that can benefit the host, even though not all result in a feeling of restored health. This level would require human testing in an appropriate sample, perhaps around 100 subjects. Regular yogurt would meet this category, as by definition it contains live *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* and lactose intolerant individuals can consume it without adverse effects. An example of a health claim in this category would be: *This probiotic product has been shown in humans to potentially benefit your health.*

**Level 2.** Products in Level 2 would have been tested in two or more randomized controlled studies that have been published in peer-reviewed journals; preferably including data that provides a rationale for probiotic effects. While Category 1 products such as yogurt might also have undergone at least two clinical studies, the extent of benefit provided would be at a lower level than products in Level 2. Thus, a probiotic yogurt that would improve intestinal transit time, or reduce bloating and pain as well as products that might help achieve clinically

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relevant maintenance of remission of pouchitis, prevent or reduce adverse events induced by an antibiotic or other drug, or prevent or reduce the duration of the common cold or flu, might be included in Level 2. An example of a health claim in this category would be: *This product may reduce the incidence of vaginal malodor.*

**Level 3.** Products in Level 3 would be supported by a higher level of evidence of efficacy, more stringent regulatory assessment, or have been studied in more vulnerable consumer populations such as the young or elderly, or others targeted because of their lifestyle, than products in Level 2. They might include recombinant strains of large numbers (e.g., 15-40 strains) designed to simulate a healthy target niche for application to individuals with severe or chronic conditions not resolved by standard pharmaceutical or surgical interventions. An example of a health claim in this category would be: *This probiotic helps reduce the risk of necrotizing enterocolitis in newborns.*

e. **Seal of Approval**

Another potential avenue to address under-regulation of claims is a seal of approval for probiotics. Seals of approval are relatively common in the consumer market, primarily used by trade organizations and coalitions, to indicate that a product has met a certain level of safety, quality and/or efficacy. A seal of approval might be a useful way for the probiotic industry to come together to establish quality standards and weed out manufacturers who cannot meet those standards. It would also provide a tool for consumers to make more educated purchasing decisions. In terms of models for a seal of approval, the organic food certification framework merits consideration.\(^{229}\)

While the seal of approval concept has merit, in practice it has met with challenges because of high-profile cases in which seals have been more geared to entice consumers and increase profits rather than ensure quality. For instance, in 2010, the Better Business Bureau—a historic leader in the concept of neutral determinations of quality and service—was criticized for

giving businesses better grades if they became dues-paying members.\(^{230}\) In another case, the American Cancer Society accepted $1 million from SmithKline Beecham in exchange for permission to use the American Cancer Society’s name and logo to promote the sale of nicotine patches and gum.\(^{231}\) These missteps likely have caused many consumers to lose faith in seals and the entities providing the seals. Another criticism of the seal of approval concept is that it harms smaller companies that cannot afford the fee for the seal, if a fee is required. Finally, a seal will not be meaningful unless embraced by the entire industry. USP tried a certification for dietary supplements which was not effective because it was not picked up across the industry. Notwithstanding these concerns, if done with integrity and neutrality, a seal of approval might be a useful vehicle to provide assurances of quality for certain probiotics.

An alternative to an industry-initiated seal of approval would be for the FDA to authorize an agency or organization to assign privileged use of the term “probiotic” on a label to products meeting certain standards. Although it is unclear whether the FDA has the ability to do this without additional statutory authority, this authorization could provide a financial incentive for companies to do research, because it would grant a degree of exclusivity to companies with adequate substantiation. A standard for calling a product “probiotic” might be an effective regulatory tool because it does not require the consumer to conduct research—the agency/organization granting the privilege to use the term “probiotic” will have done the research or reviewed the research conducted by the industry.

f. Surgeon General Label and Probiotics Website

Another suggestion raised by the Working Group to address under-regulation of product claims was to create a “Surgeon General-type” label for probiotic products similar to the nutrition facts panel that would direct the consumer to a website with links to publicly available


studies about the product. The label could note that the product has not been reviewed for effectiveness by the FDA. The website could also link to data from an organization like NIH or CDC about genus/species categories for probiotics and/or include a list of published studies about the product. For more information, the consumer could be referred to the company actually sponsoring the product.


g. Medical Foods

The Working Group also considered whether the existing medical foods category would be an appropriate vehicle—if clarified and expanded—to regulate certain probiotics. One Working Group member suggested that Congress or the FDA clarify that the statutory definition of “medical food” expressly includes foods containing probiotics. Medical foods can play a critical role in “managing” existing disease conditions—and can bear claims to that effect (assuming such claims are substantiated) without being classified as drugs or biological products. Clarification along these lines could help ensure that probiotics can be investigated (without resort to the IND process) for their role in “managing” a disease condition that is, for example, directly related to gut health or immunity. The clarification seems advisable in order to avoid a narrow interpretation of the “distinctive nutritional requirements” wording of the current statutory and regulatory definitions of medical food.232

h. Registration of Certain Probiotic Products

Another concept that gained traction among some Working Group members was that of a registration system for certain probiotic products. Countries such as Australia 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 the marketing and sale of a product so that they can monitor the product. 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

232 See essay submitted by Working Group Member Fred Degnan (on file with the investigators).
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 (GMPs), labeling, transportation, and storage.

i. Distinction between Structure/Function and Drug Claims

The distinction between structure/function claims and drug claims remains murky, as illustrated by the examples in the table on page 77. Additional guidance in this area would be helpful to manufacturers and researchers. In some cases, it appears to be a matter of specificity about the condition or disease to be treated. In other cases, it appears to be an issue about whether something to be “treated” is a “normal condition,” e.g., insulin resistance, occasional constipation; or a disease, e.g., diabetes, chronic constipation. The line between what constitutes a “normal condition” and a disease is also not a clear one and our concepts of what is normal or healthy and what is unhealthy can change over time. This has actually been an issue raised about the Human Microbiome Project and its effort to determine if humans have a “core” microbiome. The researchers sought “healthy” volunteers for the study excluding many individuals with certain conditions who might be considered healthy or normal if one looks at the percentage of individuals in the population with those conditions, e.g., gum disease and obesity. Thus, one could argue that the “healthy” volunteers were actually “super healthy” and rare individuals among the broader population. This issue presents a challenge to both regulators and scientists.

j. Clarification of the Substantiation Requirements for Qualified Health Claims and Claims Regulated by FTC

For health-related claims, FTC requires adequate substantiation to establish a reasonable basis for a manufacturer’s claim. However, as evidenced by the Dannon and Nestlé HCN settlements (discussed on pages 81-83) manufacturers find it difficult to know what constitutes

233 See Relman, supra note 2.
adequate substantiation and, in the case of probiotics, whether FTC’s substantiation rules will apply to their claim. Clarification regarding what constitutes sufficient substantiation for product claims by FTC via the courts or the FTC would be useful.

It would also be useful for the FDA to codify the current rubric for the discretion-based enforcement of qualified health claims used by the FDA and, in the process, provide a mechanism for qualified health claims to be based not only upon FDA review but also upon statements from authoritative public health bodies. Doing so would allow use of an “authoritative body” to substantiate a qualified health claim as is allowed for health claims. This amendment would help encourage research with respect to the role of probiotics as a part of the diet of healthy people and in reducing the risk of various chronic diseases and health conditions. It would also reward such research with the possibility of avoiding FDA review of a proposed qualified health claim should an authoritative body agree that supportive but non-conclusive research exists for the relationship between consumption of a probiotic and reducing the risk of a given disease.234

Conclusion

In establishing a regulatory framework for probiotics in the United States and other countries, policy makers should be guided by certain foundational principles. These include proportionality to risk, universal quality guidelines, and flexibility.235

Regulatory burden should be proportional to risk. This principle is already reflected in both Canada and the United States in the distinction between food and drugs. In the context of probiotic products, the fact that products identified as “probiotic” can have very different risk profiles that are affected not just by the intrinsic risk of the strain itself, but also by the intended application, needs to be recognized and communicated to regulators, researchers, industry, and most importantly, to consumers. Minimally, there should be a meaningful distinction in the

234 See essay submitted by Working Group Member Fred Degnan (on file with the investigators).
235 See essay submitted by Working Group Member Daniel Buijs (on file with the investigators). The description of these principles is taken in large part from his essay.
descriptive language and regulatory requirements for products that are intended to treat, prevent or cure diagnosable health conditions from those products that are intended to modify structure or organic function in a way that is non-specific or for which the long-term health benefits are less certain. The use of the word “probiotic” to describe these types of products should be further qualified in some way (i.e., general probiotic vs. clinical probiotic), and the qualifications clearly defined and enforced. Because the intended application needs to be considered during risk classification, there should be a mechanism for a strain to be regulated simultaneously at different risk levels for different applications. There should be a mechanism through which consumers can optionally obtain more information on the underlying evidence supporting a particular product without regulatory intervention.

A significant determinant of the risk of probiotic products, including the risk of failed efficacy, is quality control during manufacturing. This risk is not always easy to assess by researchers, regulators or consumers. The manufacture of probiotic products that are pure and sufficiently stable for retail distribution is technically challenging. Both Canada and the United States have pre-market approval systems that are appropriate for assessing the quality control systems of the highest risk products, biologics and live biotherapeutics, respectively. However, this level of rigorous pre-market review is not appropriate or sustainable for lower-risk products. An adequate level of control and enforcement could be achieved for lower-risk products at the expense of flexibility of implementation through the publication of universal quality standards.

The last and most important principle that should be considered in the regulation of probiotics is flexibility. The science and technology surrounding these products are progressing rapidly. In addition to being able to simultaneously accommodate products of different risk profiles, the regulatory framework for probiotics should take into account the eventuality that the level of scientific certainty associated with these products, and the methods used to study them will change over time. This new knowledge will result in some products becoming lower-risk over time, but may also identify new hazards that were previously unknown or under-appreciated.
Probiotics face challenges similar to other areas of development where there is a dearth of conclusive findings as to safety and the product landscape is evolving. The FDA has struggled with such questions before, establishing collaborative pathways for products that may not fit within traditional categorizations. In the context of probiotics, the FDA should focus on implementing similar collaborative efforts. We wholeheartedly endorse this process as it is the process we employed during this project. Bringing together NIH-funded researchers and administrators, legal academics, food and drug law attorneys, government regulators, consumer advocates, bioethicists, and industry representatives was an invaluable way to raise and address the issues raised by probiotics and create a written record of the thoughts, concerns, and broad recommendations of the leading stakeholders in the field. We believe the FDA should undertake a similar process to address the issues raised by the burgeoning field of probiotics so that its promise can be realized in a way that is safe and reasonable for all stakeholders—most importantly consumers. We hope this document can be a starting point for that discussion.
Appendix A

Federal Regulation of Probiotics

Participant List

Investigators and Meeting Organizers

• Diane E. Hoffmann, MS, JD, Professor of Law and Director, Law and Health Care Program, University of Maryland Francis King Carey School of Law (Principal Investigator)
• Claire M. Fraser, Ph.D, Professor of Medicine and Director, Institute for Genome Sciences, University of Maryland School of Medicine
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• 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 Francis King Carey School of Law
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• Chris D’Adamo, Ph.D., Assistant Professor, Family and Community Medicine, University of Maryland School of Medicine
• Alessio Fasano, MD, Professor of Pediatrics and Director, Center for Celiac Research, University of Maryland School of Medicine
• Patricia Hibberd, MD, PhD, Chief, Division of Global Health, Massachusetts General Hospital
• Pinaki Panigrahi, M.B.B.S., Ph.D, Associate Professor, Pediatrics, University of Maryland Baltimore Medical School
• Elaine Puppa, RN, MEd, MSN, University of Maryland School of Medicine
• Gregor Reid, Ph.D, MBA, Chair, Human Microbiolgy and Probiotics at Lawson Health Research Institute and Professor, Microbiology & Immunology, and Surgery, Western University, Canada
• Julie Segre, Ph.D, Senior Investigator, Genetics and Molecular Biology Branch, Head Epithelial Biology Section, National Human Genome Research Institute, NIH*
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- Frederick Degnan, JD, Partner, King & Spalding, Washington, DC
- Wes Siegner, JD, Partner, Hyman Phelps & McNamara, Washington, DC

Government Agency Representatives

- Daniel Buijs, MSc., Natural Health Products Directorate, Health Canada
- Richard Cleland, JD, Federal Trade Commission
- Linda C. Duffy, Ph.D., MPH, HSA Program Director, National Center for Complementary and Alternative Medicine (NIH)
- Marguerite Klein, MS, Health Science Administrator, Office of Dietary Supplements, NIH*

Legal and other Academics

- Rebecca M. Bratspies, JD, CUNY School of Law*
- Gary Marchant, JD, MPP, Ph.D, Arizona State University Law School*
- J. Glenn Morris, Jr., MD, MPH, Emerging Pathogens Institute, University of Florida
- James O’Reilly, JD, University of Cincinnati School of Law
- Pilar Ossorio, Ph.D., JD, University of Wisconsin School of Law
- Jordan Paradise, JD, Seton Hall School of Law
- Karen Rothenberg, MPA, JD, University of Maryland Francis King Carey School of Law

Advocacy and Trade Organizations

- Jay E. Sirois, Ph.D., Director of Regulatory & Scientific Affairs, Consumer Healthcare Product Association*
- Taylor C. Wallace, Ph.D., FACN, Senior Director, Scientific & Regulatory Affairs, Council for Responsible Nutrition*
- Douglas MacKay, N.D., Vice President, Scientific & Regulatory Affairs, Council for Responsible Nutrition*

Bioethicists and Philosophers

- Rosamond Rhodes, PhD, Associate Program Director & Professor of Bioethics, Professor of Medical Education, Mount Sinai School of Medicine
- John Huss, Ph.D., Assistant Professor of Philosophy, University of Akron*

Industry and Consultants

- June Austin, Regulatory Affairs, Procter & Gamble, Cincinnati, OH
- James T. Heimbach, Ph.D., F.A.C.N., JHeimbach LLC
- Laurel Lagenaur, Osel Inc., Santa Clara, CA
- Mary Ellen Sanders, Ph.D., Dairy & Food Culture Technologies
Nora L. Zorich, M.D., PhD., former Vice President Corporate Research and Development, Procter & Gamble, Cincinnati, OH (Dr. Zorich served in her role at Procter & Gamble while a member of the Working Group).

*Only attended one of three meetings held.
## Appendix B

### Commercial Strains Sold As Probiotics

Selected probiotic strains and products available in the US and Europe

<table>
<thead>
<tr>
<th>Strain(^1)</th>
<th>Product containing strain(^2)</th>
<th>Sold by:</th>
</tr>
</thead>
</table>
| *L. acidophilus* NCFM  
*B. lactis* Bi-07  
*B. lactis* HN019 (DR10)  
*L. rhamnosus* HN001 (DR20) | Sold as ingredient | DuPont Nutrition Biosciences ApS (Madison WI) |
| *Saccharomyces cerevisiae* boulardii | Florastor | Biocodex (Creswell OR) |
| *B. infantis* 35624 | Align | Procter & Gamble (Mason OH) |
| *L. rhamnosus* R0011  
*L. acidophilus* R0052 | Sold as ingredient | Lallemand (Montreal, Canada) |
| *B. lactis* Bb-12  
*L. acidophilus* LA5  
*L. paracasei* CRL 431  
*L. fermentum* VRI003 (PCC)  
*L. reuteri* RC-14  
*L. rhamnosus* GR-1  
*L. paracasei* F19 | Sold as ingredient | Chr. Hansen (Milwaukee WI) |
| *L. casei* ShirotA  
*B. breve* Yakult | Yakult | Yakult (Tokyo, Japan) |
| *L. casei* DN-114 001 (“*L. casei* Immunitas”)  
*B. animalis* DN-173 010 (“*Bifidus* regularis”) | DanActive fermented milk  
Activia yogurt | Danone (Paris, France)  
Dannon (Tarrytown, NY) |

\(^{236}\) List developed by the California Dairy Research Foundation available at http://cdrf.org/home/checkoff-investments/usprobiotics/products-with-probiotics/#commercial
**L. johnsonii** Lj-1  
(NCC533; *L. acidophilus* La-1)  
Nestlé (Lausanne, Switzerland)

**L. plantarum** 299V  
**L. rhamnosus** 271  
Good Belly  
Probi AB (Lund, Sweden)NextFoods  
(Boulder, Colorado)

**L. reuteri** ATCC 55730  
(“Protectis”)  
BioGaia Probiotic chewable tablets or drops  
Biogaia (Stockholm, Sweden)

**L. rhamnosus** GG  
(“LGG”)  
Culturelle  
Valio Dairy (Helsinki, Finland)

**L. rhamnosus** LB21  
*Lactococcus lactis* L1A  
Sold as ingredient  
Essum AB (Umeå, Sweden)

**L. salivarius** UCC118  
University College (Cork, Ireland)

**B. longum** BB536  
Sold as ingredient  
Morinaga Milk Industry Co., Ltd. (Zama-City, Japan)

**L. acidophilus** LB  
Sold as ingredient  
Lacteol Laboratory (Houdan, France)

**Bacillus coagulans**  
BC30  
Sustenex, Digestive Advantage; Sold as ingredient

This table does not constitute an endorsement of any of these products, nor does it include all strains/mixtures currently available.

1Parenthetic entries indicate alternative strain designations; *B. lactis* is a shorthand designation for *Bifidobacterium animalis* subsp lactis.

2Strains sold as ingredients are available in numerous consumer products; contact responsible company for product list.
Appendix C

Summary of 11/16/10 Meeting at FDA with Office of Policy Staff Regarding University of Maryland Baltimore Federal Regulation of Probiotics Project

Present at meeting:
Ritu Nalubola, FDA Office of Policy
Jarilyn Dupont, FDA Office of Policy
Diane Hoffmann
Frank Palumbo
Virginia Rowthorn

We submitted questions for FDA prior to the meeting – this summary tracks the questions we submitted.

Discussion:

We started by discussing the questions we submitted for FDA as a whole (our questions are in bold).

1. When does the FDA think an IND or clinical trial is necessary in the case of probiotics? Would an IND or clinical trial be required in the case of a probiotic product that is not making drug claims? Has FDA required an IND or clinical trial of any probiotic products?

The FDA representatives gave us two recent guidance documents that they suggested would go a long way to answering those questions: Early Clinical trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information and Draft Guidance, Guidance for Industry, INDs—Determining Whether Human Research Studies Can Be Conducted Without an IND.

They stated that, as a general matter, probiotics are not treated differently by FDA than any other class of products. FDA believes probiotics fit in with current regulatory categories. FDA does not “track” probiotic products and further, this would be very difficult because products may contain live organisms but not be called probiotics, so tracking such products would be difficult. Probiotics fit most comfortably in the “Live Biotherapeutic Products” category.

The FDA representatives analogized probiotics to nanotechnology. Both are new classes of products that may require regulatory “fixes” but not a new statutory framework. While probiotics may have certain unique characteristics, many new classes of products bring unique questions and FDA has the framework to deal with these questions.

In terms of what studies can be conducted without an IND – the FDA representatives made clear that, even if an IND is not required, FDA still has jurisdiction over the final marketed product. Many subjects studied in the academic setting are IND exempt.

2. Does the FDA coordinate with the FTC on claim substantiation requirements?
Coordination between the two agencies is on an informal basis only. While consultation may take place, there is no regulatory requirement to do so.

3. **Has there been any effort on the part of FDA as a whole to regulate probiotics differently than other products?**
   No. FDA does not believe this is necessary as the agency’s current framework can adapt to new scientific methods.

4. **Have there been any concerns with probiotic products not fitting in the current regulatory categories?**
   No. At this point, we talked briefly about other possible ways that probiotics could be regulated:
   - We asked if FDA had considered using the monograph process for probiotics as Health Canada has done. The FDA representatives said they did not know but would not be at liberty to say if they did know.
   - We then discussed tobacco regulation. Congress set up a different pathway for tobacco but the FDA representatives commented that first, FDA could have regulated tobacco under its current framework and that tobacco is very different from other regulated products (unlike probiotics that clearly fit into the live biotherapeutic products category).
   - In terms of the fecal transplant issue, the FDA representatives did not know how a pill of this sort would be regulated – maybe as a biologic. The concept that a substance can evolve/change over time is not unique to probiotics. Further, the concept that characterization may be difficult is also something FDA has dealt with before.
   - The FDA representatives acknowledged that probiotics are unique in terms of transit, characterization, shelf life, and in terms of what is inherent in the human gut but stated that this is common to all microorganisms and FDA has handled these issues long before probiotics, e.g., with cheese and yogurt.
   - The FDA representatives noted that current regulations may be burdensome but FDA’s primary concern is safety.

5. **How is the FDA dealing with issues of identification of probiotic strains, standardization, and Good Manufacturing Practices in the case of probiotics? Who is responsible for developing guidelines in this area? Are current requirements for specificity and characterization of new drugs and food additives appropriate for probiotic products?**
   Probiotics do not represent a challenge in this area. They recommended we look at guidance for low acid canned food, dietary supplements, water, infant formula (this is still draft guidance), and foods in general.

6. **Is the FDA preparing a probiotics monograph? Is USP involved in any way?**
   They were not sure. They did not know if USP is involved because it is a separate organization outside of FDA.

7. **How does FDA determine which product classification/definition applies to a probiotic product and how does FDA determine which Center will evaluate the product?**
   It depends on the intended use of the product. If FDA requires an IND or clinical trial, FDA considers the product a drug. Traditional foods can be drugs if the manufacturer makes drug claims – this has always been true – long before probiotics.

Questions for each of the following four Centers –

Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
Center for Drug Evaluation and Research
Center for Food Safety and Applied Nutrition Organization

1. Approximately how many inquiries has each Center received about probiotic products? (We are not looking for exact figures but ballpark figures.)
   As mentioned earlier, because FDA does not track probiotic products specifically, they did answer this question.

2. How many actions (pre-market approvals, GRAS application approvals, claims approvals, claims denials, warning letters, product recalls/market withdrawals, consent orders) has each Center performed for probiotic products?
   We can find this information on the Warning Letters database. The database is searchable.

3. What kind of products has each Center evaluated? Specifically, what diseases/conditions are the products designed to address or what areas of health are the products designed to improve? Can the names of the products be shared?
   As mentioned earlier, because FDA does not track probiotic products specifically, they could not answer this question. They suggested we check www.clinicaltrials.gov which is hosted by NIH. We should take note that it is difficult to ascertain whether clinical trials listed on this webpage are for products in the FDA pipeline – even if FDA is listed as “Oversight Health Authority.”

4. Are the Centers proactively looking at marketed probiotic products for compliance with FDA regulations? Is FDA seeing significant noncompliance in this area? Have any probiotic products received final approval or pre-market approval from any Center?
   FDA is not looking at probiotic products specifically. FDA is mainly attuned to safety issues before labeling concerns.

5. Have the relevant Centers accepted disease, health, or qualified health claims for probiotic products?
   We should look at the list of accepted health claims on the FDA website but they indicated that none had been accepted for a probiotic product.

6. If a Center has rejected any probiotic products or rejected any claims about any probiotic products can you let us know the circumstances?
   We should look at the list of accepted/rejected health claims on the FDA website.

7. Do the Centers treat probiotic products differently from the other products the Center regulates? If so, how?
   No.

For CFSAN specifically –

1. Are food products with probiotic components evaluated as foods or food additives or both?
   It depends on the product. They suggested we look at GRAS notifications for cheese and wine – these products change over time. The variability over time is not an impediment to GRAS status. GRAS is a safety designation and, as long as a product is safe over time, it can fit within the GRAS designation.

2. Has CFSAN encountered any food additive applications for probiotic products with genetically modified strains of bacteria or products in which certain bacterial strains have been encouraged to grow over other strains?
The FDA representatives said there may be one but was not more specific.

3. **Does CFSAN have concerns about the GRAS process for probiotics?**
   No – there are no specific concerns. We should look at microorganism feeding studies as an example.

Final discussion:
- They were not sure if there was a probiotics advisory committee or working group at FDA but recommended we check the advisory committee link on the FDA website.
- In terms of what are perceived as regulatory hurdles, they suggested we look at the Critical Paths Report just prepared by FDA. While they do not believe this report touched on probiotics specifically, there is mention of the biomarker/endpoint issue in the report.
Appendix D
Meeting Agendas

Federal Regulation of Probiotics Agenda – Meeting One

June 14, 2010

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)

11:00-11:15 The Current State of Probiotic Research (Patricia 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 Closing Remarks
Federal Regulation of Probiotics Agenda – Meeting Two

February 3-4, 2011

Thursday, February 3 (Hotel Monaco)

(12:30-1:30) Meeting – Abbreviated IND Working Group
1:30-1:45 Welcome (Diane Hoffmann)
1:45-2:15 Presentation by Abbreviated IND Working Group
2:15-2:45 Plenary Discussion of Abbreviated IND Working Group Findings
2:45-3:15 Presentation on Safety Issues (Frank Palumbo)
3:15-3:30 Break
3:30-4:00 Presentation on Characterization (Jacques Ravel)
4:00-5:30 Small Group Discussions on Safety and Characterization
5:30-6:00 Break before Dinner
6:00-7:00 Dinner (Hotel Monaco)
7:00-8:00 Reports from Small Group Discussions on Safety and Characterization

Friday, February 4

8:45-8:50 Overview of Day (Diane Hoffmann)
8:50-9:30 Claims – Consumer Perspective (David Schardt), Patient Perspective (Ruth Farrell)
9:30-9:55 Claims – Industry Perspective (Nora Zorich)
9:55-10:10 Break
10:10-10:35 Claims – Scientific Perspective (Mary Ellen Sanders)
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<td>10:35-11:00</td>
<td>Alternatives/Solutions to Under Regulation – Private Right of Action (Richard Cleland and Peter Holland)</td>
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<td>11:00-12:00</td>
<td>Small Group Discussion – Private Right of Action and Other Recommendations</td>
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<td>12:00-12:30</td>
<td>Presentation of Small Group Discussions/Recommendations</td>
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<td>12:30-1:15</td>
<td>Lunch</td>
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<td>1:15-2:00</td>
<td>Alternatives/Solutions – Over Regulation/Under Regulation – Monograph (Daniel Buijs and James O’Reilly)</td>
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<td>2:00-3:15</td>
<td>Small Group Discussions – Monograph and Other Recommendations</td>
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<td>3:30-4:00</td>
<td>Report on Small Group Discussions and Recommendations</td>
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Federal Regulation of Probiotics Agenda – Meeting Three

February 16-17, 2012

Thursday, February 16

12:00-1:30 Abbreviated IND Subcommittee Meeting – Deans Conference Room
1:30-1:40 Introduction and Welcome
1:40-2:15 Abbreviated IND Subcommittee Report
2:25-3:45 International Models for Regulation of Probiotics
  • Update on Canada – Dan Buijs, MSc. (Natural Health Products Directorate, Health Canada)
  • EU – James Heimbach, Ph.D., F.A.C.N. (JHeimbach LLC)
  • International Regulatory Overview – Kevin Gillies (Vice President, Regulatory Affairs, Danisco)
3:45-4:00 Break
4:00-5:00 Discussion groups re: international models
5:00-5:45 Reports from Discussion Groups
6:00-6:30 Reception
6:30-7:30 Dinner

Friday, February 17th

8:45-9:00 Introduction to the Day and Continental Breakfast
9:00-9:30 “The Human Microbiome Project – A New Paradigm?” John Huss, Ph.D., (University of Akron)
9:30-10:00  “The Human Microbiome Project and the Future of Probiotics” Patricia Hibberd, MD, PhD, Chief, Division of Global Health, Massachusetts General Hospital

10:15-11:15  Discussion Groups

11:15-12   Report to Group

12-1:00   Lunch

1:00-2:00  Review of AHRQ Report on Safety of Probiotics - Linda C. Duffy, Ph.D., Natural Products Branch, National Center for Complementary and Alternative Medicine

The AHRQ Report: Issues to Consider – Taylor C. Wallace, PhD, FACN (Senior Director, Scientific & Regulatory Affairs, Council for Responsible Nutrition)

2:00-4:00  Working Group Member Essay Presentations

4:00-4:30  Closing Comments