HHS Public Access

Author manuscript

Food Drug Law J. Author manuscript; available in PMC 2018 August 29.

Published in final edited form as:

Food Drug Law J. 2014 ; 69(2): 237–ii.

Probiotics: Achieving a Better Regulatory Fit[1]

Diane E. Hoffmann, MS, JD[*] [Professor of Law and Director], **Claire M. Fraser, PH.D.[**] [Professor of Medicine and Director]**, **Francis Palumbo, PH.D., JD[***] [Professor and Executive Director]**, **Jacques Ravel, PH.D.[****] [Professor and Associate Director of Genomics]**, **Virginia Rowthorn, JD[*****] [Managing Director]**, and **Jack Schwartz, JD[******] [Adjunct Professor and Senior Research Associate]**

[*]Law and Health Care Program, University of Maryland Francis King Carey School of Law.

[**]Institute for Genome Sciences, University of Maryland School of Medicine

[***]University of Maryland School of Pharmacy, Center on Drugs and Public Policy

[****]Institute for Genome Sciences, University of Maryland School of Medicine

[*****]Law & Health Care Program, University of Maryland Francis King Carey School of Law

[******]University of Maryland Francis King Carey School of Law

I. Introduction

In 2007, the National Institutes of Health (NIH) launched the Human Microbiome Project (HMP), a $150 million 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.[2] Many lines of research have demonstrated the significant role of the microbiota in human physiology. The microbiota is involved, for example, in the healthy development of the immune system, prevention of infection from pathogenic or opportunistic microbes, and maintenance of intestinal barrier function. Goals of the HMP have been described as "identifying new ways to 'determine health and predisposition to diseases [as well as defining] the parameters needed to design, implement and monitor strategies for intentionally manipulating the human microbiota, to optimize its performance in the context of an individual's physiology.'"[3]

As part of the HMP, NIH funded the "Healthy Cohort Study," an effort to create a reference catalogue of microbial DNA in healthy adults[4] as well as fifteen demonstration projects focusing on bacterial, fungal, and viral changes in microbiomes in individuals with various

[1]This article is taken, in large part, from a longer White Paper available at http://www.law.umaryland.edu/programs/health/events/probiotics/documents/FinalWhitePaper.pdf.

[2]*See* Office of Strategic Coordination, *Human Microbiome Project*, nat'l inst. of HealtH, http://commonfund.nih.gov/hmp/ (last visited Feb. 7, 2014).

[3]Diane E. Hoffmann, J. Dennis Fortenberry, & Jacques Ravel, *Are Changes to the Common Rule Necessary to Address Evolving Areas of Research? A Case Study Focusing on the Human Microbiome Project*, 41 J. laW, Med. & etHiCs 454, 455 (2013) (quoting Peter J. Turnbaugh et al., *The Human Microbiome Project*, 449 nature 804, 804 (2007)).

[4]*See* Press Release, NIH Human Microbiome Project Defines Normal Bacterial Makeup of the Body (June 13, 1013), http://www.genome.gov/27549144. 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* David A. Relman, *Learning About Who We Are*, 486 nature 194 (2012).

diseases. Early findings of the HMP were published in June 2012.[5] While the findings are helping us understand the role and variation of microorganisms within and across individuals, they are also promoting interest in the development of probiotic products.[6]

Probiotics are substances containing live microorganisms that are thought to have a beneficial effect on the human body by manipulating microbiome and host properties.[7] Research has shown that it is possible to categorize the microbiota components on the basis of whether they exert potentially pathogenic or health-promoting aspects. 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. While several probiotics are now undergoing preclinical and clinical trials,[8] none have as yet been approved as drugs in the United States. Probiotics have, however, been available as foods and dietary supplements for many years. Initially marketed in yogurts and dairy products, the use of probiotics in commercial products has skyrocketed in recent years.[9] Other probiotic products include juices, nutrition bars, infant formulas, relishes and condiments, sweeteners, waters, pizza crust, gum, lozenges, dietary supplements, toothpaste, and cosmetics.[10]

In addition to funding the Healthy Cohort Study and the demonstration projects, NIH set aside a portion of HMP funds to study the ethical, legal, and social implications (ELSI) of the HMP's scientific goals. Among the funded ELSI studies was an effort to look at the current regulatory framework for probiotics[11] and to determine if it 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. New claims are being made about the role and value of probiotics in promoting human health and well-being, and there is both uncertainty and debate about how these products should be regulated.[12]

---

[5] The Human Microbiome Project Consortium, *A Framework for Human Microbiome Research*, 486 nature 215 (2012).

[6] *See* Jeffrey I. Gordon, *Honor Thy Gut Symbionts Redux*, 336 SCIENCE 1251 (2012). With the advent of the HMP, research relating to probiotics has increased significantly 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.

[7] There is no statutory or regulatory definition of probiotics in the United States. The most widely used definition of probiotics is the definition proposed in the report of a Joint FAO/WHO Expert Consultation. FOOD & AGRIC. ORG. OF THE U.N. & WORLD HEALTH ORG., EVALUTION OF HEALTH AND NUTRIONAL PROPERITES OF PROBIOTICS IN FOOD INCLUDING POWDER MILK WITH LIVE LACTIC ACID BACTERIA (2001), *available at* http://www.who.int/foodsafety/publications/fs_management/en/probiotics.pdf. In that document, probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host." *Id.* at 5.

[8] *See* Bernat Olle, *Medicines from Microbiota*, 31 NATURE BIOTECHNOLOGY 309, 314 tbl.3 (2013).

[9] *See Functional Foods Lead the Probiotic Market's Continued Growth*, NUTRACEUTICALS WORLD (June 10, 2013), http://www.nutraceuticalsworld.com/contents/view_breaking-news/2013-06-10/functional-foods-lead-the-probiotic-markets-continued-growth/. *See also* Ewa Hudson, *Challenging Economic Climate No Threat to Probiotics*, NATURAL PRODUCTS INSIDER (Oct. 19, 2012), http://www.naturalproductsinsider.com/articles/2012/10/challenging-economic-climate-no-threat-to-probiot.aspx; Jeff Gelski, *Staking Out Probiotic Claims*, FOOD BUS. NEWS (Sept. 30, 2010), http://www.foodbusinessnews.net/News/News%20Home/Features/2010/9/Staking%20out%20probiotic%20claims.aspx?cck=1.

[10] *See Commercial Strains Sold as Probiotics*, CAL. DAIRY RES. FOUND., http://cdrf.org/home/checkoff-investments/usprobiotics/products-with-probiotics/#commercial (last visited Jan. 31, 2014).

[11] The grant was awarded to researchers at the University of Maryland, Baltimore and was an interdisciplinary collaboration between faculty members from the University of Maryland Schools of Law, Pharmacy and Medicine. *See* Grant Number, *supra* note 1.

[12] *See* Jon A. Vanderhoof & Rosemary Young, *Probiotics in the United States*, 46 CLINICAL INFECTIOUS DISEASES S67, S67 (2008) ("Although the use and scientific understanding of probiotics are rapidly increasing, it is evident that there is a need to clarify the regulatory issues, which, at present, are unclear and subject to misinterpretation."). *See also* Freddie Ann Hoffman et al., *Executive Summary: Scientific and Regulatory Challenges of Development of Probiotics as Foods and Drugs*, 46 CLINICAL INFECTIOUS DISEASES S53 (2008); Diane E. Hoffmann et al., *Probiotics: Finding the Right Regulatory Balance*, 342 SCIENCE 314 (2013).

As probiotics begin to proliferate in the market, policy makers and regulators need to critically consider the regulatory structure that is most appropriate for them. This consideration should incorporate the wide range of probiotic products that are and may become commercially available as foods, food additives, drugs, dietary supplements, and cosmetics, and should anticipate the future types of probiotic products that may be developed. Scientists have 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. Experts in the field also expect that there will be more interest in genetic engineering of probiotics for specific medical purposes as more is known about probiotic mechanisms of action. In order to protect and guide consumers and health care providers who may use or recommend the use of probiotics, a regulatory structure that adequately accounts for the risks of probiotics as well as the accuracy of claims of effectiveness is necessary. 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.[13]

This article reports on the findings of a Working Group (WG) consisting of NIH-funded HMP scientists, physicians, legal academics, government regulators, industry and consumer representatives, bioethicists, food and drug lawyers, and health policymakers who were assembled to address the adequacy of the current regulatory framework for probiotics under the HMP ELSI funded project.[14] Specifically, after discussion of the features of probiotics that are relevant to their regulation and an overview of FDA's current regulation of probiotics, the article addresses the following questions: 1) Do current regulations adequately address the safety of new probiotic products? 2) Should probiotic foods and dietary supplements be classified as drugs and required to go through the drug approval process? 3) What types of product characterization requirements are appropriate for probiotics? 4) Are current claim regulations appropriate for probiotics and, if not, how might they be improved?

II. Features of Probiotics Relevant to Regulation

A. Nature of Probiotics

A foundational question in determining the appropriate regulatory framework(s) for probiotics is whether probiotics have intrinsic and distinct characteristics that sufficiently distinguish them from other FDA regulated products. 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 are also likely to lose viability and degrade under certain circumstances.[15] As a

[13] *See, e.g.*, Hoffmann et al., *supra* note 12.

[14] *See* Grant Number, *supra* note 1. The NIH grant funded a number of meetings of the Working Group (WG). A list of WG members is available at http://www.law.umaryland.edu/programs/health/events/probiotics/documents/Probiotic_Participant_list.pdf. While this article reflects the discussions of the WG, it is not a consensus document. It is written from the perspective of the authors, who considered the relevant literature as well as the opinions of the WG members in drafting this paper.

[15] *See* Hoffmann et al., *supra* note 12. *See also* Andi L. Shane et al., *Guide to Designing, Conducting, Publishing and Communicating Results of Clinical Studies Involving Probiotic Applications in Human Participants*, 1 GUT MICROBES 243, 246 (2010) (stating that a "unique aspect of probiotics is their viable nature").

result, probiotic research and manufacturing involve a greater number of variables than research with many other substances, such as the effect of the environment on the viability and effectiveness of the probiotic; the interaction between the human genome and the human microbiota; and triggers within the human body that may activate or deactivate the probiotic.[16] Thus, without quality control, "specific probiotics may lose the properties that once formed their isolation and selection criteria."[17] Animal models may be of limited utility in probiotic research because of the complexity of the human microbiome and the major differences between human microbiomes and animal microbiomes.[18] Given these differences, dosing of probiotics for therapeutic purposes is more problematic, as is manufacture, storage, and shelf life. Similar to botanicals, there are differences that appear from batch to batch when manufacturing probiotics. Finally, unlike other products, probiotics are often derived from microbes living in human bodies. While the import of these intrinsic characteristics may be difficult to translate into regulatory processes, they should be the foundation 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 many are intended to promote human wellness and the balance of the microbiota in the gut, mouth, and other body sites where microbial communities exist. Although the HMP and related research are likely to lead to therapeutic (i.e., drug) uses for certain probiotics, many 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 are now sold as foods and dietary supplements. The field of probiotics contemplates the role of foods in preventing or reducing disease and illness. Many of those conducting research on probiotics believe probiotics in food are 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).

B. Safety of Probiotics

A recent article on the safety of probiotics begins with the statement that "[a]ny discussion of probiotic safety would be misleading were it not to acknowledge the remarkably low rate of adverse events recorded with probiotic consumption, either as specific products in the context of controlled trials or as constituents in fermented food products, over a long history of widespread use."[19] The article goes on to say, however, that "there are important caveats regarding probiotic safety that need emphasis."[20] The available literature indicates that

[16] *See* Hoffmann et al., *supra* note 12.
[17] *Id.* at 314 (citing Grzekowiak et al., *Manufacturing Process Influences Properties of Probiotic Bacteria*, 105 BRIT. J. NUTRITION 887 (2011)).
[18] *See id. See also* Shane et al., *supra* note 15, at 249 ("For most chemical substances, most of the burden of evaluating safety falls on tests performed on well-understood animal models. For the safety-related endpoints important in the assessment of probiotics, validated animal models do not exist and, as a result, the determination of safety rests primarily on human studies."). *See also* James T. Heimbach, *Health-Benefit Claims for Probiotic Products*, 46 CLINICAL INFECTIOUS DISEASES S122, S124 (2008) (asserting that, although animal and in vitro studies may be helpful in establishing the biological mechanism of therapies, the use of an appropriate animal model with probiotics is challenging "because there has been little published research demonstrating that rats, mice, or other frequently used laboratory animals are valid models for the safety or efficacy of probiotic microorganisms in the human").
[19] Fergus Shanahan, *A Commentary on the Safety of Probiotics*, 41 GASTROENTEROLOGY CLINICS N. AM.869, 869 (2012).

safety evaluations of probiotics should consider "pathogenicity, infectivity, virulence factors, toxicity, metabolic activity and intrinsic properties of the microbes."[21] Evidence exists that specific strains of probiotics are safe for human use, but for other strains there is limited data on safety. This underscores the point that probiotic bacteria are heterogeneous and should be evaluated for safety individually on a "strain-by-strain basis."[22]

This point is exemplified by the issue of lateral gene transfer, which refers to the transfer of genetic material between organisms other than from vertical transmission, 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 the transfer of bacterial antibiotic resistance.[23] Genes that are responsible for antibiotic resistance in one species of bacteria can be transferred to another species of bacteria through various mechanisms. There is no evidence of this having happened with probiotics to date, but it is important to the extent that probiotic therapy is often used or recommended in conjunction with antibiotics.[24]

In 2009, the 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 of the safety of probiotics used in research to reduce the risk of, prevent, or treat disease.[25] In April 2011, AHRQ published the most extensive report to date on the safety of probiotics based on this review. The report *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."[26]

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."[27] In 235 studies, only nonspecific safety statements were made (e.g., the product is "well tolerated"); the remaining 387 studies reported the presence or absence of specific adverse events. The conclusion of the AHRQ report was hindered by the lack of well-documented studies and the authors could only conclude that "[t]he available evidence in RCTs [randomized controlled trials] does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the

---

[20] *Id.*
[21] Christophe Chassard et al., *Probiotics and Health Claims: Challenges for Tailoring Their Efficacy*, *in* PROBIOTICS & HEALTH CLAIMS 51 (Wolfgang Kneifel & Seppo Salminen eds., 2011) (citing Norio Ishibashi & Shoji Yamazaki, *Probiotics and Safety*, 73 aM. J. CLINICAL NUTRITION 465S (2001)).
[22] *See* Shanahan, *supra* note 19, at 874.
[23] *See* OECD, SAFETY ASSESSMENT OF TRANSGENIC ORGANISMS, VOLUME 4: OECD CONSENSUS DOCUMENTS 171–74 (2010).
[24] One response to this concern is to require testing to determine the antibiotic resistance patterns of probiotics at the strain level and to eliminate the possibility of the probiotic strain(s) carrying transmissible antibiotic resistance genes.
[25] 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 Center for Food Safety and Applied Nutrition (CFSAN).
[26] AGENCY FOR HEALTHCARE RESEARCH & QUALITY, SAFETY OF PROBIOTICS TO REDUCE RISK AND PREVENT OR TREAT DISEASE, at vi (2011), *available at* http://www.ahrq.gov/research/findings/evidence-based-reports/probiotic-evidence-report.pdf.
[27] *Id.*

current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence."[28]

More specifically, the authors 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. Long-term effects are largely unknown. Existing studies primarily examined *Lactobacillus* alone or in combination with other genera, often *Bifidobacterium*. Few studies directly compared safety-related outcomes among different interventions or participant subgroups. Indirect comparisons indicated that effects of delivery vehicles (e.g., yogurt, other dairy products) 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.

C. Environmental Risk

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, has not been studied. The need for such research is particularly important in the case of genetically engineered probiotics. Issues of environmental regulation, however, are beyond the scope of this article.

III. Current Regulation of Probiotics by the FDA

The primary agency with regulatory authority over probiotics is the FDA, although the Federal Trade Commission (FTC), through its authority to regulate certain aspects of product advertising and marketing, also regulates probiotics. The FDA, unlike the FTC, regulates products by category, e.g., foods, drugs (including biologics), dietary supplements, medical devices, and cosmetics.

The FDA places products in categories by their intended use. Intended use is typically determined by claims which the manufacturer wants to make about the product rather than its ingredients or other characteristics. Particularly relevant to the regulation of probiotics are the following product categories: foods;[29] substances within the food class, i.e., food additives,[30] substances generally regarded as safe (GRAS),[31] medical foods,[32] and foods for special dietary use;[33] dietary supplements;[34] cosmetics;[35] medical devices;[36] and drugs.[37]

---

[28] *Id.* Critics have asserted 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. Taylor C. Wallace & Douglas MacKay, *The Safety of Probiotics: Considerations Following the 2011 U.S. Agency for Health Research and Quality Report*, 141 J. NUTRITION 1923, 1924 (2011). The authors argued that "in the absence of drug-like safety data, the safety of traditional foods should be based on the *totality of evidence* in healthy populations." *Id.* at 1923 (emphasis added). They define totality of evidence as including "history of safe use as well as RCT, epidemiological data, animal studies, and in vitro cell work …." *Id.*

[29] FDCA Sec. 201(f) (codified at 21 U.S.C. § 321(f)).

[30] FDCA, Secs. 201(s), 409 (codified at 21 U.S.C. §§ 321(s), 348); 21 C.F.R. § 170.30 (2013).

[31] FDCA, Secs. 201(s), 409; 21 C.F.R. § 170.30 (2013).

[32] Section 5(b) of the Orphan Drug Act, 21 U.S.C. § 360ee(b)(3) (2012).

Each product category is regulated by a center at the FDA that evaluates and monitors many aspects of the life cycle of a product. Of most relevance to the regulation of probiotics for human use are the Center for Food Safety and Applied Nutrition (CFSAN), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER).

In addition to the centers devoted to a specific product class, 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. Where a product contains, for example, a drug and a biologic or a drug and a medical device, it is termed a "combination product"[38] and regulated according to its primary mode of action.[39] 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.[40]

Probiotics have traditionally appeared in foods, which, along with cosmetics, are among the least regulated products consumers use in or on their bodies. 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.[41] There are also probiotic products that could fall into the medical device category, such as probiotic tampons.[42]

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. When questions arise regarding into which category a probiotic belongs, the answer is determined on a case-by-case basis. The issue of category assignment is of significant import for probiotic manufacturers and researchers. Classification as a drug triggers the extensive and costly Investigational New Drug application (IND) process, which typically includes Phase I, II, and III clinical trials. All drugs must be approved prior to marketing by the FDA. Foods and dietary supplements, however, do not require agency premarket approval.

---

[33]Foods for special dietary use are 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." 21 C.F.R. §§ 105.66, 105.62, 105.65 (2013).

[34]Dietary Supplement Health & Education Act (DSHEA) of 1994, FDCA Sec. 413(c) (codified at 21 U.S.C. § 350(b)).

[35]FDCA, Sec. 201(i) (codified at 21 U.S.C. § 321(i)).

[36]21 U.S.C. § 321(h) (2012).

[37]21 U.S.C. § 321(g)(1) (2012).

[38]The OCP was established in 2002 and determines regulatory responsibilities for products combining elements of drugs, devices, and biologics among the relevant centers—CDER, CBER, and the Center for Devices and Radiological Health. *See Combination Products*, FOOD & DRUG ADMIN., http://www.fda.gov/CombinationProducts/ (last visited Jan. 31, 2014).

[39]*See* Jordan Paradise, *Reassessing Safety for Nanotechnology Combination Products: What Do Biosimilars Add to Regulatory Challenges for the FDA?*, 56 ST. LOUIS U. L.J. 465 (2012).

[40]*See Frequently Asked Questions About Combination Products*, FOOD & DRUG ADMIN, http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm (last visited Jan. 31, 2014).

[41]For example, Align, a daily probiotic supplement containing *Bifidobacterium infantis* (BifantisTM) bacteria, made by Procter and Gamble, and Redness Solutions Makeup SPF 15 with Probiotic Technology, made by Clinique are both probiotic cosmetics. Although probiotics can be cosmetics, the WG did not focus on probiotics that fall into the cosmetic product category.

[42]An example is the Saforelle Florgynal Probiotic Tampon. Tampons have traditionally been regulated as medical devices. *See, e.g.*, 21 C.F.R. § 884.5470 (2013).

The current regulatory framework does not address the role of foods in treating, mitigating, or curing disease. Probiotic foods and dietary supplements that attempt to take on such a role are automatically placed in the drug category. According to some, the "regulatory box paradigm" adopted by the U.S. and many other countries "imposes substantial hurdles for research, consumer understanding and marketing of functional foods," i.e. foods that may play a role in improving health and treating disease.[43]

Because probiotics fall into multiple product categories, some experts in the field argue that expertise about probiotics is spread unevenly across multiple centers at the FDA without a single authoritative agency voice on the issue. This may lead to inter-center inconsistencies in interpretation and application of regulations, data requirements, and the content of potentially relevant guidance documents about probiotics. 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 given that recent CBER guidance implies that probiotics are live biotherapeutics[44]—a category of products considered drugs. CBER, however, may not always be the most appropriate center to regulate probiotics traditionally found in foods or sold as dietary supplements with added microorganisms.

IV. Do Current Regulations Adequately Address the Safety of New Probiotic Products?

Safety is 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, probiotic products must be safe in both practice and perception. Although current FDA safety standards for foods, food additives, and drugs appear largely adequate for probiotics, some aspects of probiotic safety regulation could be improved.

A. Safety of Probiotic Foods

The safety of foods and food components are generally not studied via RCTs,[45] and few foods have in fact been subject to toxicological studies.[46] Many of the studies on safety in probiotic 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.[47] Challenges to RCTs in foods include difficulties in preparing an appropriate placebo and accounting for simultaneous changes in an individual's diet when a new food is introduced.[48] Because of these challenges, food safety has often

[43] Mary Ellen Sanders et al., *Health Claims Substantiation for Probiotic and Prebiotic Products*, 2 GUT MICROBES 127 (2011). Others argue that FDA's regulatory scheme assumes a more distinct and rigid line between categories and the role of products in each category than is reflected by the complex and fluid biology underlying concepts such as "health" and "disease." *See, e.g.*, Jeffrey Blumberg et al., *Evidence-based Criteria in the Nutritional Context*, 68 NUTRITION REV. 478, 480 (2010).

[44] *See* FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: EARLY CLINICAL TRIALS WITH LIVE BIOTHERAPEUTIC PRODUCTS: CHEMISTRY, MANUFATURING, AND CONTROL INFORMATION (Feb. 2012), *available at* http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/general/ucm292704.pdf; *see also infra* note 80 and accompanying text.

[45] *See* Arthur C. Ouwehand et al., *Probiotics: from Strain to Product, in* PROBIOTICS & HEALTH CLAIMS, *supra* note 21, at 46.

[46] *See* A. Constable et al., *History of Safe Use as Applied to the Safety Assessment of Novel Foods and Foods Derived from Genetically Modified Organisms*, 45 FOOD & CHEMICAL TOXICOLOGY 2513, 2513 (2007).

[47] *See* Wallace & MacKay, *supra* note 28.

been determined by history of safe use where a food has been consumed for decades without significant adverse events.[49] An internationally accepted criterion for a safe food is a reasonable certainty of no harm resulting from consumption.[50]

Despite the long history of apparently safe use of some probiotic foods, notably yogurt, one issue related to food safety that merits attention is the process by which a substance used in food is determined to be "generally recognized as safe" (GRAS). A 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.[51] The FDCA provides a mechanism for manufacturer self-determination of GRAS status and notification to the FDA prior to marketing of GRAS substances but does not require such notification. Prior to 1997, a manufacturer could submit a petition to FDA requesting GRAS affirmation. Since 1997, manufacturers have been allowed to (but need not) notify the FDA of their GRAS self-determination and provide evidence supporting their decision. After 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 status. Critics have challenged various aspects of the GRAS process, including the wisdom of allowing food manufacturers to make their own GRAS determinations.[52] To the extent that GRAS self-determination reflects limited regulatory oversight, the problem extends to probiotics. Despite this regulatory gap, FDA has approved a number of microorganisms and microbial-derived ingredients that are used in foods as GRAS.[53] In addition, some probiotic manufacturers have submitted GRAS notifications to the agency, including at least four probiotics for use in infant formula.[54]

---

[48] Ouwehand et al., *supra* note 45, at 46 (stating that "[i]f energy intake is to remain the same, something else will have to be excluded from the diet, with unknown consequences, something already noticed in the early days of cholesterol-lowering diets." (citing George V. Mann & Anne Spoerry, *Studies of a Surfactant and Cholestemia in the Maasai*, 27 AM J. CLINICAL NUTRITION 464 (1974))).

[49] *See* Constable et al., *supra* note 46, at 2513.

[50] *Id.*

[51] FDCA, Secs. 201(s), 409 (codified at 21 U.S.C. §§ 321(s), 348); 21 C.F.R. § 170.30 (2013). 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.

[52] *See* Letter from Gordon F. Tomaselli, Pres. of the American Heart Association, to the FDA and the USDA (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.) *See also* U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-10-246, FOOD SAFETY: FDA SHOULD STRENGTHEN ITS OVERSIGHT OF FOOD INGREDIENTS DETERMINED TO BE GENERALLY RECOGNIZED AS SAFE (GRAS) (2010), *available at* http://www.gao.gov/products/GAO-10-246. But, not all stakeholders agree with this assessment. *See, e.g.*, Ray A. Matulka, *The GRAS Process: Does It Need an Overhaul?*, FOOD & DRUG POL'Y F., June 13, 2012, http://www.fdli.org/resources/resources-order-box-detail-view/the-gras-process-does-it-need-an-overhaul- (subscription required) (asserting that the current GRAS process is adequate).

[53] *See Microorganisms and Microbial-Derived Ingredients Used in Food (Partial List)*, U.S. FOOD & DRUG ADMIN. (July 2001), http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/MicroorganismsMicrobialDerivedIngredients/default.htm.

[54] These manufacturers include Ganeden Biotech, Yakult and several infant formula manufacturers. Ganaden 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. *See* Letter from Dennis M. Keefe, Dir., Office of Food Additive Safety, to John R. Endres, Chief Scientific Officer, AIBMR Life Sciences, Inc., Agency Response Letter to GRAS Notice No. GRN 000399 (July 31, 2012), *available at* http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm314145.htm. 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 notified FDA of this GRAS self-determination in March 2012. *See* Letter from James T. Heimbach (for Yakult) to Paulette Gaynor, Supervisory Consumer Safety Advisor, FDA (Mar. 20, 2012), *available at* http://www.accessdata.fda.gov/scripts/fcn/gras_notices/GRN000429.pdf. The FDA responded in December 2012 stating that it had no questions regarding Yakult's self-determination of GRAS status. *See* Letter from Dennis M. Keefe, Dir., Office of Food Additive Safety to James T. Heimbach (Dec. 10, 2012), *available at* http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm335746.htm. Infant formula manufacturers submitting GRAS Notifications to the FDA include Mead Johnson for *Lactobacillus casei* subsp. *rhamnosus* strain GG (GRAS Notification 231);

B. Safety of Probiotic Dietary Supplements and Dietary Ingredients

A primary concern regarding the safety of probiotic dietary supplements is that the Dietary Supplement Health and Education Act (DSHEA) of 1994 "does not require manufacturers to submit dietary supplements to the FDA for safety testing or approval prior to sale."[55] While dietary supplement manufacturers, by law, must ensure that their products are safe, they need not submit data to the FDA substantiating how they established safety. However, the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006 does require that the manufacturer of a dietary supplement marketed in the US "submit to FDA all serious adverse event reports associated with use of the dietary supplement in the United States."[56] Given that manufacturers do not need to register their products with FDA or obtain FDA approval before producing or selling dietary supplements, the FDA generally only takes action against the manufacturer after the product has been on the market and been shown to be unsafe.[57] Moreover, the burden of proof to show that a dietary supplement is unsafe is on the FDA.[58]

Inadequacies in the regulation of dietary supplements generally will have an impact on probiotic products but certain probiotics will be subject to enhanced regulation if the probiotic is considered a "new dietary ingredient" (NDI). If a probiotic is added to a dietary supplement, it is likely to be considered a "dietary ingredient" or NDI. If the latter, it will be subject to more extensive regulation than dietary supplements without NDIs. The law considers a dietary supplement that contains a "new dietary ingredient" (i.e., a dietary ingredient that was not marketed in the United States in a dietary supplement before Congress passed DSHEA on October 15, 1994) to be "adulterated unless it meets one of two statutory requirements: the supplement must contain only dietary ingredients that have been present in the food supply, or there must be a history of use or other evidence of safety establishing that the dietary ingredient will reasonably be expected to be safe."[59] The manufacturer must determine if the substance is an NDI and notify the FDA of its plan to market the NDI or to market the NDI in a dietary supplement 75 days prior to marketing the product. 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

---

Nestle Nutrition, US for *Lactobacillus reuteri* strain DSM 17938 (GRAS Notification 410); Fonterra Co-operative Group, New Zealand for *Lactobacillus rhamnosus* strain HN001 produced in milk-based medium, and Nestle USA for *Bifidobacterium lactis* strain Bb12 and *Streptococcus thermophiles* (GRAS Notification 49).

[55] OFFICE OF INSPECTOR GENERAL, U.S. DEP'T OF HEALTH & HUM. SERVS., NO. OEI-01-11-00210, DIETARY SUPPLEMENTS:STRUCTURE/FUNCTION CLAIMS FAIL TO MEET FEDERAL REQUIREMENTS (2012), *available at* https://oig.hhs.gov/oei/reports/oei-01-11-00210.pdf.

[56] *Dietary Supplements*, U.S. FOOD & DRUG ADMIN., www.fda.gov/Food/DietarySupplements/ (last visited Feb. 10, 2014).

[57] *Id.*

[58] *See* 21 U.S.C. § 342(f)(1) (2012).

[59] OFFICE OF THE INSPECTOR GENERAL, *supra* note 55, at 2 n.16 (citing 21 U.S.C. § 350b). In the 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, 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.

See Draft Guidance for Industry: Dietary Supplements: New Dietary Ingredient Notifications and Related Issues, U.S. FOOD & DRUG ADMIN. (July 2011), http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/DietarySupplements/ucm257563.htm [hereinafter *Draft Guidance for Industry: New Dietary Ingredient Notifications*].

conditions of use.[60] The manufacturer must include evidence of a history of safe use, safety studies, or both.[61] As of May 8, 2014 the FDA had not published guidance defining the specific information that the submission must contain.[62] Rather, the agency has stated that the manufacturer or distributer is responsible for determining what information provides the basis for its conclusion but suggests that the submission include "evidence of safety found in the scientific literature, including an examination of adverse effects associated with the use of the substance."[63]

There is no authoritative, FDA-approved list of dietary ingredients that were marketed in dietary supplements before October, 1994. Although trade associations have created a number of such lists, including the probiotics listed below,[64] there remains some uncertainty as to whether the FDA considers them grandfathered.[65] The burden of proof is on the FDA to show that these substances were not marketed before 1994.[66] Probiotics marketed before 1994 include:[67]

- Bifidobacterium bifidum
- Bifidobacterium infantis
- Bifidobacterium longum
- Bifidus adolescentis
- Lactobacillus acidophilus
- Lactobacillus casei
- Lactobacillus jugartldelbrueckii (bulgaricus)
- Lactobacillus plantarum
- Lactobacillus rhamnosus
- Saccharamyces boulardii

---

[60] *See* 21 U.S.C. § 350b(a)(2) (2012).
[61] *See Draft Guidance for Industry, New Dietary Ingredient Notifications*, *supra* note 59.
[62] *New Dietary Ingredients in Dietary Supplements – Background for Industry*, U.S. FOOD & DRUG ADMIN., www.fda.gov/Food/DietarySupplements/ucm109764.htm (last visited May 8, 2014).
[63]

> *Id.* Experts in the field have recommended that the submission identify any pathogens phylogenetically related at the species and genus level; identify toxins or other dangerous substances known to be present in the same species; document and detail any known antibiotic resistance (assess the ability of resistant genes to mobilize and transfer pathogens); assess, for historical use data, the level of historical exposure including how any excipients used in it affect delivery of the NDI tract; and include, if historical use is inadequate, safety studies in humans or appropriate animal models. Human safety studies should include measurements of the persistence of the organisms in the body after administration, the ability of the organism to translocate outside of the gastrointestinal tract, and tolerance of the ingredient using the proposed serving form.

See Steve Myers, *Probiotics, NDIs and Species Identification*, SUPPLYSIDE MARKETPLACE 3 (June 2012), *available at* http://www.accugenix.com/media/asset-probiotics-ndis-and-species-identification.pdf.
[64] *See* Myers, *supra* note 63.
[65] 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 dietary ingredient. INT'L PROBIOTICS ASS'N, EUROPEAN FOOD & FEED CULTURES ASS'N & INT'L FOOD ADDITIVES COUNCIL, POSITION PAPER (May 2011), *available at* http://www.internationalprobiotics.org/files/news/7/11.pdf.
[66] *See* Myers, *supra* note 63.
[67] Id.

- Streptococcus faecium (Enierococcus faecium)
- Streptococcus salivarius
- Streptococcus thermophilus

C. History of Safe Use

The FDA uses history of safe use to establish the safety of substances in several categories of regulated products, including GRAS substances and NDIs. While we agree that historical use should be used to establish safety in probiotics, there are several caveats to this recommendation. History of safe use should be considered only if the same target population and essentially the same dose and delivery system are to be used in the proposed use. 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.

V. Should Probiotic Foods or Dietary Supplement be Classified as Drugs and Required to go through the Drug Approval process?

A major concern relating to probiotic regulation is when and whether a researcher or manufacturer conducting research on the benefits of a probiotic product must conform to the rigorous and costly IND process. This is a question that is increasingly being asked by institutional review boards (IRBs) that are receiving applications "that propose the use of dietary supplements, foods, food-derived products regulated as dietary ingredients"[68] as part of a clinical trial.[69] NIH and the FDA may 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. The fact that the proposed research use would not increase risk to subjects in comparison to risks to consumers of products that are already legally marketed as a food may not be determinative of whether an IND is required.[70] Moreover, "there are no categorical determinations in this regard; for the same product, INDs may be required for some studies and not for others."[71]

The IND requirement has been a significant problem for some investigator-initiated researchers. Under the investigator-initiated IND process, academic or independent researchers must depend on the cooperation of the product manufacturer to obtain necessary 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.

---

[68] *See Research Involving Food or Food-Derived Products, Spices/Herbs, or Dietary Supplements*, JOHNS HOPKINS MEDICINE (Apr. 2012), http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/guidelines/ind_not_drugs.html.

[69] 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. *See* 21 C.F.R. § 312.2 (2013).

[70] *See* JOHNS HOPKINS MEDICINE, *supra* note 68.

[71] *Id.*

A. Probiotics and Research Endpoints

Whether or not the proposed research is subject to an IND often depends on the studied indication. If a clinical research trial measures an outcome that relates to a substance's ability to diagnose, cure, mitigate, treat, or prevent disease, and the study will be used to make claims about the substance (e.g., substance × lowers blood pressure), the FDA will consider the substance a drug. The measured outcomes are considered "disease endpoints". Use of a disease endpoint has two important consequences: first, the research becomes drug research[72] and is therefore subject to higher levels of scrutiny and human subject 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.[73] Because probiotics generally promote health and wellness, many of the studies that have been undertaken on probiotics have been conducted using endpoints that FDA considers disease endpoints, thereby rendering them drugs. This is the case even if the product has been marketed as a food. The traditional definition of "drug" does not consider the use of food products to promote a healthy balance of the microbiota, the role of such products in generally healthy individuals, or the role of food in promoting health.

The implications of this are illustrated by a 2010 study which tested a fermented milk's ability to reduce the incidence of common infectious diseases (CIDs) in healthy children in day care centers.[74] Even though the study documented a decreased incidence rate for 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. If the manufacturer of the fermented milk made a claim that referred to this study, the milk would be considered a drug.

Some believe this result to be over-regulation and assert that it will have a chilling effect on research designed to test the therapeutic properties of probiotic foods and dietary substances. The lack of such research may deprive patients and consumers of beneficial information. The ability to conduct research with disease endpoints would provide greater opportunities to conduct basic research on probiotic foods and dietary supplements. However, researchers and manufacturers are concerned that, under the current regulatory framework, studies with disease endpoints will take their products into the drug category and out of the food and dietary supplement market where they believe most of these products belong.

Compounding this problem is the paucity of non-disease endpoints. It is challenging to measure health maintenance, healthy balance of microbiota, or improvement in wellness of a healthy person. Some researchers have suggested that the focus of probiotic studies could be in measurement of homeostasis, a term referring to stability in physiological parameters.[75]

---

[72] *See* Fred Degnan, *Clinical Studies Involving Probiotics: When FDA's Investigational New Drug Rubric Applies and When it May Not*, 3 GUT MICROBES 1 (2012). *See also* JOHNS HOPKINS MEDICINE, *supra* note 68.
[73] *Id.* As discussed *infra*, notes 114–125 and accompanying text, there are narrow exceptions to this prohibition.
[74] D. Merenstein et al., *Use of a Fermented Dairy Probiotic Drink Containing Lactobacillus casei (DN-114 001) to Decrease the Rate of Illness in Kids: the DRINK Study, a Patient-Oriented, Double-Blind, Cluster-Randomized, Placebo-Controlled, Clinical Trial*, 64 EUR. J. CLINICAL NUTRITION 669 (2010).
[75] L. Michael Romero et al., *The Reactive Scope Model – A New Model Integrating Homeostasis, Allostasis, and Stress*, 55 HORMONES & BEHAV. 375, 376 (2009).

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. According to an article co-authored by Tancredi,[76] one challenge to demonstrating the value of this approach is to identify appropriate biomarkers that can be studied. The article notes that 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.[77]

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.[78] 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.[79]

B. Probiotics as Live Biotherapeutic Products Subject to IND Requirements

In addition to requiring INDs for research with disease endpoints, FDA considers probiotics to be live biotherapeutic products (LBPs) subject to IND requirements. In 2010, the FDA published draft FDA guidance[80] that appeared to define all probiotics as live biotherapeutic products (which are drugs) and therefore would require all probiotics—including ones being marketed as foods or dietary supplements—to go through the IND process. This appeared to be the case even if the product manufacturer intended the research to test claims that are legal for foods (i.e., structure/function (S/F), risk reduction, or medical food claims). This articulation of the law is troubling to many stakeholders and may be inappropriate and inaccurate under current law given that, historically, assignment of a particular use of a substance or microorganism was properly based on the claims made, rather than on the nature of the research supporting those claims.

In February 2012, this concern was addressed to a certain degree by the FDA. In final guidance relating to clinical trials with LBPs, the FDA stated that “[t]his guidance … does not apply to products lawfully marketed as conventional foods or dietary supplements that

---

[76] Mary Ellen Sanders et al., *Health Claims Substantiation for Probiotic and Prebiotic Products*, 2 GUT MICROBES 127 (2011).
[77] *Id.*
[78] *Id.*
[79] *Id.*
[80] *See* Draft Guidance for Industry: Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information, 75 Fed. Reg. 63,188 (Oct. 14, 2010).

are proposed for investigation solely to evaluate an LBP's use in affecting the structure or any function of the body."[81] As such, it appeared that an IND would not be required for studies of foods and dietary supplements that are conducted to make S/F claims. However, this impression was dispelled in September 2013 when the FDA published guidance relating to INDs and human research studies.[82] In this guidance, the FDA clearly indicated that an IND would be required for clinical investigations to substantiate both drug *and* S/F claims. Under the new guidance, it seems that the only food studies that will be allowed by the FDA to substantiate an S/F claim are those that relate to the food's taste, aroma, and nutritive value.[83] The guidance notes

> [i]f an edible product that might otherwise be a conventional food is intended for a use other than providing taste, aroma, or nutritive value, such as blocking the absorption of carbohydrates in the gut, that product becomes a drug because the primary purpose of consuming it has changed. In other words, the product is no longer being consumed as a food—primarily for taste, aroma, or nutritive value—but used as a drug for some other physiological effect.[84]

This new guidance raises multiple concerns. The first is that it appears to support a broader interpretation of the definition of drug than has been used in the past. As noted earlier, the definition of drug is any article "(other than food) intended to affect the structure or any function of the body of man or other animals."[85] The "other than food" construction has typically been interpreted to mean that S/F claims are acceptable for foods and, in fact, most probiotic products now on the US market make S/F claims.[86] Although the guidance relates to human research and does not by its terms affect product claims, one expert noted that "if you can't do the research to support a product claim, you'll never be able to make a product claim."[87] Based on FDA's most recent guidance, it appears that the only avenue to study the effect of food on the structure and/or function of the human body is through its taste, aroma or nutritive value. So, for example, under this guidance, a study could not be used to show increased balance of gut microflora (a typical S/F claim used currently) because such a study does not relate to the taste, aroma, or nutritive value of the food. Further, critics have noted that the guidance will make it difficult to conduct studies of novel medical foods by requiring that research on medical food be conducted under an IND.[88]

---

[81] *See* FDA, GUIDANCE FOR INDUSTRY, *supra* note 44.

[82] FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS)—DETERMINING WHETHER HUMAN RESEARCH STUDIES CAN BE CONDUCTED WITHOUT AN IND (Sept. 2013), *available at* http://www.fda.gov/downloads/Drugs/…/Guidances/UCM229175.pdf [hereinafter IND GUIDANCE FOR INDUSTRY].

[83] *Id.*

[84] *Id.*

[85] Food, Drug & Cosmetic Act of 1938 (FDCA), Pub. L. No. 75-717, Sec. 201(g), 52 Stat. 1040, 1041 (codified at 21 U.S.C. § 321(g)).

[86] Although the 2013 guidance references *Nutrilab v. Schweiker*, 713 F.2d 335 (7th Cir. 1983), as support for its narrow interpretation of the "other than food" exception, at least one commentator has noted that FDA's interpretation "is in direct conflict with the opinion of the Seventh Circuit as well as subsequent case law that relied on *Nutrilab*." Wes Siegner & Paul M. Hyman, *Medical Food Mumbo Jumbo: Confusing FDA Guidance Documents Will Discourage Medical Food Development*, FDA LAW BLOG (Sept. 18, 2013), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/09/medical-food-mumbo-jumbo-confusing-fda-guidance-documents-will-discourage-medical-food-development.html. Siegner and Hyman also note in their blog that one court specifically used the *Nutrilab* case to support the proposition that the "other than food" exception "suggests that Congress did not want to inhibit the dissemination of useful information concerning a food's physiological properties by subjecting foods to drug regulation …." *Id.* (quoting Am. Health Prods. Co., Inc. v. Hayes, 574 F. Supp. 1498, 1507 (S.D.N.Y. 1983).

[87] Mary Ellen Sanders, *Human Research, Functional Foods and the FDA*, CAL. DAIRY RES. FOUND. BLOG (Oct. 20, 2013), http://cdrf.org/2013/10/20/human-research-functional-foods-and-the-fda/.

C. The "Lock-In" Problem

A further concern raised by the 2013 guidance relates to the statutory "lock in" provision created by section 912 of the FDA Amendments Act of 2007, which added subsection 301(ll) to the FDCA, prohibiting the sale of food to which any of the following have been added: a drug, licensed biological product, or biological product for which "substantial clinical investigations" have been instituted. From a historical perspective, this marks a significant change in the regulation of food and drugs. 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. This "lock in" provision potentially prohibits the marketing of a food where the food is first studied under an IND, even if the study is ultimately intended to support food, rather than drug, use of the product.[89]

The 2013 guidance makes specific reference to subsection 301(ll) and warns that those who conduct or sponsor research intended to support labeling claims for conventional foods or dietary supplements should be aware that subsection 301(ll) may "restrict the marketing of products containing substances that have been the subject of 'substantial clinical investigations' whose existence has been made public."[90] The guidance offers the suggestion that "[m]arketing the substance of interest [as a dietary supplement or food] before seeking an IND or beginning any clinical investigations preserves the option to continue to market the substance in those forms after substantial clinical investigations have been instituted and their existence has been made public." However, as noted by commentators, the FDA has still not defined "substantial," and this subsection may inhibit manufacturers and researchers from pursuing research that studies the role of foods in preventing disease, improving health, or treating disease, because it may prevent them from selling the product as a food for general consumption rather than as a drug with a more limited distribution.[91]

D. Recommendations

In order to address concerns expressed by probiotic researchers and manufacturers, the FDA should adopt clear guidelines for when an IND is or is not required. We recommend, consistent with current law, that if proposed research is to support the development of a new drug, then an IND should be required. However, no IND should be required for research on probiotic products to evaluate the following claims: S/F claims, food for special dietary use claims, disease management claims for "medical foods" pursuant to the Orphan Drug Act

---

[88] Siegner & Hyman, *supra* note 86. *See also* Letter to FDA signed by 62 food science and nutrition academics who wrote that the guidance would "have a paralyzing effect on clinical research in the U.S. and stifle innovation and product development" in food research. Letter from Prof. Connie Weaver, Purdue Univ., et al., to Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA (Nov. 6, 2013), *available at* http://www.hpm.com/pdf/blog/FDA%20IND%20Connie%20Weaver%20letter.pdf.

[89] *See* Sanders, *supra* note 87.

[90] *See* FDA, IND GUIDANCE FOR INDUSTRY, *supra* note 82.

[91] Due to extensive concerns and comments raised about the guidance, on January 16, 2014, the FDA took the unusual step of announcing that the agency would reopen the comment period during which members of the public could submit comments on proposed guidance for an additional 60 days. *See FDA to Reopen Comment Period on the Cosmetics and Food Portions of Its Guidance on Determining if Human Research Studies Require an Investigational New Drug Application*, FOOD & DRUG ADMIN. (Jan. 16, 2014), http://www.fda.gov/Food/NewsEvents/ConstituentUpdates/ucm381474.htm. The comment period was only reopened for subsections of the final guidance that address the applicability of the IND regulations to clinical research studies involving cosmetics and foods (including dietary supplements). *See* 79 Fed. Reg. 7204-01 (Feb. 6, 2014) (opening the comment period until Apr. 7, 2014).

Amendments of 1988, or health claims (disease risk reduction claims) as provided for in the Nutrition Labeling and Education Act (NLEA) of 1990. The FDA should base assignment of a substance or microorganism to a particular category on the claims made, rather than on the nature of the research supporting those claims, e.g., the endpoints of the study. Furthermore, the S/F 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 an S/F or other non-drug claim. This assumes that the study will be conducted pursuant to the usual protections for study participants such as IRB approval and informed consent. In addition, no IND should be necessary for safety studies being conducted to support a GRAS determination or NDI submission.

The concerns relating to research endpoints lead to several recommendations. First, research with disease outcomes 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 for 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 in probiotics research, but one that is particularly difficult for probiotics because many endpoints tested for probiotics do not have validated biomarkers. Furthermore, the FDA should encourage the study of 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.

We further recommend that FDA adopt guidelines establishing an abbreviated IND process that would allow researchers, in certain situations, to bypass Phase 1 clinical safety studies.[92] Probiotics would be eligible for such an abbreviated IND process only if adequate evidence of safety in the target population at the desired use levels is available. Under this proposal, for probiotics in the abbreviated IND category: (1) 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; and (2) if the sponsor wishes to conduct a study to support a therapeutic benefit for an at-risk population, then the FDA must make a determination if the available information on safety is suitable for this new target population.

The abbreviated IND process application would include an introductory statement and general investigational plan;[93] a clinical study protocol for which IRB approval would be required; a summary of clinical safety data and/or in-market exposure data (e.g., material time and extent[94]); reference to GRAS specifications or a copy of the NDI notification[95] as

[92] *See, e.g.*, Hoffmann et al., *supra* note 12, at 314.
[93] Such a plan is described in 21 C.F.R. § 312.23(a)(3) (2013).
[94] 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

appropriate; documentation that the strain being investigated is GRAS or the subject of an NDI; and an FDA-approved certificate of analysis.[96]

VI. What Types of Product Characterization Requirements Are Appropriate for Probiotics?

A. Current Guidance and its Application to Probiotics

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."[97] 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.

The FDA uses different characterization standards for the different categories of regulated products. According to our research, the agency has not set forth characterization requirements specifically for probiotics either at the research or manufacturing stage.[98] However, as mentioned above, in 2012 the agency published guidance that sets forth requirements for chemistry, manufacturing, and controls (CMC) for early clinical trials using live biotherapeutic products (LBP).[99] Without using the word "probiotic," the language used in the guidance and its definition of LBP indicate that the FDA believes that probiotics fit within the LBP category.[100] This is problematic as the characterization requirements in the LBP guidance may not be appropriate for probiotics, even if the probiotic meets the definition of a drug and falls squarely within the parameters of the guidance. The guidance provides that:

OTC to a material extent and for a material time. Second, if the drug product is found eligible, the 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 use(s). *See* CENTER FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: TIME AND EXTENT APPLICATIONS FOR NONPRESCRIPTION DRUG PRODUCTS (Sept. 2011), *available at* http://www.fda.gov/downloads/Drugs/…/Guidances/ucm078902.pdf.

[95]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 Feb. 10, 2014).

[96]The FDA has not published a formal definition of Certificate of Analysis (COA), but notes in the final rule relating to good manufacturing practices for dietary supplements that a COA is a "document, provided by the supplier of a component prior to or upon receipt of the component that documents certain characteristics and attributes of the component." *See* 72 Fed. Reg. 34,752, 34,834 (June 25, 2007).

[97]Célia Lucia Perreira et al., *Probiotics: from Origin to Labeling from a European and Brazilian Perspective*, *in* PROBIOTICS & HEALTH CLAIMS, *supra* note 21, at 75, 79.

[98]However, in January 2012, the U.S. Pharmacopoeia (USP) released draft standards—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 Food Chemicals Codex. News Release, Critical Quality Considerations for Probiotics and Other Microbial Food Cultures Offered in New Draft FCC Standards (Jan. 3, 2012), *available at* http://us.vocuspr.com/Newsroom/ViewAttachment.aspx?SiteName=USPharm&Entity=PRAsset&AttachmentType=F&EntityID=109245&AttachmentID=89eaa2c7-02d6-453f-b16c-94e7d2592e4a. While still untested, these new standards may be helpful in the characterization of probiotics.

[99]*See* FDA, GUIDANCE FOR INDUSTRY, *supra* note 44.

[100]According to the guidance, "[a live biotherapeutic product] LBP … is a biological product that: 1) contains live microorganisms, such as bacteria; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine." *Id.* at 3.

> 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 the following:
>
> - 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
> - 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.[101]

These requirements are not adequately customized for probiotics. Specifically, the current LBP guidance requires a summary of the phenotype or genotype of the strain with specific attention to the genetic loci that may indicate activity or potency. It is very difficult to pinpoint the genetic loci for probiotics, especially in early clinical trials. Furthermore, 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 DNADNA 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.[102]

A specific and unique application of probiotics—fecal microbiota transplantation (FT) or fecal transplant—is useful to understand the complexity of characterizing probiotics. FT is an existing treatment that involves the process of transplantation of fecal material (including the microbiota) from a healthy individual into a recipient as a treatment for patients suffering

[101] *Id.* at 7–8.
[102] *See* Perreira et al., *supra* note 97, at 79.

from various severe intestinal disorders such as *Clostridium difficile* infection. If the stool contents could be made into a tablet, capsule or suppository for ingestion,[103] it would raise the question of whether it would, or could, meet the FDA standards for characterization. The current standards would be difficult to meet because it would likely be impossible to identify and characterize to current standards all the microbes in the tablet, capsule or suppository, therefore causing the "microbial limit" test in the guidance to be exceeded. Furthermore, the chemical and microbiological components of the formulation would clearly vary from batch to batch and therefore run afoul of the requirement for consistency in product composition. In a recent article, Olle discusses the challenges stating that:

> [a]lthough CBER's [LBP] guidelines seem clear for products based on defined compositions of live organisms, it is still unclear how these guidelines will be applied to FT. Technically, FT meets the definition of LBPs, but in practice, the guidelines are ill-suited to this type of product. Reproducibly obtaining well-characterized CMP-grade materials for trials according to the criteria outlined by CBER would require a titanic effort outside the reach of current technologies (e.g., meeting the microbial test limits, would not be possible.)[104]

The FDA acknowledged the inadequacy of current IND requirements to evaluate FTs when it did a turnaround in 2013 regarding the need to seek FDA approval prior to performing the treatment. In May 2013, FDA announced that physicians performing FTs would need to seek an IND in advance of using the procedure on patients.[105] FDA justified this position based on the concept that fecal microbiota falls within the agency's definition of a biologic and therefore requires an IND before it can be used in humans.[106] However, in guidance released in July 2013, FDA acknowledged that applying IND requirements might make FT unavailable to patients who could benefit from the procedure and therefore agreed to "to exercise enforcement discretion regarding the IND requirements" for the use of FT to treat *C. difficile* infection not responding to standard therapies.[107] FDA also noted that an "alternative regulatory approach" may be needed to ensure the widespread availability of FT.[108]

B. 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

---

[103] Current FT delivery methods include endoscopic procedures and enemas. Faith Rohlke & Neil Stollman, *Fecal Microbiota Transplantation in Relapsing Clostridium Difficile Infection*, 5 THERAPEUTIC ADVANCES IN GASTROENTEROLOGY 403 (2012).

[104] Olle, *supra* note 8, at 310.

[105] *See* Letter from Karen Midthun, Dir., Ctr. for Biologics Evaluation and Research, to Dr. C. Richard Boland et al., Am. Gastroenterological Soc'y (Apr. 25, 2013), *available at* http://highroadsolution.com/file_upload_2/files/fda+response+letter+to+fmt+inquiry.pdf (noting in response to inquiry by gastroenterologists that fecal microbiota for transplantation fell within the definition of drug and "would be an Investigational New Drug for which an Investigational New Drug application must be submitted"); *see also* Joyce Frieden, *FDA Backs Down on Fecal Transplant Rules*, MEDPAGE TODAY, July 22, 2013, http://www.medpagetoday.com/Gastroenterology/GeneralGastroenterology/40628.

[106] *See* Frieden, *supra* note 105.

[107] *See* U.S. FOOD & DRUG ADMIN., 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 2 (July 2013), *available at* http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM361393.pdf.

[108] *Id. See also* Mark B. Smith et al., *How to Regulate Faecal Transplants*, 506 NATURE 290 (2014) (noting that "the long-term status of [FT] for *C. difficile* infection is unresolved, and regulatory policy is complicating research into the exploration of FMT for other conditions, such as inflammatory bowel diseases or obesity.").

technologies has enormously increased sequencing capability, significantly reducing sequencing costs."[109] Given these new techniques and the reduction in their costs, current genome sequencing technology should be required, as it allows for whole genome analysis and could serve as the standard for characterization.

In terms of developing characterization requirements for probiotics, the FDA should consider the following suggestions:

- Characterization requirements should be developed for probiotics in foods and dietary supplements, as well as probiotics in drugs. Differences between the requirements for both groups should be clearly set forth by the FDA.
- The agency 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 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 technologies and must be specific enough to allow for proper/precise identification of strains.
- 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, and in what quantity. It should also include testing for potential contaminants.[110]
- Regulators should clarify the degree to which probiotics are characterized in different contexts, i.e., in labeling, NDI notification, or development of good manufacturing practices.[111]

VII. Are Current Claim Regulations Appropriate for Probiotics and, If Not, How Might They Be Improved?

A. Jurisdiction over Claims

For health-related products, both the FDA and the FTC regulate what manufacturers can say about a product. Furthermore, the claims a manufacturer makes about a product also relate to

[109] Perreira et al., *supra* note 97, at 81.
[110] *See* Patricia Hibberd, Recommendations for Modifications to the FDA Regulatory Framework for Probiotics (on file with the authors).
[111] Note that some of these recommendations are already in place for certain NIH-funded studies.

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. Because different FDA regulatory categories require vastly different degrees of scientific substantiation (and therefore investment) for claims, the issue of how claims are regulated is very complex and often controversial. As some probiotics do not squarely fit into current FDA product categories, the issue of claims regulation is further complicated and unclear.

The FDA regulates claims that appear in labeling of prescription and over-the-counter (OTC) drugs, medical devices, dietary supplements, cosmetics, and food, and claims made in advertising of prescription drugs. Labeling includes any "text or graphics" on websites where these products are sold.[112] The FTC regulates claims made in advertising of OTC drugs, foods, dietary supplements, non-restricted medical devices, and cosmetics (including TV, radio, internet and print ads).

B. FDA Claims Regulation

Products under the FDA's jurisdiction are subject to an array of differing regulatory requirements regarding permissible product claims. Claims describing the effect of a substance on the diagnosis, treatment, mitigation, cure or prevention of disease are considered drug claims.[113] These claims must be approved by FDA prior to marketing the drug. An example of a drug claim is that a product "reduces the pain and stiffness associated with arthritis."

Foods and dietary substances may make four types of claims: (1) structure/function (S/F); (2) nutrient content; (3) health; and (4) qualified health claims. S/F 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 preapproval 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 the FDA within 30 days of marketing a dietary supplement with an S/F claim. In addition, S/F 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."[114] An example of an S/F claim is: "Helps maintain normal cholesterol levels."[115] Nutrient content claims characterize nutrient levels. An example is "this product contains 40% omega-3 fatty acids, 10 mg. per cap."[116]

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, under the NLEA,

---

[112] *See* 21 CFR § 1.3 (2013) ("Label means any display of written, printed, or graphic matter," applicable to all FDA-regulated products).

[113] An exception to this is health claims, i.e., claims for reduction of risk of disease (which are a category of prevention claims). Health claims can be made for foods and dietary supplements. *See* notes 118–121 *infra*.

[114] 21 U.S.C. § 343(r)(6)(c) (2012).

[115] Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, 65 Fed. Reg. 1000 (Jan. 6, 2000) (to be codified at 21 C.F.R. pt. 101).

[116] For a full description of nutrient content claims, see *Claims that Can be Made for Conventional Foods and Dietary Supplements*, FOOD & DRUG ADMIN. (Sept. 2003), http://www.fda.gov/food/ingredientspackaginglabeling/labelingnutrition/ucm111447.htm.

Congress carved out an allowance for foods and dietary supplements wishing to make reduction of risk of disease claims.[117] Health claims for foods and dietary supplements may be approved by FDA if there is "significant scientific agreement" that the claimed relationship between the nutritional product and reduction of risk of disease is true OR on the basis of an authoritative statement by a U.S. government scientific body.[118] Under the Food and Drug Administration Modernization Act of 1997 (FDAMA), manufacturers may also make health claims for food (but not dietary supplements) if the health claim is based on an authoritative statement from a scientific body of the U.S. Government or the National Academy of Sciences.[119]

Qualified health claims require less than significant scientific agreement and must be accompanied by a disclaimer or qualifier explaining the level of scientific evidence support for the claim.[120] Manufacturers wishing to use a qualified health claim must file a petition with the FDA within 30 days of marketing a product.[121] The FDA may or may not issue a letter of enforcement discretion during that time.[122]

A unique category of foods, i.e., medical foods, has separate regulations for claims. Medical food claims are exempt from the requirement to bear nutrition labeling[123] and from the health claim and drug requirements that attend the mention of a disease relationship on a product label[124] if the product is specially formulated and processed for partial or exclusive feeding of a patient orally or by enteral tube; *intended* for dietary management of a patient when it cannot be achieved by modifying the normal diet (e.g., chronic medical needs;

---

117 *See* Pub. L. No. 101-535, 104 Stat. 2353 (codified as amended at 21 U.S.C. §§ 301, 321, 337, 343, 371).

118 The mechanism for approval for health claims was established by the NLEA and DSHEA. 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*, FOOD & DRUG ADMIN. (Jan. 2009), http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm. 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 for probiotics. A list of approved health claims appears at *Health Claims Meeting Significant Scientific Agreement*, FOOD & DRUG ADMIN, http://www.fda.gov/food/ingredientspackaginglabeling/labelingnutrition/ucm2006876.htm#Approved_Health_Claims (last visited Feb. 10, 2014).

119 Pub. L. No. 105-115, Sec. 303, 111 Stat. 2296, 2357 (codified at 21 U.S.C. § 343(r)(3)). FDAMA specifically lists the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) as scientific bodies that would satisfy the statutory requirement. FDA has also stated that the Surgeon General within the Department of Health and Human Services, the Food and Nutrition Service, the Food Safety and Inspection Service, and the Agricultural Research Service within the Department of Agriculture, may serve as qualified "scientific bodies." *See Guidance for Industry: Notification of a Health Claim or Nutrient Content Claim Based on an Authoritative Statement of a Scientific Body*, FOOD & DRUG ADMIN.(July 11, 1998), http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm056975.htm.

120 Qualified health claims (QHCs) were created by judicial rulings over the past decade and a half. In *Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999)*, the plaintiffs challenged the 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. *Id.* at 658–60. Based on this ruling, the FDA created the QHC. An example of a QHC is the following: "One small study suggests that chromium picolinate may reduce the risk of insulin resistance … FDA concludes, however, that the existence of such a relationship … is highly uncertain." There are currently no qualified health claims for any probiotic product.

121 21 U.S.C. § 343(r)(6)(c) (2012).

122 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. *See, e.g., Qualified Health Claims: Letter of Enforcement Discretion – Chromium Picolinate and Insulin Resistance*, FOOD & DRUG ADMIN. (Aug. 25, 2005), http://www.fda.gov/food/ingredientspackaginglabeling/labelingnutrition/ucm073017.htm.

123 *See* 21 C.F.R. § 101.9(j)(14) (2013).

124 *See* 21 C.F.R. § 101.14(f) (2013).

limited/impaired capacity to ingest, digest, etc.; other special medically determined nutrient needs); providing nutritional support to manage unique nutrient needs resulting from a specific disease/condition (per medical evaluation); *intended* for use only under medical supervision; and *intended* only for patients receiving active/ongoing medical supervision.[125]

C. FDA Labeling Requirements

The FDA has the responsibility for administering federal food labeling requirements in accordance with the FDCA.[126] The Act prohibits labeling that, among other things, is false or misleading or that fails to list the amounts of certain ingredients.[127] 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.[128] The Nutrition Labeling and Education Act (NLEA) of 1990[129] "requires most foods to bear nutrition labeling and requires food labels that bear nutrient content claims and certain health messages to comply with specific requirements."[130] The FDA stipulates that all food products must have a principal display panel that contains the statement of identity (name of the food) and the net quantity statement (amount of product).[131] Food labels must meet FDA standards but do not require preapproval.[132]

Labeling of dietary supplements is covered by DSHEA. DSHEA amended the FDCA by defining "dietary supplements" and adding specific labeling requirements for them, as well as optional labeling statements. 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. Currently, probiotic food and dietary supplement 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.

---

[125] *See* 21 C.F.R. § 101.9(j)(8) (2013). All other food labeling requirements (e.g., statement of identity, listing of ingredients, declaration of net weight, nutrient content claim restrictions, etc.) and all food safety standards apply to medical foods. *See* FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: FREQUENTLY ASKED QUESTIONS ABOUT MEDICAL FOODS 5–6 (2d ed. 2013), *available at* http://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/MedicalFoods/UCM362995.pdf.

[126] 15 U.S.C. § 1453 (2012).

[127] 15 U.S.C. § 1452 (2012).

[128] U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-08-597, FOOD LABELING: FDA NEEDS TO BETTER LEVERAGE RESOURCES, IMPROVE OVERSIGHT, AND EFFECTIVELY USE AVAILABLE DATA TO HELP CONSUMERS SELECT HEALTHY FOODS 2 (2008), *available at* http://www.gao.gov/assets/290/280466.pdf.

[129] Pub. L. No. 101-535, 104 Stat. 2353 (codified as amended at 21 U.S.C. § 301, 321, 337, 343, 371).

[130] *See* FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: A FOOD LABELING GUIDE 4 (Sept. 1994, rev. Apr. 2008, rev. Oct. 2009, rev. Jan. 2013), *available at* http://www.fda.gov/downloads/Food/GuidanceRegulation/UCM265446.pdf.

[131] 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, then it need not be declared on the label. *Id.* at 17–18.

[132] To determine the nutrient levels in foods, however, companies may develop or use databases, and the databases may be submitted voluntarily to the FDA for review. *Id.* at 31.

When FDA approves a New Drug Application, that approval includes the drug labeling.[133] This preapproval mechanism gives the FDA greater control over the labeling than it has for foods and dietary supplements. Under the FDA's prescription drug labeling guidelines, specific information must be included on the label or a package insert. A drug label must provide information about the safe and effective use of the drug that is informative and accurate; contain no promotional, false, or misleading claim; and make no implied claims or suggestions for use if evidence of safety or effectiveness is lacking.

D. Impact of FDA Claim Regulation on Probiotic Products

1. Confusion among Health Claims, Structure-Function Claims and Drug Claims—

An issue for probiotic manufacturers is what claims can be made about probiotic products and the substantiation required for each type of claim. Because most probiotics appear in foods and dietary supplements, there are significant limits on what claims can be made without crossing the line into the heavily regulated drug arena. Moreover, because consumers do not perceive health claims as better or more substantive than S/F claims,[134] 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. Anecdotally, manufacturers are reluctant to avail themselves of the process in place for approval of authorized health claims because of the amount of time and resources such a process takes and a lack of understanding of the FDA's guidance in this area. This is borne out by the fact that the FDA has only approved 12 health claims by regulation to date.[135]

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 complicated and sometimes difficult to discern. This confusion is in part a result of the origin of this type of claim. As stated above, the statutory definition of a drug in the FDCA includes an article intended to diagnose, cure, mitigate, treat or prevent disease.[136] 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."[137] The phrase "other than 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.[138]

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,[139] the guidance has not always been helpful. It is often difficult

---

[133] In the case of products subject to an OTC monograph, described *infra* note 175 and accompanying text, because the monograph includes approved claims and approved labeling, these products can enter the market without preapproval by the FDA if the claims and labels are allowed by the monograph.

[134] GEN. ACCOUNTING OFFICE, RCED-00-156, IMPROVEMENTS NEEDED IN OVERSEEING THE SAFETY OF DIETARY SUPPLEMENTS AND 'FUNCTIONAL FOODS' (2000), *available at* http://www.gao.gov/assets/230/229289.pdf.

[135] *See Health Claims Meeting Significant Scientific Agreement*, *supra* note 118.

[136] FDCA, sec. 201(g)(1) (codified at 21 U.S.C. § 321(g)).

[137] *Id.*

[138] *See supra* notes 86–88 and accompanying text.

to distinguish drug claims from S/F claims for dietary supplements and foods. Examples of the difficulty in discerning where a claim falls are illustrated in Table 1, below.

2. Difficulty Conducting Research for Structure/Function Claims—Despite the fact that S/F claims have typically been considered less regulated and thus easier to make, some industry representatives believe that it is increasingly difficult 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.[141] 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."[142] 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.[143] Some have argued that in doing this, the FDA overreached its statutory authority under DSHEA.[144] This is another area in which more clarity is required, especially given the fact that any prohibition on "implied" statements requires judgment calls that probiotic manufacturers may not be able or willing to make.

3. Prevention versus Risk Reduction Claims—A complex area of the law that impacts regulation of probiotics is the difference between a disease prevention claim and a risk reduction claim and how these claims may be handled differently by the FTC and the 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 developing a disease, but it becomes a drug claim, rendering the product an unapproved drug, if it suggests mitigation, cure or treatment of an existing disease. With the exception of classical nutrient deficiency diseases, a claim that a food may prevent future disease may also render a product an unapproved drug. For example, the express claim that a food product prevents cardiovascular disease (CVD) is a drug claim, while the express claim that a food reduces the risk of development of CVD is a health claim if it is authorized by the Secretary under the provisions of the NLEA. This distinction allows food manufacturers to,

---

139 *Guidance for Industry: Structure/Function Claims, Small Entity Compliance Guide*, FOOD & DRUG ADMIN.(Jan. 9, 2002), http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/DietarySupplements/ucm103340.htm; *Claims That Can Be Made for Conventional Foods and Dietary Supplements*, FOOD & DRUG ADMIN. (Sept. 2003), http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm111447.htm.

141 FDCA, sec. 201(g)(1) (codified at 21 U.S.C. § 321(g)).

142 *Dietary Supplement Health & Education Act* of 1994 (DSHEA), FDCA Sec. 413(c), 21 U.S.C. § 350(b) (2012).

143 *Guidance for Industry: Structure/Function Claims, Small Entity Compliance Guide*, *supra* note 139.

144 *See, e.g.*, *Dietary Supplement Health and Education Act: Is the FDA Trying to Change the Intent of Congress?, Oversight Hearing Before the H. Comm. on Government Reform*, 106th Cong. (1999), *quoted in* William D. McCants, *Take a Label Claim, and Pay Me in the Morning: A Challenge to FDA's Argument that its Final Rule (Jan. 2000) on Structure/Function Claims for Dietary Supplements Does Not Constitute a Compensable Regulatory Taking Under the Fifth Amendment*, HARV. LEGAL ELEC. DOCUMENT ARCHIVE (LEDA) PAPER (Mar. 2000), *available at* http://dash.harvard.edu/bitstream/handle/1/8965592/McCants,_William_D..html?sequence=1.

in effect, make reduction of risk claims but be subject to a lower standard of evidence than that imposed on drug manufacturers wishing to make prevention or reduction of risk claims. This might happen when, for example, a drug manufacturer has an existing product that already makes a claim regarding the product's ability to mitigate, cure or treat a disease and the manufacturer wants to add a prevention or risk reduction claim. Because the product is already in the drug category, the manufacturer would have to meet the claim substantiation standard for a prevention claim (rather than the arguably lower standard that a food would have to meet to make a reduction of risk of disease claim).[145]

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. This difficulty is exacerbated by the fact that many S/F claims are based on small, preliminary unpublished studies or 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.

4. **Probiotics as Medical Foods—**The medical foods category has been mentioned as 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. The 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 the FDA's narrow view of this category, without modification it is likely not a useful avenue for regulation for probiotics outside of those probiotics that currently fit into the regulations noted above.

E. FTC Regulation of Advertising Claims

The FTC rules regarding substantiation for health-related product claims are different from those of the FDA. Section 5 of the FTC Act prohibits "unfair or deceptive acts or practices in or affecting commerce,"[146] and Section 12 of the FTC Act 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.[147]

---

[145]Richard L. Cleland (personal communication, December 24, 2013).

[146]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. Deceptive advertisements are those that include false claims, fail to disclose material facts, or make unsubstantiated claims. In determining if an advertisement meets FTC requirements, the FTC interprets them from the perspective of a reasonable consumer in the target audience. As advertisements may have more than one reasonable interpretation, where an ad conveys more than one meaning, only one of which is misleading, a seller is liable for the misleading interpretation even if non-misleading interpretations are possible. An advertisement will be considered misleading if a significant number of reasonable consumers, which can be as low as ten percent, believe the misleading claim. Sec. 5 of the Federal Trade Commission Act (codified at 15 U.S.C. § 45).

[147]15 U.S.C. § 52 (2012). For more information about FTC regulation of health claims, see online webinar by Working Group Member Richard Cleland (Bureau of Consumer Protection, Federal Trade Commission) prepared for the Working Group at http://www.law.umaryland.edu/programs/health/events/probiotics/claims_webinars.html.

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.[148] 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 product
- the consequences of a false claim
- 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.[149]

These principles apply to foods, dietary supplements, and drugs and claims that would be considered by the FDA to be S/F, health claims, qualified health claims or drug claims.[150] 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. 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.[151] 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. It appears from recent FTC enforcement activity that to meet this standard 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.[152] For claims that relate to prevention or reduction of risk of a health-related problem, the FTC has allowed evidence other 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.

In general, the FTC gives great deference to an FDA determination of whether there is adequate support for a health claim.[153] Nonetheless, the FTC's Enforcement Policy Statement on Food Advertising notes that there may be certain limited instances when a

---

[148] FTC Policy Statement Regarding Advertising Substantiation, Appended to Thompson Med. Co., 104 F.T.C. 648, 839 (1984), *aff'd*, 791 F.2d 189 (D.C. Cir. 1986), *available at* http://www.ftc.gov/bcp/guides/ad3subst.htm.

[149] *Id.*

[150] *See* Memorandum of Understanding Between the Federal Trade Commission and the Food and Drug Administration, MOU 225-71-8003 (1971), *available at* http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm115791.htm.

[151] BUREAU OF CONSUMER PROTECTION, FTC, DIETARY SUPPLEMENTS: AN ADVERTISING GUIDE FOR INDUSTRY(2001), *available at* http://business.ftc.gov/sites/default/files/pdf/bus09-dietary-supplements-advertising-guide-industry.pdf.

[152] Note that S/F 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* Heimbach, *supra* note 18, at S123.

[153] BUREAU OF CONSUMER PROTECTION, *supra* note 151. The FDA and FTC work under a memorandum of understanding that sets forth their respective responsibilities for "preventing injury and deception of the consumer." *See* Memorandum of Understanding, *supra* note 150.

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.[154]

An area of concern in relation to FTC regulation of probiotics is the degree of substantiation that is required to make health-related claims. Manufacturers could run into trouble with FTC regulators for using studies that the FTC considers inadequate to support the claim at issue, in that the study related to a different product, different dosage, different target population, or inappropriate endpoint for the claim.[155]

While the distinction between disease prevention and risk reduction claims has been largely settled in the context of the FDA oversight of claims, the distinction between prevention and reduction of risk claims is less clear under the FTC Act. NLEA did not amend the FTC Act, and therefore the 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 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."[156] The standard allows for much flexibility on the part of the FTC and generally requires differing levels of evidence for different types of claims. There is no fixed formula for the number or type of studies required, sample size or study duration. Historically, the 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.

The FTC has not historically followed the FDA's approach to regulation of health claims.[157] However, that practice may be changing as evidenced by two actions against probiotic food manufacturers. 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.[158] These statements, according to the 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 agreed to a consent order that was signed in May, 2010.[159] The consent order prohibited Nestlé HCN from making claims that a product prevents or reduces the risk of upper respiratory tract infections (URTIs) "unless the FDA has issued a regulation

---

154 *See Enforcement Policy Statement on Food Advertising*, FED. TRADE COMM'N (May 1994), http://www.ftc.gov/bcp/policystmt/ad-food.shtm.
155 *See* BUREAU OF CONSUMER PROTECTION, *supra* note 151.
156 *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)).
157 *Id.* at 66.
158 Complaint at 6–7, *In re* Nestlé Healthcare Nutrition, Inc., No. C-4312 (FTC Jan. 18, 2011). All the pleadings and orders related to this case are available at http://www.ftc.gov/os/caselist/0923087/index.shtm.
159 Agreement Containing Consent Order at 4, *In re* Nestlé Healthcare Nutrition, FTC No. 092-3087 (FTC May 18, 2010), http://www.ftc.gov/sites/default/files/documents/cases/2010/07/100714nestleorder.pdf.

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."[160] The FTC considers this "significant scientific agreement" standard to be what "experts in the field of diet-disease relationships would consider reasonable substantiation for an unqualified health claim."[161] Going beyond the FTC Enforcement Policy Statement, the FTC required Nestlé HCN to obtain FDA preapproval *before* it could make a URTI risk-reduction claim for its products, because this preapproval would "facilitate compliance with the order."

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."[162]

In further action, in 2010, the 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 probiotic products, 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. Dannon agreed to cease making such claims for these two products.[163] These actions on the part of the FTC may foreshadow FTC's leaning toward a higher standard for making health claims.[164]

F. Probiotic Product Labeling and Claim Recommendations

1. Labeling Recommendations—Labeling of probiotic products should include additional information than that currently required for other foods and dietary supplements. For example, 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.[165] Manufacturers of probiotic products should also be required to specify the number of live microbes of each strain that the

---

[160]Nestle Healthcare Nutrition, Inc.; Analysis of Proposed Consent Order to Aid Public Comment, 75 Fed. Reg. 42,752, 42,752 (July 22, 2010).

[161]U.S. FTC, ENFORCEMENT POLICY STATEMENT ON FOOD ADVERTISNG (May 1994), *available at* http://www.ftc.gov/bcp/policystmt/ad-food.shtm.

[162]Agreement Containing Consent Order, *supra* note 159, at 4.

[163]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, filed in January 2008, 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/fi-yogurt-settlement19.

[164]At least one commenter on the Nestlé HCN consent order characterized the requirements on the manufacturer as an "unusually high standard" for making claims. *See* Jeff Gelles, *Bursting Nestlé Boost's Bubble on 'Probiotic' Claims*, PHILLY.COM (July 14, 2010), http://www.philly.com/philly/blogs/consumer/FTC_bursts_BOOSTs_bubble_on_probiotic_claims.html.

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.

For dietary supplements, DSHEA requires dietary supplement manufacturers to have substantiation of label claims and to notify the FDA, within thirty days after first marketing a product with a statement of nutritional support, that such a statement is being made. Anecdotally, some members of the WG noted that, in practice, the FDA has not requested this substantiation. The FDA should do so for both probiotic supplements and 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.[166] Finally, 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.[167] These guidelines recommend the inclusion of the following information:

- Colony Forming Units count or other appropriate measure of live bacteria at the time of expiration (guaranteed minimum) of the product.
- Storage conditions: Specific directions about the conditions under which the probiotic-containing product must be maintained in order to ensure viability and potency.[168]
- Lot number or production code on the product containers.
- 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 included on the label.[169]
- Contact information for the manufacturer, including an address or a telephone number that consumers can call if they have any questions or concerns.[170]
- Directions for suggested usage.

2. Probiotics Monograph—The lack of prior approval for many claims made by food and dietary supplement manufacturers creates an opportunity for false, misleading and unsubstantiated claims. A recommendation that may streamline the number of claims that a manufacturer can make and provide for a more efficient oversight process of claims is a

---

[165] INT'L SCIENTIFIC ASS'N FOR PROBIOTICS AND PREBIOTICS (ISAPP), THE P'S AND Q'S OF PROBIOTICS: A CONSUMER GUIDE FOR MAKING SMART CHOICES (2009), *available at* http://www.isapp.net/Portals/0/docs/Consumer_Guidelines-probiotic.pdf.
[166] *See* David Schardt, Recommendations for Modifications to FDA's regulatory framework for probiotics (on file with the authors).
[167] *See* essay submitted by Working Group Members June Austin (Regulatory Affairs, Procter & Gamble) and Nora L. Zorich (former Vice President Corporate Research and Development, Procter & Gamble) (on file with the investigators) referring to CONSUMER HEALTH PRODUCTS ASS'N, VOLUNTARY LABELING GUIDELINES FOR DIETARY SUPPLEMENT PRODUCTS CONTAINING PROBIOTICS (adopted Nov. 17, 2011), *available at* http://www.chpa.org/VolCodesGuidelines.aspx.
[168] CONSUMER HEALTH PRODUCTS ASS'N, *supra* note 167. 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.
[169] *Id.* This information gives consumers the knowledge and opportunity to research the strains.
[170] *Id.* For products that lack adequate space on the label, a company should list a website where the consumer can obtain contact information.

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 as needed to add additional ingredients and allowable claims. For many years, the FDA has used a monograph for OTC drugs under which products such as some sunscreens, laxatives, cough-cold and other products can be sold and marketed without premarket approval.

Canada currently uses a monograph to regulate certain probiotics sold in the Canadian market and has taken a proactive role in regulating probiotic products. Probiotic product classes in Canada do not correspond exactly with those in the United States; however, most probiotic products that would be considered dietary supplements in the United States are regulated as natural health products in Canada and are regulated by a probiotics monograph. The monograph was written based on the FAO/WHO 2006 Guidelines[171] and a targeted review of the scientific literature. All probiotic natural health products in Canada require pre-market assessment and licensing and must be supported by evidence of safety and efficacy under recommended conditions of use. Compliance with the monograph requirements leads to expedited review of the application for marketing the product. 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).

Natural health products are not limited to these claims; however, additional evidence supporting the product’s safety and efficacy is required for claims not specified by the monographs. 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 July 19, 2013, Health Canada had received approximately 78,500 applications for pre-market approval of natural health products. Specific to probiotics, at that date, 437 probiotic products had been licensed through the monograph process, 438 probiotic products had been licensed outside of the monograph process, and 48 probiotic submissions were in queue for evaluation.[172]

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:

- Inadequate 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.[173]

[171] *See* FOOD & AGRIC. ORG. OF THE U.N. & WORLD HEALTH ORG., *supra* note 7.
[172] Michael Steller, Health Canada, Health Products and Food Branch, Natural Health Products Directorate (personal communication July 25, 2013).

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.

The probiotics monograph established in Canada could serve as a model for the U.S. The U.S., in fact, already has experience with monographs; a monograph for OTC drugs has been in place for over 40 years. When the FDCA was signed in 1938, it required that all new drugs obtain FDA approval of a New Drug Application (NDA) prior to marketing. Drugs that were already on the market, however, were "grandfathered" and exempt from the new drug safety requirements. When the FDCA was amended in 1962, through the Kefauver-Harris Amendments, it required proof of effectiveness for all new drugs. These amendments continued the grandfathering of pre-1938 drugs, provided that they were generally recognized as safe and effective (GRAS/E) for their indication.[174]

In order to deal with the vast number of OTC drugs that were already on the market prior to the requirement that all drugs obtain an NDA, the FDA created the OTC monograph system to review classes of drugs and categorize them as GRAS/E after review by expert panels. This meant that certain classes of OTC drugs would not be required to obtain an NDA and could remain on the market if they conformed to the monograph guidelines for doses, labeling, and warnings, which are finalized in the Code of Federal Regulations.[175]

Professor James O'Reilly has recommended using the FDA's existing OTC drug monograph structure as a model for the development of a monograph for probiotics.[176] His proposal is 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 the FDA's current OTC monographs, a probiotics monograph would include a list of active ingredients found to have achieved a specified benefit; levels of active ingredients needed to achieve the benefit; product claims that the FDA believes fairly communicate that benefit; mandatory warnings for this category of products; purity standards for active ingredients; permissible excipient and/or inactive ingredients; and methods and standards of testing.

There are several benefits to using the OTC drug monograph as a model for regulating probiotics. The monograph mechanism has been in place for 40 years at the FDA and is a well-established mechanism for facilitating the marketing of certain products. Moreover, a probiotics monograph would generate a well-understood set of claims accepted by the FTC and useful in private enforcement claims. The process is open and familiar to industry and NGOs. A monograph would create a strong basis for active ingredient characterization and for use of specifications or production controls on key ingredients. The process could also be

---

[173] *See* DANIEL BUIJS, HOW PROBIOTIC NATURAL HEALTH PRODUCTS ARE REGULATED IN CANADA (PowerPoint presentation, Feb. 4, 2011), *available at* http://www.law.umaryland.edu/programs/health/events/probiotics/documents/Buijs_Health_Canada_Probiotics_Monograph.pdf.

[174] Stan Stringer, *What Has Been Happening with Over-the-Counter Drug Regulation*, 53 FOOD & DRUG L.J. 633, 633 (1998).

[175] Gen. Accounting Office, HRD-82-41, FDA's Approach to Reviewing Over-the-Counter Drugs Is Reasonable, but Progress Is Slow (1982), *available at* http://gao.gov/assets/140/137203.pdf; Food & Drug Admin., Regulation of Nonprescription Drug Products, *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM148055.pdf (PowerPoint presentation) (last visited May 7, 2014).

[176] James O'Reilly, "Yes, it walks like a duck …" Changing the Culture of Those Who Market Probiotic Cultures (on file with the authors).

used as an avenue to assure safety. Furthermore, a monograph would likely meet with success in court challenges because of the history of successfully overcoming past criticisms of the OTC drug monographs.[177] It would also 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.[178]

A monograph could address foods or dietary supplements that want to make health claims by indicating which claims could be made about which ingredients, such as those permitted in Canada.[179] A monograph could also address characterization issues specific to probiotics. Finally, although Canada's monograph requires pre-market approval, the FDA OTC monograph does not. Borrowing from both models would allow for a streamlined process that could reduce the number of unsubstantiated probiotic claims and allow marketing without prior individual product approval.[180]

VIII. 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.[181]

Regulatory burden should be proportional to risk. This principle is already reflected in both Canada and the United States in the distinction between the regulation of 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. 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 publicly available mechanism through which consumers can obtain more information on the underlying evidence supporting a particular product.

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

---

[177] *Id.*

[178] *Id.* Another potential benefit of a probiotic monograph is that if user fees were an option for companies seeking approval under the monograph, the fees could be used to enhance the FDA's enforcement efforts. Finally, depending on how it was designed, a probiotic monograph could probably be established without requiring statutory approval. *Id.*

[179] *See* Table 2, *supra*. Any claim that would be considered a drug claim, however, would likely require statutory approval.

[180] 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.

[181] *See* Daniel Buijs, Recommendations for Establishing a Regulatory Framework for Probiotics (on file with the investigators). The description of these principles is taken in large part from Mr. Buijs' recommendations.

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 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 underappreciated. The regulatory regime must be nimble enough to respond.

Acknowledgments

Support for this article was provided by Grant Number: 5R01HG005171-02, from the National Human Genome Research Institute (NHGRI), National Institutes of Health (NIH). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NHGRI or the NIH.

Table 1:

Differences between Structure/Function and Drug Claims[140]

Structure/Function Claim (no prior approval needed)	Drug Claim (approval needed)
Helps maintain normal cholesterol levels	Lowers cholesterol
Maintains healthy lung function	Maintains healthy lung function in smokers
Provides relief of occasional constipation	Provides relief of chronic constipation
Suppresses appetite to aid weight loss	Suppresses appetite to treat obesity
Supports the immune system	Supports the body's antiviral capabilities

[140]Center for Science in the Public Interest, *Claims Crazy, Which Can You Believe?*, NUTRITION ACTION HEALTHLETTER, June 2003, http://www.cspinet.org/nah/06_03/claim.pdf.

Table 2.

Probiotic Product Claims Allowed by Health Canada Probiotics Monograph

Microorganism	Eligible Specific Claims
• *Lactobacillus johnsonii* La1 • *L. johnsonii* Lj1 • *L. johnsonii* NCC 533	An adjunct to physician-supervised antibiotic therapy in patients with Helicobacter pylori infections
• *Lactobacillus rhamnosus* GG	• Helps to manage acute infectious diarrhoea. • Helps to manage antibiotic-associated diarrhoea. • Helps to reduce the risk of antibiotic-associated diarrhoea
• Saccharomyces boulardii	Helps to reduce the risk of antibiotic-associated diarrhoea
	Eligible General Claims
• Lactobacillus johnsonii La1 • L. johnsonii Lj1 • L. johnsonii NCC 533 • Lactobacillus rhamnosus GG	• Probiotic that forms part of a natural healthy gut flora. • Provides live microorganisms that form part of a natural healthy gut flora. • Probiotic that contributes to a natural healthy gut flora. • Provides live microorganisms that contribute to a natural healthy gut flora.
• Saccharomyces boulardii • Lactobacillus johnsonii La1 • L. johnsonii Lj1 • L. johnsonii NCC 533 • Lactobacillus rhamnosus GG	• Probiotic to benefit health and/or to confer a health benefit. • Provides live microorganisms to benefit health and/or to confer a health benefit.