Second Meeting Summary

Federal Regulation of Probiotics: An Analysis of the Existing Regulatory Framework and Recommendations for Alternative Frameworks – Meeting #2

February 3 and 4, 2011

University of Maryland Baltimore

On February 3rd and 4th, 2011, researchers at the University of Maryland Baltimore (UMB) held the second meeting as part of a project that is being funded by a grant from NIH’s Human Microbiome Project (HMP). The HMP is a $150 million, five-year NIH initiative. A portion of HMP funds were set aside to study the Ethical, Legal, and Social Implications (often referred to as the ELSI issues) of the HMP’s scientific goals. The UMB probiotics project is an interdisciplinary collaboration between faculty members from the University of Maryland Schools of Law, Pharmacy and Medicine. The NIH grant is funding a number of meetings to explore regulation of probiotics with a selected group of stakeholders and experts (the “Working Group”). The Working Group includes NIH-funded researchers and administrators, food and drug law attorneys, government regulators, legal academics, consumer advocates and industry representatives. A list of Working Group members and other materials relating to the project appear on the project website.

One of the most significant implications of the HMP is a potential expansion of the number of probiotic products available on the commercial market. Because this is a relatively new area of study, new claims are being made about the role and value of probiotics in promoting human health and wellbeing, and there is a great deal of uncertainty about how these products should be regulated. The goal of this multi-disciplinary collaborative project is to examine the legal and regulatory issues raised by probiotics and to determine whether the current regulatory framework is a good fit for the range of probiotics that are on the market, under development, or that may be developed in the future as a result of the HMP. Our goal is both ambitious and modest. We hope to look at the growing field of probiotic products and the current regulatory structure and create a written record of the thoughts, concerns, and broad recommendations of the leading

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3 Available at [http://www.law.umaryland.edu/programs/health/events/probiotics/meeting1.html](http://www.law.umaryland.edu/programs/health/events/probiotics/meeting1.html).
stakeholders in the field. We are also studying discrete regulatory changes that may improve the way that probiotics are currently regulated in order to ensure that probiotic products are made available to the general public in an appropriate manner.

**Brief Recap of First Meeting (6/14/10)**

At its first meeting, the Working Group focused primarily on the science of probiotics. After a number of preliminary talks by experts in the field, Working Group members were asked to reflect on any gaps in probiotic science and policy from their professional vantage points and to share their thoughts on what they hoped the probiotics project would accomplish. A detailed summary of the first meeting appears on the project’s website but, briefly, the issues raised at the first meeting were roughly grouped into the following categories: concerns with current Food and Drug Administration (FDA) regulation of probiotics, in particular overregulation as regards the requirement of an IND for research on probiotic foods or dietary supplements; under-regulation of claims; gaps in the current research on probiotics; concerns about the quality of probiotic research; ethical issues related to probiotic research and marketing, consumer and claims issues; and issues for future consideration of the Working Group.

The purpose of the first meeting was to engage in critical issue spotting and not to develop conclusions or recommendations. However, a general consensus emerged that the following issues should be considered by the Working Group:

1. Creation of an authoritative entity within the FDA Commissioner’s Office that would determine if an investigational new drug (IND) application is necessary to perform probiotic research rather than requiring researchers to approach a specific center (e.g., CFSAN or CBER) that may offer opinions reflecting Center rather than FDA policy.
2. Creation of a new regulatory pathway for some types of probiotics within FDA. This new pathway could be created either through reinterpretation of current law or a regulatory modification. The pathway could be regulated by a dedicated Center or Office that would make initial determinations about the product and then, depending on the type of probiotic product, either assign the product to the new pathway or another FDA Center for oversight. Probiotics eligible for this new pathway might be subject to an abbreviated IND process. The Working Group termed this new route “IND Lite.” Probiotics that fall into this new category would have certain similar characteristics that would distinguish them from drugs.

**“IND Lite” Working Group**

Based on the above recommendations, meeting organizers formed an IND Lite subgroup between the first and second general body meetings to consider whether an abbreviated IND process might make sense for certain probiotic products. This abbreviated process would be one in which phase 1 clinical trials might be formulated differently or waived. The task of the subgroup (still ongoing) is to suggest which products would go through an IND Lite process; what the IND Lite process would look like; and whether such a process could fit in the current statutory framework or would require statutory change.
Relevant to the discussion of the IND Lite concept is recent FDA guidance entitled “Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND.” 4 Several members of the Working Group and the IND Lite subgroup in particular expressed concern that aspects of the draft guidance proposed by FDA’s Centers for Drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER) is flawed. The main concern of these members of the Working Group is that the guidance appears to expand the reach of INDs to include virtually all products that have any effect on the structure or function of the body, notwithstanding the historic, lawful marketing of foods and dietary supplements to impact the structure and function of the human body and reduce the risk of disease, without prior marketing approval. The Working Group discussed inconsistent provisions in the guidance – some of which indicate that any intent to affect the structure or function of the body (or even an intent to discover if there is any such effect) triggers the requirement for an IND while other provisions of the guidance concede that such intent alone does not trigger such a requirement absent a therapeutic purpose.5 Furthermore, the guidance indicates that FDA will determine if a substance is a drug (and therefore require the manufacturer or sponsor to submit an IND) based on endpoints selected in human studies instead of the intended use of the substance and the claims made, as has historically been the case. The subgroup noted that it would be helpful if the guidance recognized that a single substance or a single microorganism may simultaneously have food, dietary supplement, and drug applications and, taking this into consideration, assign the substance to an FDA category based on the intended use of the substance (unless the substance falls within the definition of drug for another reason such as listing in the United States Pharmacopeia–National Formulary, for instance). The IND Lite subgroup referred to the guidance in its preliminary conclusions (see below).

At the February 3-4 meeting that this document summarizes, the IND Lite subgroup met prior to the full group meeting and then presented the results of its preliminary discussions to the larger Working Group. These results included the following points:

1. The concept enunciated in the new IND guidance from FDA that all live biotherapeutic products are drugs, 6 even if the intended use of the product is only to affect the structure

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4 This guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175.pdf

5 Concerns relating to the definition of a drug in the new guidance are set forth in detail in a comment submitted to FDA by the International Scientific Association for Probiotics and Prebiotics (ISAPP). The comments are available at: http://www.law.umaryland.edu/programs/health/events/probiotics/documents/Comment%20IND_2011.pdf

6 See Guidance noted in footnote 4. Lines 349-351: “Although the challenge organism [in research to study the host response to the organism] is not intended to have a therapeutic purpose, there is intent to affect the structure or function of the body. Thus, the organism is a biological product and a drug.”
and/or function of the body or to reduce the risk of disease, is inappropriate and inaccurate.

2. For foods or dietary supplements, no IND should be required if a manufacturer or product sponsor wishes to make only structure/function (S/F) claims.

3. For food or dietary supplement products with an established history of safe use for which the manufacturer wants to make a drug claim (i.e., a claim that the product is useful for the cure, mitigation, treatment, prevention, or diagnosis of disease), an expedited IND process should be allowed. For this to happen, clear guidelines need to be established between foods and dietary supplements and drugs and what claims can be made about foods and dietary supplements. Thought must be given to what population a history of safe use relates. If the history of safe use is as a food for the generally healthy population, then a claim that the product will prevent a disease should be appropriate for an IND lite process. But if the sponsor wishes to claim a therapeutic benefit for an at-risk population, then some judgment is in order as to whether the available information on safety based on historical use is suitable for this new target population.

4. For foods and dietary supplements with no or little established history of safe use for which the manufacturer wants to make a drug claim, a full IND should be required.

5. An IND should not be required for a clinical study performed to support a risk reduction claim of the type allowed under the Nutrition Labeling and Education Act (NLEA) for a food/dietary supplement. As an example, no IND was required for calcium/osteoporosis studies conducted in the past. Probiotic foods making reduced risk claims should be treated the same way.

In addition to the points noted above, the subgroup is also discussing the following suggestions as it develops the IND Lite concept.

**Clinical Studies Conducted with a Probiotic**

1. If a probiotic is currently marketed or intended to be marketed as a food or dietary supplement no IND is needed UNLESS the clinical study is investigating the diagnosis, cure, mitigation, treatment, or prevention of disease. However, if the study meets the IND Exemption noted below, an IND would not be required.

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7 Although prevention claims are considered disease claims, risk reduction claims are permitted under the Nutrition Labeling and Education Act (NLEA) of 1990 for foods and dietary supplements. See L. Satine, “Is my Yogurt Lying? Developing and applying a Framework for Determining Whether Wellness Claims on Probiotic Yogurts Mislead” 63 Food &Drug L.J. 537 (2008), noting that “[b]ecause Congress created overlapping definitions when it approved health claims for foods, FDA needed to distinguish between the two types of claims in order to prevent every product with a health claim from triggering drug regulation and thereby thwarting Congressional intent. FDA resolved the ambiguity by distinguishing between prevention claims and treatment claims, a division that was ultimately upheld in *Whitaker v. Thompson*, 353 F.3d 947,949 (D.C. Cir. 2004). A permissible health claim can suggest that a food reduces the risk of contracting a disease, but it becomes a drug clam if it suggests prevention, mitigation, cure or treatment of an existing disease.”
2. If the probiotic is marketed or intended to be marketed as a food or dietary supplement, the S/F impacts of the probiotic can be investigated in a diseased population without an IND if the study is being conducted to support an S/F or other non-disease claim and use of the probiotic in the diseased population is reasonably expected to be safe.

3. No IND would be needed for safety studies being conducted to support a Generally Recognized as Safe (GRAS) determination or new dietary ingredient (NDI) submission.

IND Lite Process

For probiotics that are GRAS under the food additive regulations or being marketed as a Dietary Ingredient and the study is being conducted to investigate the diagnosis, cure, mitigation, treatment or prevention of disease, the IND Lite application would include:
- An introductory statement and general investigational plan (per 21 CFR 312.23 (a)(3)).
- A Clinical study protocol for which IRB approval would be required.
- A summary of clinical safety data and/or in market exposure data (time and extent).
- Reference to GRAS specifications or a copy of the NDI as appropriate.
- Documentation that the strain being investigated is GRAS or the subject of a NDI.

IND Exemption

The clinical investigation of a probiotic product that is lawfully marketed in the U.S. and is being conducted to study the diagnosis, cure, mitigation, treatment or prevention of disease, would be exempt from the requirements of 21 CFR §312 if:

1. The investigation is not intended to support a new indication or significant labeling change.
2. The investigation is not intended to support a significant change in advertising of a prescription drug product.
3. The investigation does not involve a route of administration, dosage level, use in a patient population, or other use, that significantly increases the risks (or decreases the acceptability of the risks) associated with use of the product.
4. The investigation is conducted in compliance with IRB and Subject Informed Consent regulations.
5. The product cannot be promoted nor commercialized on the basis of the investigation.

The subgroup also agreed that the monograph process may be an avenue to implement these suggested changes to the IND process. Finally, the subgroup noted that, in discussing these concepts, precise terminology is important.

The IND Lite Working Group will continue to develop a more detailed proposal to submit to the larger working group for review and comment.
Summary of Second Meeting – February 3 and 4, 2011

The focus of the second meeting was safety and characterization of probiotics and probiotic product claims.

Day One – Safety and Characterization

Safety

To initiate the discussion on safety, Dr. Frank Palumbo, Director of the UMB School of Pharmacy’s Center on Drugs and Public Policy, provided meeting participants with an overview of current FDA standards relating to product safety. Because probiotic products can potentially fit into many of FDA’s product categories, Dr. Palumbo reviewed safety standards for drugs, conventional foods, dietary supplements, and food additives. A summary of the safety standards for each category is presented below.

Drugs

Definition

- Articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease; and articles (other than food) intended to affect the structure or function of the body

Safety Standards

- The drug must be safe and effective for the product’s indication.
- A drug manufacturer/sponsor must file an Investigational New Drug Application (IND) with FDA. An initial filing of an IND contains:
  - Results of pharmacological and toxicological evaluations
  - Chemistry and pharmaceutical manufacturing and controls data
  - A clinical plan for the development of the new drug product and a specific protocol for the initial clinical trial proposed to be conducted
- Safety data, i.e. data on morbidity and mortality, is compiled throughout the clinical trials process which is conducted in three phases prior to marketing.
- Results of premarketing studies are submitted to FDA in the form of a New Drug Application.

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8 This summary is a report on the issues discussed at the second meeting and does not represent a consensus among Working Group members on any of the topics addressed in the report. Materials from the second meeting (including speakers’ Power Point presentations and the webinars) are available at the project’s website: http://www.law.umaryland.edu/programs/health/events/probiotics/meeting2.html.

9 For drugs, safety is a separate determination from the ultimate approval decision which includes a risk/benefit analysis that takes into consideration, among other things, the condition being treated and other available treatments.
• Post market safety data are collected via Medwatch and entered into FDA’s Adverse Event Reporting System (AERS).
• Safety is continually evaluated.\(^{10}\)

**Conventional Foods**

**Definition**
- Articles used for food or drink for man or other animals
- Chewing gum, and
- Articles used for components of food.

**Regulation**
- In general, FDA has much less regulatory authority over foods lacking premarket clearance authority over any substance considered a food.

**Safety Standards**
- Food must not be “ordinarily injurious to health” and must not be adulterated.
- The standard for adulteration of food caused by naturally occurring substances is less rigorous than the standard for added substances.
- Food is considered adulterated if it:
  - bears or contains any poisonous or deleterious substance which may render it injurious to health, but if the substance is a naturally occurring substance, the food is not considered adulterated if the quantity of the substance does not ordinarily render it injurious to health.
  - bears or contains:
    - any added poisonous or deleterious substance that is unsafe within the meaning of section 406 of the Food Drug & Cosmetic Act (FDCA), i.e., tolerances for poisonous ingredients;
    - Pesticide residue; and/or
    - An unsafe food additive or unsafe new animal drug.
  - consists in whole or in part of any filthy, putrid, or decomposed substances, or if it is otherwise unfit for food.
  - is prepared, packed or held under unsanitary conditions.
- Food manufacturers must adhere to Good Manufacturing Practices (GMPs)
  - FDA does not have explicit statutory authority to promulgate legally-binding GMP regulations for food but established them under the general authority of section 402(a) of the FDCA which outlines general standards for food processing and handling deemed necessary to prevent/avoid contamination of food (21 C.F.R. § 110)
  - In enforcement actions, FDA usually does not rely on the food GMP regulations as creating legally binding requirements against the food industry but instead uses evidence gathered during factory inspections to prove a direct violation of the FDCA.

\(^{10}\) The cost for a manufacturer or drug sponsor to undertake the IND process is about $1 billion.
• Food must meet Hazard Analysis & Critical Control Points and Principles (HACCP)
  HACCP is a management system for use in all areas of the food industry in which food
  safety is targeted through review and control of biological, chemical, and physical
  hazards from raw material production, procurement and handling, to manufacturing,
  distribution and consumption of the end product.

Food Additives

Definition
Any substance that is reasonably expected to become a component of food is a food additive and
is subject to premarket approval by FDA, unless the substance a) is generally recognized as safe
(GRAS) among experts qualified by scientific training and experience to evaluate its safety
under the conditions of its intended use, or b) meets one of the other exclusions from the food
additive definition in section 201(s) of the FDCA.\(^{11}\)

Safety
• A manufacturer wishing to market a new ingredient in a conventional food can
  – Make a self determination that the ingredient is GRAS;\(^{12}\) or
  – File a food additive petition supported by extensive toxicology testing.
• Food Additive Petition Contents
  – Information about the chemical composition and substances used in the additive’s
    preparation.
  – Amount of additive in the food and its proposed use in the food.
  – Methods to determine the amount of the additive in the food.
  – Data that it will have its intended effect.
  – Required safety data.
• Food Additive-Safety Standard
  – There is a general two-part food additives standard: 1) legislative history
    indicating that the substance is not hazardous to the health of man or animal; and
    2) “reasonable certainty” that no harm will result from use of the additive.

\(^{11}\) In addition, there are subcategories of food additives, including direct food additives
(substances intentionally added to food to serve a continuing technical function), secondary
direct additives (substances intentionally added to food to serve a technical function during
processing but largely removed or inactivated and serving no technical function in the finished
food—often referred to as processing aids), and indirect additives (substances becoming a
component of foods through contact and resulting migration).

\(^{12}\) After performing a GRAS determination, the manufacture may optionally notify FDA of this
fact. FDA may either “have no questions at this time” regarding the notice or indicate that the
notice does not provide adequate basis for GRAS. If the FDA response indicates that the notice
does not provide an adequate basis for GRAS, this response does not invalidate the GRAS
determination, although it would be inadvisable for a manufacturer to proceed in this case.
– The Delaney Clause (in the FDCA) requires that “no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal.”

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

**GRAS (Generally Recognized as Safe) Substances**

• A substance added to food that is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use.
• A food 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.
  – Under 21 CFR 170.30(b), general recognition of safety through scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive and ordinarily is based upon published studies, which may be corroborated by unpublished studies and other data and information.
  – Under 21 CFR 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.
• Contents of a GRAS notification
  – Information about the identity and properties of the substance and a discussion of the notifier’s reasons for considering the substance GRAS. Information is generally chemical, toxicological and, if applicable, microbiological in nature.
• GRAS Safety Standard
  – The same safety standards that apply to food additives (see above) apply to GRAS substances. The *Redbook* (see footnote 14) provides guidance for GRAS determinations as well as for food additives.

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13 Because of the use of the word “additive” in the Delaney Clause, some argue that the Clause does not apply to GRAS substances which are – for statutory purposes – not food additives.
14 The *Redbook* is the common name for an FDA guidance document entitled “Guidance for Industry and Other Stakeholders; Toxicological Principles for the Safety Assessment of Food Ingredients” (July 2000; Revised July 2007).
Genetically Modified Organisms (GMO) in Food and Food Ingredients

- The FDA uses the term genetic modification to refer to all forms of breeding -- both modern, e.g. genetic engineering, and conventional.
- Bioengineered foods and food ingredients (including food additives) must adhere to the same standards of food safety and adulteration provisions under the FDCA as traditional foods and food ingredients.

Food Safety Modernization Act of 2011

- The Act replaces the reactive legal structure under which FDA responded to problems of adulterated or misbranded foods already on the market with a preventive mandate and gives FDA much greater oversight over the food industry, including requiring facilities to register every two years, to develop new food safety plans, and to provide the Agency with test results. It also gives the FDA the power to mandate recalls and the industry and importers greater incentives to implement strong food safety programs.

Dietary Supplements

Definition

- A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
  (A) a vitamin
  (B) a mineral
  (C) an herb or other botanical
  (D) an amino acid
  (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
  (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in A-E.
- Furthermore, the product must not be represented as a conventional food or as the sole item of a meal or diet.

Safety Standards

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

Small Group Conclusions and Recommendations Relating to Safety

The Working Group broke into small groups to discuss the following question: are current FDA standards/guidance/practices for establishing safety adequate for probiotics in each of the FDA-regulated product categories (drugs, conventional foods, food additives, and dietary supplements)?

As a general matter, the Working Group agreed that safety is a critical concern and lack of data regarding safety should be a primary focus of regulatory efforts – even before efficacy.

A major issue raised during the meeting was the safety of probiotics and what researchers have learned regarding safety to date. At the time of the meeting, there were a handful of studies that indicated some potential safety issues. However, since the second meeting, the Agency for Healthcare Research and Quality (AHRQ) published a study entitled “Safety of Probiotics Used to Reduce Risk and Prevent or Treat Disease” (April 2011)\(^{15}\) that looked at what is known about the safety of interventions containing *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and/or *Bacillus* strains used as probiotic agents to reduce the risk of, prevent, or treat disease. The report found that

> There is a lack of assessment and systematic reporting of adverse events in probiotic intervention studies, and interventions are poorly documented. The available evidence in RCTs does not indicate an increased risk; however, rare adverse events are difficult to assess, and despite the substantial number of publications, the current literature is not well equipped to answer questions on the safety of probiotic interventions with confidence.\(^{16}\)

AHRQ’s findings are consistent with the Working Group’s findings that well-designed studies designed to assess the safety of probiotics are critical and should be undertaken.

With some minor exceptions, the Working group generally agreed that current FDA safety standards for **foods, food additives, and drugs** are adequate for probiotics although current guidance is needed as to how to apply safety standards to probiotics. Although the standards may be adequate, many agreed that oversight and enforcement of safety standards by FDA is not

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\(^{16}\) Id. (Executive Summary).
sufficient, particularly with regard to preparation and enforcement of GRAS determinations made by manufacturers about which FDA is not notified (as permitted by statute).

There was a great deal of discussion regarding the concept of historical usage of food as a measure of safety. While most Working Group participants agreed that historical use is particularly useful to establish safety in probiotics (many of which have been used throughout history in traditional foods such as yogurt), many suggested that the more the intended use of the probiotic gets away from historical usage, the more persuasive the argument that safety analysis should be required.

The Working Group generally agreed that safety standards for probiotic dietary supplements are not sufficient. This is particularly the case for dietary supplements sold prior to 1994 which were “grandfathered” in by the Dietary Supplement Health and Education Act of 1994 (DSHEA) and for which manufacturers need not submit any safety data to FDA. Post-DSHEA dietary supplements – or ingredients marketed in the USA after 1994 - are called New Dietary Ingredients (NDIs). NDIs are required to go through a safety review by FDA. Several Working Group members noted that safety standards for dietary supplements will get stronger once the recently enacted federal food safety bill is implemented because the bill mandates enforcement of NDI (new dietary ingredient) notification requirements.

In the area of safety, the following comments emerged from small group discussions:

- FDA or an industry consortium should establish recommended procedures for establishing the safety of probiotics, similar to the Redbook (see footnote 14) guidelines for assessing the safety of chemicals intended for addition to food. FDA should improve safety reporting generally and require companies to report adverse serious events to FDA of probiotics. On this point, others noted that, even when adverse events are reported, establishing causality for adverse events in a non-controlled setting is problematic.
- FDA or another government agency should categorize safety risks and create “classes” of probiotic products based on safety risk. FDA should look to the Cosmetic, Toiletry, and Fragrance Association (CTFA) safety review process as a model. CTFA established the Cosmetic Ingredient Review (CIR), an independent nonprofit organization comprised of a group of scientists, that reviews the safety of cosmetic product ingredients. CIR is

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17 The term "new dietary ingredient" means a dietary ingredient that was not marketed in the United States in a dietary supplement before October 15, 1994. (See section 413(e) of the FDCA, 21 U.S.C. 350b). There is no authoritative list of dietary ingredients that were marketed in dietary supplements before October 15, 1994. Therefore, manufacturers and distributors are responsible for determining if an ingredient is a "new dietary ingredient" and, if not, for documenting that a dietary supplement that contained the dietary ingredient was marketed before October 15, 1994. Manufacturers are required to notify FDA if the dietary ingredient has not been present in the food supply as an article used for food in a form in which it is not chemically altered or, prior to passage of DSHEA in 1994, in dietary supplements and why consumption of a new dietary ingredient is reasonably expected to be safe under the conditions recommended or suggested in the labeling.
financed by the cosmetic industry and is composed of independent academics who are prohibited from working for any cosmetic company while serving on CIR.\(^\text{18}\)

- FDA should clarify when something is a NDI and specify whether it must be based on the strain or genus of the organism. (Note – since the meeting, on July 1, 2011, FDA published guidance relating to NDI determinations.)\(^\text{19}\)
- The FDA or another agency or non-governmental organization might consider creating something similar to the American Academy of Pediatrics Red Book\(^\text{20}\) which lists “bad bugs” but that would list “good bugs” instead.
- FDA should improve GMPs for probiotics.\(^\text{21}\)

**Characterization**

Dr. Jacques Ravel, Associate Professor at UMB’s Institute for Genome Sciences, provided the Working Group with analysis of current FDA rules relating to characterization. Ravel focused on characterization requirements for live biotherapeutic products (LBP) because, while others might disagree, FDA has indicated that probiotics fit within the LBP category and the FDA definition of LBP appears to encompass probiotics.\(^\text{22}\)

Ravel noted that FDA recently published guidance that sets forth requirements for chemistry, manufacturing, and controls for early clinical trials using LBPs.\(^\text{23}\) Although this guidance does

\(^{18}\) While the FDCA does not require premarket approval of cosmetics, it prohibits the marketing of adulterated or misbranded cosmetics in interstate commerce. Violations of the Act involving product composition--whether they result from ingredients, contaminants, processing, packaging, or shipping and handling--cause cosmetics to be adulterated and subject to regulatory action.


\(^{20}\) The Red Book is a guide published by the American Academy of Pediatrics Committee on Infectious Diseases that sets forth the latest findings and clinical guidelines on the manifestations, etiology, epidemiology, diagnosis, and treatment of more than 200 common childhood conditions. It is not the same Red Book referred to in footnote 14 or the bullet point #1 on page 12.

\(^{21}\) Although GMPs do not relate to safety beyond the issue of contaminants, some in the Working Group noted that GMP standards could be enhanced to ensure product safety.

\(^{22}\) “A live biotherapeutic product (LBP), for the purposes of this guidance document, is a biological product that: 1) contains live microorganisms, such as bacteria or yeast; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine.” This definition is taken from “Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information,” available on FDA’s website at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM229312.pdf

not clearly state that these characterization requirements would apply to probiotics – they are likely intended to. With his background as an HMP scientist, Dr. Ravel discussed whether the characterization standards in this guidance are appropriate for probiotics. Generally, the guidance requires the following:

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

To provide a concrete example of a potential probiotic application, Dr. Ravel posed the case of a manufacturer who formulated a pill from material used for fecal transplants and asked whether such a product could meet the characterization standards set forth in the guidance document. A fecal transplant is a medical treatment for patients with certain colon conditions which involve restoration of colon homeostasis by reintroducing normal bacterial flora from stool obtained from a healthy donor. If the stool contents could be made into a pill for oral ingestion it raises the question of whether it would or could meet FDA standards for characterization. Dr. Ravel concluded that current standards would be difficult to meet because it would be impossible to identify all the microbes in the pill, therefore causing the “microbial limit” test in the guidance to be exceeded. Further, the chemical and microbiological components of the pill formulation would clearly vary from batch to batch and therefore run afoul of the requirement for consistency in product composition.

Small Group Conclusions and Recommendations and Conclusions Relating to Characterization

The Working Group broke into small groups to discuss whether current FDA standards/guidance/practices for characterization of probiotics in each of the FDA-regulated product categories (drugs, conventional foods, food additives, and dietary supplements) are adequate and appropriate. Most meeting participants agreed that the current characterization framework is not adequately customized for probiotics. A prominent theme that emerged was

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24 See footnote 22.
25 In a plenary discussion of the Working Group, most participants felt that a fecal transplant is a unique and unusual application of probiotics and agreed that it should not necessarily be categorized with other probiotic products but rather regulated in the same way organ transplants or blood donations are regulated. Further, as fecal transplants are a therapy of last resort, there may be an acceptable level of risk for such a procedure that would not be acceptable with other probiotics. However, they also agreed that if a pill could be formulated that contained microorganisms in fecal matter, under current characterization standards, this type of pill could not, and probably should not, be approved by FDA.
that probiotics are not inert and therefore change over time,\textsuperscript{26} making it more challenging to be certain of the characteristics of the product post-manufacture. Therefore any recommendations relating to characterization must address this inherent fact as well as to what degree it matters in terms of assessing safety.

The LBP characterization guidance discussed by Dr. Ravel is designed for researchers conducting early clinical trials as part of the IND process and therefore applies to LBPs in drugs and to products making drug claims that are historically considered foods and dietary supplements. It does not apply to products lawfully marketed as conventional foods or dietary supplements that are solely intended to affect the structure or any function of the body or to reduce the risk of disease. For foods and dietary supplements not making drug claims, characterization requirements have not been specified by FDA. This raised a number of questions for meeting participants, e.g.:

- Should probiotic foods and dietary supplements that do not make drug claims meet characterization standards and if so, what standards are appropriate?
- Should probiotic foods and dietary supplements meet characterization standards because people expect certain standards when buying products labeled as probiotics?

The scientists in the Working Group discussed specific problems with using the characterization standards set forth in the LBP guidance for probiotic drug products:

- Current 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.
- The guidance refers to genotypic methods that are inadequate and outdated. In terms of the test for microbial burden, the guidance needs to specify what kind of assay is required. Current genome sequencing technology allows for whole genome analysis to serve as the standard for characterization.
- Characterization requirements for enzymes (these appear in separate guidance relating specifically to enzymes\textsuperscript{27} – not LBPs) are generally not applicable to probiotics except the requirement that the manufacturer list allergenic components. This should be incorporated in LBP characterization standards.

\textsuperscript{26} Some Working Group members noted that, while probiotics are alive, in a dried format, they are quite close to inert.
\textsuperscript{27} See FDA guidance “Guidance for Industry: Enzyme Preparations: Recommendations for Submission of Chemical and Technological Data for Food Additive Petitions and GRAS Notices (Revised 2010) at http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodIngredientsandPackaging/ucm217685.htm
- While use of germ-free mice in research would likely allow probiotics to meet characterization standards, using such mice does not make a great deal of sense given that probiotics are designed to work in complex microbiological environments.
- LBP characterization standards are focused on the product; this may be inappropriate for probiotics because safety and effectiveness may be dependent on both the characteristics of the product and the microbiome of the consumer. On this point, others noted that the interaction between an introduced agent and the consumer is not unique to probiotics although probiotics may present unique questions of host/agent interaction.
- The LBP guidance requires specific information about the active ingredient(s). For probiotics, the active ingredients and the level of specificity with which to describe them, i.e., genome; cellular, or protein level, may be difficult to determine.

Meeting participants generally agreed that characterization standards should be customized to address the unique qualities of probiotics. Other recommendations included the following:

- Characterization requirements for foods and dietary supplements should be as well defined as they are for drugs.
- The GRAS determination process requires additional information about characterization that is not required by the LBP guidance and should be required.
- Characterization standards must be flexible enough to encompass new technology and must be specific enough to allow for proper/precise identification of strains.
- An organization outside of the FDA such as the American National Standards Institute (ANSI) could develop characterization standards for probiotics.
- The microorganism added to make a probiotic should be deposited in an independent reference culture collection as a means of assuring consistency between the product taken by consumers and the product as marketed.

**Day Two – Product Claims**

The second day of the meeting focused on the claims that manufacturers can make about products. In order to provide Working Group members with basic background information about the current legal framework for product claims, the Investigators hosted two webinars prior to the February meeting. The first webinar, “Regulation of Health Product Advertising and Marketing by the Federal Trade Commission,” was presented by Rich Cleland, JD (Bureau of Consumer Protection, Federal Trade Commission). The second webinar, “Regulation of Product Claims by the Food and Drug Administration,” was presented by Barbara Binzak, JD, Ph.D. (Food and Drug Law Attorney at Buchanan Ingersoll & Rooney).

In the area of 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 how that product is regulated by the FDA, e.g., products making what 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), the issue of how claims are regulated is very complex and controversial. As probiotics do not squarely fit into current FDA product categories, the issue of
claims is further complicated and unclear. The goal of the second day of the meeting was to look at product claims from the probiotics perspective, determine areas of concern, and develop initial recommendations in the area.

As background, claims are regulated by both the FDA and the Federal Trade Commission (FTC). FTC regulates advertising of over the counter drugs, foods, dietary supplements, medical devices, and cosmetics (including TV, radio, internet and print ads). The FDA regulates advertising of prescription drugs and labeling of prescription and over the counter drugs, dietary supplements, medical devices, cosmetics, and foods. Under FDA, regulation of claims differs based on which category the product falls within. For example, a disease claim describes the effect of a substance on the diagnosis, treatment, mitigation, cure or prevention of disease. This type of claim may only be used for drugs, and the claim requires pre-approval by FDA. Any product making a claim of this nature will be required by FDA to undergo the drug approval process. An example of this type of claim is “reduces the pain and stiffness associated with arthritis.”

Generally, the following types of claims can be made about foods and dietary supplements:

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

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

**Health claims** which describe the effect of a product on the reduction of risk of disease in a healthy or at-risk population. These claims require pre-approval by FDA or an authoritative body and must be supported by significant scientific agreement. Example: “Use of calcium in the diet on a regular basis may help to reduce the risk of osteoporosis.” (FDA has evaluated very few health claims; none for probiotics have been evaluated.)

Judicial rulings over the past decade have led to an additional category of health claims – **qualified health claims (QHCs)** – for foods and dietary supplements. These claims require less

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28 Note that over the counter drugs are regulated under the monograph system and no preapproval of claims is required as long as the claim is approved under the appropriate monograph.

29 For a full description about claims, see [http://www.fda.gov/food/labelingnutrition/labelclaims/ucm111447.htm](http://www.fda.gov/food/labelingnutrition/labelclaims/ucm111447.htm).
than significant scientific agreement and must be accompanied by a disclaimer or qualifier explaining the level of scientific evidence support. Manufacturers wishing to use a qualified health claim must file a petition with FDA, and FDA will issue a letter of enforcement discretion. 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.” 30 No qualified health claims have been granted for any probiotic product.

Although FDA has issued detailed regulations and guidance attempting to differentiate between structure/function claims for foods and dietary supplements and disease claims that may not be made without prior FDA approval, the guidance has not always been helpful. One problem is the definition of drugs, which includes any substance that claims it may “prevent” disease. It is often difficult to distinguish such claims from S/F claims for dietary supplements and foods. Examples of the difficulty in discerning where a claim falls include the following:31

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

FTC also regulates claims. Ads cannot be deceptive and must be substantiated by competent and reliable scientific evidence. To provide background for the day’s discussion on product claims, meeting organizers planned several talks to provide different perspectives on claims – the consumer/patient perspective, industry perspective, and scientific perspective.

David Shardt, Senior Nutritionist at the Center for Science in the Public Interest provided the consumer perspective. He noted that most claims for probiotics are S/F claims. They are popular with manufacturers in part because they are not subject to preapproval. Schardt informed the Working Group that based on several studies it is evident that consumers have difficulty distinguishing among the many different types of claims on food labels and, further, cannot distinguish between S/F claims and health claims. 32 Shardt believes that this difficulty is exacerbated by the fact that many S/F claims are ambiguous and misleading, because they are based on small, preliminary unpublished studies or based on studies conducted on diseased

30 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 must file a petition in advance of making a qualified health claim. When the agency chooses to exercise its enforcement authority in this area, one available measure is a “letter of enforcement discretion,” in which FDA informs a manufacturer of what it can and cannot do in relation to a specific claim. A letter of enforcement discretion was issued for chromium picolinate and insulin resistance on August 45, 2005. See http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm073017.htm.

31 Examples provided by Nora Zorich, MD, PhD, Proctor & Gamble.

populations rather than healthy individuals. Although the law requires claims to be truthful and based on sufficient evidence, lack of enforcement allows some inaccurate claims to reach the marketplace. Further, 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 doesn't work as claimed.

Dr. Ruth Farrell, an OB/GYN and bioethicist at the Cleveland Clinic who is the Principal Investigator on another NIH-funded Human Microbiome Project grant, spoke to the Working Group about her group’s research on patient attitudes to probiotic therapy. Her group’s research indicated that patients are savvier than average consumers about probiotics but are still somewhat confused by the various types of claims made about probiotics. She also noted that patients are likely more willing to accept a certain degree of risk in the hope of attaining a therapeutic benefit as they are often desperate for some type of relief from chronic and devastating illnesses.

Nora Zorich, M.D., Ph.D., Vice President of Product Research and Development for the Product Safety and Regulatory Affairs Division of Procter & Gamble, gave the industry perspective on claims. Dr. Zorich noted that decisions about product research and development are often driven by what claims the company can or wants to make about a product. As the approval pathway for drugs imposes the most extensive data requirements, it also represents the biggest investment in time and money. She noted that companies must decide if it is fiscally responsible to make such an investment in a probiotic product that would otherwise be regulated as a food, dietary supplement or medical food. Therefore, even though some disease prevention claims for probiotics are supported by data, companies are reluctant to invest the time and money in a product simply to make a disease or health claim when a structure/function claim is available. However, Dr. Zorich and many others at the meeting noted that, if industry wants to comply with FDA guidelines, it is increasingly difficult to make S/F claims due to the narrow range of acceptable endpoints for structure/function claims. This can result in researchers using disease endpoints in human studies that can put foods and dietary supplements in the drug category requiring an IND for clinical trials.

Dr. Mary Ellen Sanders, a food science microbiologist and consultant in the area of probiotics, spoke about claims from the perspective of research scientists. Her view is that the current regulatory framework, including the framework regarding claims, may be inhibiting probiotic research. Probiotics in food can be useful for, among other things, dietary management to reduce the risk of acute diseases (colds, flu, GI infections); of symptoms in persons who are not fully healthy (IBS); improvement of the therapeutic efficacy of a drug; and management of the side effects of a drug (such as the side effects of an antibiotic). However, the FDA would likely consider these to be disease claims and therefore consider the product creating these benefits to be drugs. Dr. Sanders noted that this conundrum inhibits research, because studies evaluating the benefits of probiotics may require INDs and may not be useful to companies for substantiating claims on foods or supplements. Since many companies marketing probiotics are

33 NIH Grant 1R01HG004877-01, “Patient Perceptions of Bioengineered Probiotics and Clinical Metagenomics.” PIs: Richard Sharp and Ruth Farrell.
not interested in marketing a drug, the research may not proceed. Conducting studies using healthy subjects on S/F endpoints with a food is also very challenging because, among other things, studying the effects of an introduced substance in healthy people can require very large number of subjects.

**Under-Regulation of Probiotics Claims**

One of the conclusions that the UMB investigators drew from the first Working Group meeting was that probiotic product claims may be both under-regulated (or non-compliance may be under-enforced), especially as regards the accuracy of claims of effectiveness, and over-regulated in terms of the evidentiary requirements for certain types of statements made about probiotic foods and dietary supplements. To address these issues, the Working Group considered recommendations to address both under- and over-regulation of claims. To initiate the discussion on under-regulation (and under enforcement), Working Group member, Richard Cleland, an attorney with the Bureau of Consumer Protection at the FTC, and University of Maryland Law School Visiting Professor Peter Holland, spoke about one possible solution to under-regulation and under-enforcement – a private right of action under the FDCA or the Federal Trade Commission Act. This proposal is a reaction to the limited enforcement resources available to the FDA and the FTC.

A private right of action is a statutorily created right of a private individual to sue a private actor (e.g. a business) for engaging in certain unlawful activities typically enforced by federal or state agencies, e.g., deceptive practices, unfair practices, misrepresentation, or failure to disclose material facts. While no federal-level private right of action exists for these types of consumer law violations, most states have what are colloquially referred to as “mini-FTC” statutes or UDAP (Unfair or Deceptive Acts or Practices) laws. These laws vary from state to state but generally, most state UDAP statutes provide Attorneys General with a broad variety of powerful remedies, including preliminary and permanent injunctive relief, restitution, civil penalties, attorney’s fees, and even the power to have a receiver appointed under certain circumstances. UDAP statutes also are being used with increasing frequency by private litigants pursuing class action relief for alleged unfair and deceptive business practices. This trend is based on the recognition in some jurisdictions that it is difficult to establish class action suits under traditional fraud laws. In these jurisdictions there has been a trend towards liberalizing the requirements for class litigation and recovery for UDAP claims.

UDAP statutes are primarily civil statutes. Some allow criminal penalties for extreme violations, but almost all enforcement is through the civil courts. The typical UDAP statute

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34 Some Working Group members noted that lack of FDA enforcement is not unique to probiotics.

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

According to a 2009 report by the National Consumer Law Center, before the adoption of
state UDAP statutes in the 1970’s and 1980’s, neither consumers nor state agencies had effective
tools against fraud and abuse in the consumer marketplace. This was so even though the Federal
Trade Commission Act had prohibited unfair or deceptive acts or practices since 1938. In most
states, there was no state agency with a mandate to root out consumer fraud and abuse, much less
tools to pursue fraudulent marketers. Consumers had even fewer tools at their disposal. A
consumer who was defrauded often found that fine print in the contract immunized the seller or
creditor. Consumers could fall back only on claims such as common law fraud, which requires
rigorous and often insurmountable proof of numerous elements, including the seller’s state of
mind. Even if a consumer could mount a claim, and even if the consumer won, few states had
any provisions for reimbursing the consumer for attorney fees. As a result, even a consumer who
won a case against a fraudulent seller or creditor was rarely made whole. Without the possibility
of reimbursement from the seller, consumers could not even find an attorney in many cases.
UDAP statutes were passed in recognition of these deficiencies. However, according to the 2009
report the effectiveness of UDAP laws varies widely from state to state. The holes are glaring.
Legislation or court decisions in dozens of states have narrowed the scope of UDAP laws
or granted sweeping exemptions to entire industries. Other states have placed substantial
legal obstacles in the path of officials charged with UDAP enforcement, or imposed
ceilings as low as $1,000 on civil penalties. And several states have stacked the financial
deck against consumers who go to court to enforce the law themselves.36

In the first small group session of the day, participants considered the value of a federal
private right of action and whether the Working Group should recommend it as a solution to
under-regulation or under-enforcement of false or unsubstantiated claims. The small groups also
considered other potential solutions to under-regulation of product claims related to probiotics.
Specifically, the small groups were given the following discussion questions:

1. Would a private right of action under the FDCA and/or the Federal Trade Commission
   Act be a useful additional approach to regulation/enforcement of probiotic claims?

36 “Consumer Protection in the States: A 50-State Report on Unfair and Deceptive Acts and
Practices Statutes,” Carolyn L. Carter (February 2009). Available at
2. Do you have any other recommendations to address under-regulation or under-enforcement of claims? Examples include (but are not limited to) a preapproval process or industry self-regulation such as a seal of approval.

Small Group Conclusions and Recommendations Relating to a Private Right of Action for Probiotics

The concept of a private right of action to address under-regulation of probiotics got a mixed review by the Working Group. Many felt that there is insufficient justification to single out probiotics for a targeted legal remedy. Many also felt that existing state law, such as state UDAP laws and tort claims for fraud, are generally sufficient to cover unsubstantiated claims and misbranding cases. Furthermore, because most UDAP cases are removed to federal court, although cases are brought at the state level, settlements tend to be national in scope without a specific federal law. Several members of the Working Group noted that it would be difficult to measure the effect of a private right of action, which would make it an unreliable method to address under-regulation and/or under-enforcement. Many noted that a private right of action might have a chilling effect on innovation and would have limited effect on unscrupulous small companies that promote products with little substantiation, as these companies do not have the “deep pockets” that attract plaintiffs and attorneys to UDAP cases. Finally, a Working Group member questioned whether a private right of action benefits the public in a tangible way.

However, other members of the Working Group agreed that a national law that created incentives for plaintiffs and lawyers to take smaller cases and/or go after smaller companies would be a useful regulatory tool. Many agreed that a private right of action would need appropriate checks and balances to discourage frivolous lawsuits, such as:

- a provision that permitted the FTC and FDA to intervene and/or dismiss a case with prejudice under certain circumstances;
- creation of meaningful criteria for safety/effectiveness as a template for a case against a company to set forth what evidence would support a successful claim; and/or
- national standards regarding sufficient evidence and proof.

Subsequent to the meeting, one of the meeting organizers, Professor Jack Schwartz (UMD Law), suggested that a private right of action could be designed that increases policing of insufficiently substantiated structure/function or qualified health claims and yet reduces the downside risks of frivolous lawsuits or plaintiffs solely going after deep pockets. Under his suggestion, the private right of action would:

- enforce the FTC Act with equitable and compensatory damages remedies plus fee-shifting;
- be limited to State AG's and tax-exempt organizations, so as to eliminate the specter of plaintiff lawyers bringing shakedown suits;
- be available only for advertising to consumers of products under the jurisdiction of the FDA;
• be subject to dismissal if the challenged advertising claim is substantially similar to a labeling claim specifically approved by the FDA; and
• be subject to notice to the FTC and the FTC's right to take over the suit, comparable to the procedure in a False Claims Act qui tam action.

Professor Schwartz notes that this proposal is designed for all FDA regulated products, not just probiotics, but may be something the Working Group could endorse.

Small Group Conclusions and Recommendations Relating to a Seal of Approval for Probiotics

The concept of a probiotic “seal of approval” was also met with mixed reviews by the Working Group. While the idea of a seal of quality, such as a seal from the Better Business Bureau, seems to be a good idea, many in the Working Group noted that seals of this sort have a mixed history. In the past, some seals have been more geared to entice consumers and increase profits rather than ensure quality. For instance, in 2010, the Better Business Bureau – a historic leader in the concept of neutral determinations of quality and service - was criticized for giving businesses better grades if they became dues-paying members. In another case, the American Cancer Society accepted $1 million dollars from SmithKline Beecham in exchange for permission to use the American Cancer Society's name and logo to promote the sale of nicotine patches and gum. These missteps have caused many consumers to lose faith in seals and the entity providing the seal. Furthermore, a seal can harm smaller companies that cannot afford the fee for the seal, if a fee is required. Finally, a seal will not be meaningful unless embraced by the entire industry. For example, USP tried a certification for dietary supplements which was not effective because it was not picked up across the industry. However, notwithstanding these concerns, many agreed that a seal might be a good idea if done with integrity and, if the certifying group is industry-funded, assurances of neutrality were provided.

Working Group members suggested that for a seal of approval, the organic food certification39 and/or herbal product certification40 frameworks may serve as effective models.

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39 The Organic Foods Production Act of 1990 requires the Secretary of Agriculture to establish a National List of Allowed and Prohibited Substances that identifies synthetic substances that may be used, and the nonsynthetic substances that cannot be used, in organic food production and handling operations. In addition, the National Organic Program, which was enacted by Congress in 2002 restricts the use of the term "organic" to certified organic producers (excluding growers selling under $5,000 a year, who must still comply and submit to a records audit if requested, but do not have to formally apply). Certification is handled by state, non-profit and private agencies that have been approved by the US Department of Agriculture (USDA).
40 Several self-regulatory standards exist for herbal products. The American Herbal Products Association (AHPA) maintains a Botanical Safety Handbook that provides information about practices affecting safety, such as cleanliness and contamination and offers guidelines for serving
An additional idea along the lines of a seal of approval is for FDA to authorize an agency or organization to assign privileged use of the term “probiotic” on a label to products meeting certain standards. This authorization could provide a financial incentive for companies to do research because it would grant a degree of exclusivity to companies with adequate substantiation. A standard for calling a product “probiotic” might be an effective regulatory tool because it does not require the consumer to conduct research – the agency/organization granting the privilege to use the term “probiotic” will have done the research or reviewed the research conducted by the industry.

One suggestion to address under-regulation of product claims was to create a Surgeon General label for probiotic products similar to the nutrition facts panel that would direct the consumer to a website with links to publicly available studies about the product. The label could note that the product has not been reviewed for effectiveness by the FDA. The website could also link to data from an organization like NIH or CDC about genus/species categories for probiotics. For more information, the consumer could be referred to the company actually sponsoring the product.

Similarly, there was a great deal of discussion about the advisability and utility of a website with useful information about probiotics for consumers and/or health care providers. A website could be created that listed strain specific probiotics for which a “reasonable assumption of safety at this date” exists. There was no agreement on which agency or organization would maintain the website although FDA, NIH, CDC and industry trade organizations were mentioned as possibilities. Others in the Working Group expressed concern that a “probiotics website” would be resource intensive and difficult to fund. A further concern raised about the concept of a probiotics website was that of proprietary information and if such information would appear on the website. This would be of concern to the probiotics manufacturers. One member of the Working Group noted that communicating with the public is difficult as members of the public have varying degrees of literacy. Finally, others felt that a website is only as good as the available science and, with probiotic science in its infancy, a website might be just as confusing as the claims on which it is designed to shed light.

Other Conclusions and Recommendations Regarding Under-Regulation of Probiotics

In addition to the above-noted conclusions and recommendations, the following suggestions were made to address under regulation of probiotics:

- size and other labeling issues. The handbook serves as a guide for health care practitioners and consumers. AHPA also maintains the Herbs for Commerce Handbook that provides a compilation of common names "standardized" to botanical names for herbs. The Handbook is used to meet FDA labeling regulations for herbal products. The Institute for Nutraceutical Advancement is developing a Methods Validation Program (MVP) which is the industry's most concerted effort to standardize test procedures for botanical products.
• A better, standard definition of probiotics would be very useful (not just to address under-
regulation). The issue was raised multiple times during the meeting. If there is no legal
definition, it is difficult to enforce appropriate use of the term and/or difficult to know if
someone is misusing it. Some noted that a strict definition that includes the concept of
safety might help ensure safety of products that call themselves probiotics while others
thought the inclusion of the concept of safety in the definition is unnecessary given that
safety for intended use is presumed for regulated products.
• The FDA could develop and maintain a list of approved probiotic products. Such a list
would be available to patients and consumers. However, as consumers already have
trouble understanding the difference between types of claims, there will be little incentive
for “bad” companies to have their studies approved for the list.

Over-regulation of Product Claims

In the afternoon, the Working Group took on the issue of over-regulation of claims. To
initiate the discussion of over-regulation of claims, i.e., prohibitions on claims that go beyond a
very strict interpretation of structure/function claims and a very broad interpretation of disease
claims, two Working Group members discussed the concept of product monographs. Generally
a monograph is a kind of “recipe book” that covers acceptable ingredients, doses, formulations,
and labeling for the product covered by the monograph. Monographs are updated to add
additional ingredients and allowable claims as needed. In the case of FDA monographs, products
conforming to a monograph may be marketed without further FDA clearance. The most well
known FDA monographs are the over-the-counter drug monographs under which products such
as some sunscreens, laxatives, cough-cold products and others can be sold and marketed without
premarket approval. One solution considered by the Working Group is whether probiotics might
be regulated under a monograph process.

Canada regulates certain probiotic products (mostly what Americans would consider dietary
supplements) via a probiotics monograph. Working Group member Daniel Buijs, an
Assessment Officer with the Natural Health Products Directorate, Health Products and Food
Branch of Health Canada, spoke about Canada’s experience with a probiotics monograph.
Canada’s probiotics monograph was written based on the FAO/WHO 2006 Guidelines 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. The monograph currently allows four specific product
claims for three specific strains of live microorganisms and allows limited generalized claims for

41 In order to ensure that all members of the Working Group are working with the same
definition of a probiotic, the Working Group agreed at the project’s first meeting to use the
WHO/FAO definition of probiotics – “a live microorganism which, when administered in
adequate amounts, confers a health benefit on the host.”
42 See http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-
prod/monograph/mono_probioti-eng.php.
combinations of strains that meet all additional requirements. Manufacturers must attest to strain-specific evidence regarding identity, safety and efficacy. Finally, the monograph requires that label quantity must be present at expiry. Buijs also shared feedback that Health Canada received from manufacturers about the monograph process. As of January 31, 2011, Health Canada had received approximately 53,000 applications for pre-market approval of natural health products. Specific to probiotics, at that date, 315 probiotic products had been licensed through the monograph process, 24 probiotic products had been licensed outside of the monograph process, and 290 probiotic submissions were in queue.

Working Group member and law professor James O’Reilly (Cincinnati College of Law) then presented the case for using FDA’s existing over-the-counter (OTC) drug monograph structure for probiotics. His full proposal appears in the project’s website but generally would be based on the concept that probiotics are a functional class of products that are generally recognized as safe and effective for a similar particular benefit. Similar to current OTC monographs, a probiotics monograph would include a list of active ingredients found to have achieved a specified benefit; levels of active ingredients needed to achieve the benefit; product claims that FDA believes fairly communicate that benefit; mandatory warnings for this category of products; purity standards for actives; a listing of permissible excipient and/or inactive ingredients; and methods and standards of testing. No probiotic products are currently approved under a monograph. In terms of monograph advisory committees, FDA could use an existing one or create a new one. This would be relatively easy because it would involve amending an existing regulation.

According to O’Reilly, there are several benefits to using the OTC drug monograph as an approach for regulating probiotics:

- An advisory committee process is already in place and chartered at FDA for this type of process;
- A non-complying product is free to “opt out” and file a new drug application for a parallel approval;
- The monograph mechanism has been in place for 40 years at FDA and is a well-established mechanism for drafting, review and finalization of certain products;
- An existing office within FDA’s Center for Drug Evaluation & Research already handles monograph questions;
- The process would not require new offices, new regulatory models or pathways for probiotics;
- Monographs have generated a well-understood set of claims accepted by the FTC and useful in private enforcement claims;
- Monographs can preempt state labeling laws once the federal OTC drug rule is effective;
- The process is open and familiar to industry and NGOs. The FDA would gather submissions (including scientific input and industry views) leading to a final enforceable rule;

• Probiotic clinical trials would not necessarily require an IND if the study is confirmatory to meet an OTC monograph;
• A monograph would create a strong basis for active ingredient characterization and for use of specifications or production controls on key ingredients;
• A monograph would likely meet with success in court challenges because of the history of successfully overcoming past criticisms of the OTC drug monographs. Products already labeled as probiotics prior to the monograph would be subject to approval by the advisory committee, which could issue a temporary monograph for new products with the possibility of requiring new information.

Small Group Conclusions and Recommendations Relating to Over-Regulation of Product Claims

The Working Group broke into small groups to consider the following discussion questions relating to over-regulation:

1. Would a monograph be a useful approach to regulating probiotics?
   a. Should probiotics be brought into the existing over-the-counter monograph structure (even if not drugs) and/or
   b. Should a separate monograph(s) be developed for probiotics (as has been done in Canada)?
2. Do you have any other recommendations for over-regulation of claims? Examples include (but are not limited to):
   a. Expansion of health claims and qualified health claims
   b. Allow research with drug outcomes to substantiate structure/function claims for foods
   c. Expand or make greater use of the Medical Foods category for some probiotic food products
   d. Make the case that FDA regulations relating to implied drug claims are overbroad

Small Group Conclusions and Recommendations Relating to a Probiotics Monograph

The Working Group (in small group and full group discussions) discussed the monograph concept and sought clarification about the details of how such a regulatory scheme might work in the United States for probiotics. There was both interest and concern shown for the idea of a probiotic monograph but a general agreement that it would have to be fleshed out further in order for the Working Group to make any formal conclusions about a monograph for probiotics.

In terms of positive aspects of a probiotics monograph, Working Group members noted the following:
• A monograph would provide assurance to the FDA and FTC that a product approved under the monograph has met a certain standard and the FTC would likely defer to it.
• The process could be used as an avenue to assure safety.
• If user fees were an option for companies seeking approval under the monograph, the fees could be used to enhance FDA enforcement efforts.
• If a product is within the monograph, it does not require an IND or IRB approval.
• Statutory change may not be required to create a probiotic monograph.
• A monograph would address foods that want to make drug-like claims, by indicating which claims could be made about which ingredients.
• A monograph would be a useful resource for the field by setting standards from which the science can develop, especially in terms of properly designed clinical trials. For example, the monograph could capture good IND criteria and establish them as standards for the field.
• A monograph could also address characterization issues specific to probiotics.
• The monograph could be used to approve various kinds of claims. Disease prevention claims are currently allowed under the OTC monograph.
• The current rules relating to monographs allow for the inclusion of combination products which would be useful in the case of probiotics.
• Although not currently done, a product approved under the monograph could carry a seal or statement that it was approved under the monograph.

The following concerns were raised about the monograph concept:

• The FDA monograph process is for drug products. Including dietary supplements in a probiotics monograph would push dietary supplements into the drug category – a result that would likely lock the supplement into the drug category and the extensive product and claim regulations that go along with it. This is something that manufacturers will avoid.
• The current OTC monograph process is rigid and stagnant and not designed to constantly reevaluate new ingredients or create new monographs. The monograph system is based on the concept of a drug as stable and unchanging over time. Probiotics are different from other products under monographs.
• The OTC monograph process is very resource intensive, so a first step might be to review the monograph system generally.
• The possible claims under a monograph are limited.
• Genetically modified products should not be included under a monograph.
• A significant challenge for the probiotic monograph is demonstrating which products are safe and effective. This will require additional data, especially clinical data, which does not exist yet. Another hurdle is that monographs are ingredient-based, and producers would need to list the strain and safety and efficacy data for that strain. Given the number of strains in probiotic products, this would be difficult.
• Since a monograph is based on publicly available information, there may not be enough available information about probiotics to create a monograph.

There was a great deal of discussion regarding the focus of the monograph. Some suggested that the monograph should focus on strains of probiotics rather than function (i.e. gut health, vaginal health, skin health etc.). However others felt that a monograph should be related to products – not strains – because there may be too many strains for a monograph to reasonably contemplate over time. Others noted that one concern with the probiotics monograph concept is
that monograph claims are disease – not structure/function – related and that an “immunity-
boosting product” would not be an appropriate subject for a monograph (although the
antidiarrheal monograph would be appropriate for some probiotics). Still others suggested that
ideally, a monograph focused on “natural health products” or “health promotion products” could
be developed similar to the Canadian probiotics monograph.

In addition to asking for more clarification and setting forth pros and cons about the
monograph concept, Working Group members noted that a probiotics monograph could be
developed and implemented by an organization outside of the FDA, as is done in the case of
homeopathy. Although there are important dissimilarities between homeopathic remedies and
probiotics and some concerns were raised about the homeopathic model, some Working Group
members noted that the homeopathic monograph is an example of a monograph managed outside
of the FDA and based on non-clinical studies. Many in the Working Group also responded
positively to the concept of a baseline safety monograph supported by a group such as the U.S.
Pharmacopeia.

Small Group Conclusions and Recommendations Relating to Authorized Health Claims
and Qualified Health Claims

Background

As noted above, there are generally three types of claims that can be made about foods and
dietary supplements – structure/function claims, nutritional content claims and health claims.
Health claims describe the relationship (explicit or implied) between an ingredient and reduced
risk of a disease or health-related condition. FDA allows two types of health claims and
provides guidance about both – authorized health claims and qualified health claims.

Authorized health claims require “significant scientific agreement” for approval; characterize
the relationship between a substance and disease risk; are based upon the totality of public
scientific evidence; and must be pre-reviewed by FDA, which then issues a regulation setting
forth the parameters for use of that specific health claim. As an example, the following health
claim can be made about calcium: “adequate calcium throughout life, as part of a well-balanced
diet, may reduce the risk of osteoporosis.” (21 C.F.R. § 101.72). A list of approved health claims

Qualified health claims are claims in which a statement about health benefits is made with a
disclaimer noting the degree of evidence supporting the claim. These claims generally use
emerging evidence of a relationship between a substance and the reduced risk of disease or
health-related condition and can be based on something less than significant scientific
agreement. This class of claims was allowed by FDA following a U.S. Court of Appeals
decision that challenged FDA’s health claims regulations for dietary supplements and FDA’s
decision not to authorize health claims for four specific substance/disease relationships based on
the "significant scientific agreement" standard. In *Pearson v. Shalala*, the appeals court held that, based on the administrative record compiled in the challenged rulemakings, the First Amendment does not permit 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.

Following the *Pearson* case and related litigation, FDA set forth the criteria for when the agency would consider allowing a qualified health claim in dietary supplement and food labeling. The FDA does not issue regulations relating to specific qualified health claims but a manufacturer is required to file a petition relating to the claim and the FDA can issue a letter of enforcement discretion. These letters, which appear online, give manufacturers an idea of what is or isn’t allowable in this area.

**Conclusions/Recommendations by Working Group**

The idea of recommending the expansion of available health and qualified health claims was not addressed by any of the small groups, most likely due to time constraints. Many Working Group members noted, however, that the FDA already has a process in place for approval of authorized and qualified health claims and very few manufacturers have availed themselves of the process because of the amount of time and resources such a process takes and a lack of understanding of FDA’s guidance in this area. Furthermore, a recent GAO report indicated that approved health claims are not regarded by consumers as better than S/F claims. So 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.

**Small Group Conclusions and Recommendations Relating to Research Endpoints**

**Background**

The statutory definition of a drug in the FDCA includes an article intended to diagnose, cure, mitigate, treat or prevent disease and “an article (other than a food) intended to affect the structure or any function of the body…” The phrase “other than a food” implicitly recognizes that a food or food ingredient can affect the structure or function of the body without thereby becoming a drug. This recognition is the basis for “structure/function” claims, which are statements regarding the effect of a food or dietary supplement on a structure or function of the body or the mechanism by which such an effect is produced. Structure/function claims may not address a disease or disorder but may be directed at healthy states that represent the absence of disease. For example, a structure/function claim for a probiotic may not suggest that the product prevents rotavirus infection, but it may state that the product helps support immune function.

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45 164 F.3d 650 (D.C. Cir. 1999).
46 See [http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/default.htm](http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/default.htm)
According to a number of Working Group members, many of the studies that have been conducted on probiotics have been conducted using endpoints that would be viewed by the FDA to be drug-use endpoints. For example, a 2010 study tested a fermented milk's ability to reduce the incidence of common infectious diseases in healthy children in day care centers.\(^{48}\) Even though this study documents a decreased incidence rate for common infectious diseases (CIDs) in the active group by 19 percent compared to a control group, use of the product in this study to prevent CID s in day care children would be considered a drug use. Under the current FDA framework for claims, this study could only be used to substantiate a drug claim, therefore making fermented milk a drug in FDA’s eyes. Working group members questioned whether this made sense.

Regarding the difficulty in measuring health improvement and/or health maintenance in a healthy person, some have suggested that the focus of studies could be in measurement of homeostasis. One article noted that, 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, assuming a biological rationale exists that tighter control of the parameter is physiologically advantageous. In other words, lessening the fluctuation around an individual’s biomarker could be interpreted as contributing to improving health. This novel idea emphasizes the importance of homeostasis as a focus of studies on health, and provides a rationale based in solid statistical theory as a way to measure wellness or health maintenance.\(^{49}\)

**Conclusions/Recommendations by Working Group**

The Working Group generally supports the use of research with drug outcomes to substantiate structure/function claims (without designating the product as a drug) as long as the effect of the product on healthy individuals is known. The ability to conduct this type of research would provide greater opportunities to conduct basic research on probiotics. The current research framework inhibits research into the use of probiotics to prevent future conditions in at-risk populations. Prevention and risk reduction studies are currently hard to complete without moving the tested product into the drug category and therefore studies that could result in appropriate structure/function claims are not conducted. Another Working Group


member suggested that there should be an acceptable way to demonstrate modulation of a condition, for example cholesterol level, in healthy individuals without making a disease claim. Such a study would be considered a drug study under current guidelines.

A significant issue discussed by the Working Group and one that requires additional discussion is that of biomarkers or endpoints. A biomarker is a characteristic that can be objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.\textsuperscript{50} Currently, it is challenging to design studies that substantiate structure/function claims because it is virtually impossible under current FDA claim substantiation requirements to find endpoints that are not disease-related, thereby pushing the product into the drug category. Validated biomarkers for disease prevention and risk reduction, especially in the gut and immune areas, for study in healthy populations are necessary. Without these acceptable endpoints, companies may not be able to conduct useful clinical trials for S/F claims. Working Group members agreed that this is a problem in research that goes beyond probiotics but one that is particularly difficult for probiotics because many endpoints tested for probiotics do not have validated biomarkers.

**Small Group Conclusions and Recommendations Relating to Medical Foods**

**Background**

A medical food (21 U.S.C. § 360ee(b)(3)) is a food which is formulated to be consumed or administered enterally (through the GI tract, whether orally or by tube) under a physician’s supervision and which is intended for specific dietary management of a disease or condition for which distinctive nutritional requirements (based on recognized scientific principles) are established by medical evaluation.

Medical foods are exempt from the requirement to bear nutrition labeling (21 CFR 101.9(j)(14)) and from the health claim and drug requirements that attend the mention of a disease relationship on a product label (see 21 CFR 101.14(f)).\textsuperscript{51} These exemption apply only if the product is

- Specially formulated and processed for partial or exclusive feeding of a patient orally or by enteral tube; and
- Intended for dietary management of a patient when it cannot be achieved by modifying the normal diet (e.g., chronic medical needs; limited/impaired capacity to ingest, digest, etc.; other special medically-determined nutrient needs); and
- Providing nutritional support to manage unique nutrient needs resulting from a specific disease/condition (per medical evaluation); and

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\textsuperscript{51} All other food labeling requirements (e.g., statement of identity, listing of ingredients, declaration of net weight, nutrient content claim restrictions, etc.) apply to medical foods. Further, all food safety standards apply to medical foods as well, including the food adulteration provisions of Section 402 of the Act and food additive and GRAS principles.
- *Intended* for use only under medical supervision; and
- *Intended* only for patients receiving active/ongoing medical supervision

There are no formal medical food regulations – just guidance. FDA advises in its guidance that it considers the statutory definition of medical foods to narrowly constrain the types of products that fit within this category of food. FDA warning letters for purported medical foods have focused primarily on the absence of distinctive nutritional requirements for the disease or condition for which the product is marketed as well as unlawful marketing practices and illegal drug claims.

Examples of medical food claims include the following:

- Phenylalanine/PKU – “A phenylalanine-free food to aid in the nutritional management of hyperphenylalaninemia including PKU.”
- Hypermetabolic states, such as severe burns, trauma, or infection – “A nutritionally complete formula that provides a concentrated source of calories for patients with restricted fluid allowance or increased energy needs…useful in the dietary management of volume-restricted patients, oncology patients, hypermetabolic conditions, trauma, sepsis, and post major surgery.”
- An example of a probiotic medical food claim is one made for a product currently available in supermarkets for lactose intolerance. The box clearly states “medical food” and the label claims that it is “the only product that uses specially isolated live cultures to help break down lactose and the complex sugars found in dairy products and other foods.”

**Conclusions/Recommendations by Working Group**

The Working Group generally concluded that expanding the Medical Foods category to encompass probiotics would not be a useful avenue for regulation of most probiotic products although it might be useful for some probiotic products.

Typically, products in the Medical Foods category are prescribed by a physician and provide a distinctive nutritional need presented by a disease condition. Medical foods can “manage” but not treat or prevent medical conditions. The “nutritional requirement” component of the statute is not well defined by the FDA, which led a number of Working Group members to conclude that the category is sufficiently flexible to incorporate a subset of probiotic products. Under the current language, a dietary need for probiotics would be required and in many cases of probiotic use by individuals, it is not clear if there is such a requirement. The original formulation of medical foods was the use of foods to help with a medical condition. Subsequently, FDA added the “nutritional need” component which makes things less clear. An outstanding question is whether probiotics satisfy a nutritional need or something else.

**Small Group Conclusions and Recommendations Relating to Implied Drug Claims**

**Background**
Under the definition of a drug in the FDCA, food labeling is permitted to include claims relating to the intended effect on the structure or function of the human body without classifying the product as a drug. Recognizing this, in the Dietary Supplement Health and Education Act of 1994 (DSHEA), Congress permitted as a “statement of nutritional support” a claim for a dietary supplement that

describes the role of a nutrient or dietary ingredient intended to affect the structure or function in humans [and] characterizes the documented mechanism by which a nutrient or dietary ingredient acts to maintain such structure or function.

In promulgating regulations under DSHEA, however, FDA stated that a structure/function claim will be considered a disease claim if it indirectly or impliedly relates to disease prevention or amelioration. Some have argued that DSHEA does not authorize FDA to regard as disease claims a structure/function claim that indirectly or impliedly relates to a disease and that FDA overreached its statutory authority.

Conclusions/Recommendations by Working Group

While this topic is one that garnered the interest of the Working Group, time limitations prevented a robust discussion of this concept.

Other Conclusions/Recommendations Relating to Over-Regulation

As noted earlier, the definition of probiotics was raised multiple times at the meeting in a variety of different contexts. Many noted the fundamental importance of an accurate definition to any discussion of regulation of probiotics. Some noted that the WHO/FAO definition includes the concept that probiotics confer a health benefit but, at the present time, we may not be able to determine which probiotics definitively confer a health benefit. One member of the Working Group suggested that we agree on a definition that grandfathers in probiotics that have been around for a long time and create a process for certifying new probiotics. Finally, in discussion groups, some noted that the Working Group should focus on harmonization with other countries in terms of their definitions and regulatory schemes relating to probiotics.

Final Thoughts

In addition to targeted discussions of specific regulatory options relating to probiotics, the Working Group engaged in broad discussions about whether, or if, probiotics present unique questions of safety or effectiveness to require modifications to the current regulatory scheme in the United States. The idea that safety and regulation should inform each other is one that has run throughout the Working Group meetings. There was substantial discussion regarding whether the group should focus on advancing the “science-side” rather than first trying to modify the “regulatory-side” or vice versa and which route is likely to achieve meaningful regulatory change.
Some Working Group members believe that the FDCA as currently crafted provides a comprehensive and potentially flexible scheme for regulating probiotic products. The Working Group members in this category note that the intended use of a probiotic product governs the regulatory category into which the product will fall and, accordingly, the regulatory requirements the product must meet. They believe that this regulatory framework offers numerous product pathways for marketing. They further note that many of the clinical testing concerns that attend probiotics can be addressed by carefully crafting study protocols to reflect and distinguish among medical food, health claim, structure/function, and drug/biologic endpoints. In this regard, if would be useful if scientific criteria for such protocols were generally agreed upon by experts so that industry and researchers would have potentially clearer pathways to develop and conduct testing and ultimately market products as supplements, foods, medical foods, or drugs/biologics as the case may be. Further, rational safety and substantiation clinical testing criteria to address the various possible regulatory categories of products (as determined by claims attending the products) would provide FDA – and the research and regulated communities – with a science-based way to meaningfully interpret, apply, and achieve the existing statutory product pathways that govern how to communicate health-related information.