

Health claims substantiation for probiotic and prebiotic products

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The topic of “Health Claims Substantiation for Probiotic and Prebiotic Products” was discussed at the 8th annual International Scientific Association for Probiotics and Prebiotics (ISAPP) meeting. The topic is especially timely considering that the regulatory review process for health benefit claims on probiotic and prebiotic products in Europe has not resulted in a single claim being approved (120 negative opinions on probiotic claims and 19 negative opinions on prebiotic claims through February 2011). This situation in Europe and elsewhere has driven companies to seek clarity on a research path that would stand up to scientific scrutiny as well as satisfy regulatory demands for health claim substantiation. It can be challenging to negotiate rigid regulatory distinctions, such as between health and disease, when these states are more realistically represented by continua. One research approach focused on improved homeostasis is explored as a statistically robust approach to measuring physiological parameters in healthy populations, which are the required target for food and supplement claims. Diverse global regulatory frameworks complicate this issue, and harmonization of different approaches globally would simplify requirements for industry, decrease consumer confusion and improve the scientific framework for the research community to set up appropriate research pathways. This report highlights key points from this discussion.

Introduction

In August, 2010, a discussion group on the topic of “Health Claims Substantiation for Probiotic and Prebiotic Products” was convened at the 8th annual International Scientific Association for Probiotics and Prebiotics (ISAPP) meeting held just outside of Barcelona, Spain. The scope of this discussion was on regulatory issues with regard to substantiation of health claims on foods and food supplements (not drugs). The group was composed of academic and industry scientists, as well as lawyers specializing in food labeling (Table 1). Although the discussion outline was comprehensive (Table 2), this report focuses on the most important themes that emerged during the discussion. All these would be worthy of further consideration and consensus development.

Regulatory Boxes vs. Continua

Key differences between the current regulatory situations in Europe, the United States, Canada, Japan, China and India were discussed. An overriding challenge is managing the different ways that consumers, healthcare professionals, regulators, legislators and scientists see the health benefit claims on probiotic and prebiotic products. A lack of unified perspective exists: while most consumers, healthcare professionals and scientists perceive a continuum between the extremes of “health and disease”, “food and drugs”, “emerging evidence and supported with significant scientific agreement”, generally legislation—and the subsequent enforcement of

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Abbreviations: ISAPP, International Scientific Association for Probiotics and Prebiotics; FDA, Food and Drug Administration

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Table 1. Composition of discussion group convened on the topic of “Health claims substantiation for probiotic and prebiotic products” at the 8th annual ISAPP meeting

Name	Affiliation	Country
Mary Ellen Sanders (Chair)	Dairy & Food Culture Technologies (Consultant), Executive Director, ISAPP	USA
Seppo Salminen (Co-Chair)	University of Turku	Finland
Lara Ambrosetti	Ginsana SA/subsidiary of Boehringer Ingelheim GmbH	Switzerland
Silvia Bañares	Professor of Commercial Law, University Abat Oliva, Barcelona	Spain
Linda Duffy	NIH, National Center for Complementary and Alternative Medicine	USA
Frederic Durmont	Institut Rosell/Lallemand	Switzerland
Reg Fletcher	Kellogg Europe Trading Ltd.	Ireland
Miguel Gueimonde	IPLA (Spanish Government Research Institute)	Spain
Raj Gupta	Biocodex	USA
James Heimbach	JHEIMBACH LLC	USA
Ulrika Hinkel	Boehringer Ingelheim GmbH	Germany
Ivana Jankovic	Nestle	Switzerland
Gunhild Kozianowski	Beneo Institute	Germany
Jha Ashok Kumar	Sathguru Management Consultants	India
Anu Lähteenmäki-Uutela	University of Turku	Finland
Niklas Larsson	Probi	Sweden
Irene Lenoir-Wijnkoop	Danone Research	France
Greg Leyer	Danisco USA	USA
Sandra Macfarlane	Microbiology and Gut Biology Group, University of Dundee	Scotland
Tami Mackle	Pfizer Nutrition	USA
Lorenzo Morelli	Microbiology Institute, Catholic University, Piacenza	Italy
Raymond O'Rourke	Food Lawyer	Ireland
Andreu Palou	Spanish Food Agency Authority	Spain
Kayla Polzin	Cargill	USA
Bruno Pot	Institut Pasteur de Lille	France
Ger Rijkers	Department of Medical Microbiology and Immunology, St. Antonius Hospital, Nieuwegein	Netherlands
Yolanda Sanz	Institute of Agrochemistry and Food Technology, Spanish National Research Council	Spain
Margriet Schoterman	FrieslandCampina Domo	Netherlands
Dan Tancredi	Assistant Professor of Pediatrics, UC Davis School of Medicine and Center for Healthcare Policy and Research	USA
Henk van Loveren	Professor of Immunotoxicology, Maastricht University	Netherlands
Carey Walker	Mead Johnson Nutrition	USA
Rob Welch	University of Ulster Coleraine	Northern Ireland
Jia Zhao	Yakult Europe	Netherlands

this legislation—partitions these entities into distinct compartments (Fig. 1). The regulatory box paradigm adopted by many countries imposes substantial hurdles for research, consumer understanding and marketing of functional foods. A scientific argument can be made that in the cases where a product meets the safety standard for a food, it would be sensible that labels on foods should be able to communicate whatever use is substantiated

(accompanied, perhaps, by an indication of the strength of the support). However, in some regulatory frameworks, substances recognized in general as foods, which are safely consumed by consumers with sub-optimal health status, are lumped together with drugs if they are labeled (or in some cases, even studied) to provide dietary management of health conditions, reduce the risk of developing an acute condition, ameliorate symptoms or improve a patient's

responsiveness to drug therapy. This conversion of foods into drugs occurs despite the fact that healthcare providers on a daily basis counsel their patients in how to incorporate foods into their diet for many of these supposed “treatment” purposes.

In many countries, the distinction between drugs and foods relies on how the product is labelled and used. A product labelled to treat or prevent disease is considered a drug by many regulatory

Table 2. Outline for discussion on the topic of “Health claims substantiation for probiotic and prebiotic products” at the 8th annual ISAPP meeting

Brief update on current situation with claims on probiotic/prebiotic products

Standards of evidence required for claims:

- How much is enough
- What types are enough
- Is scientific rigor and magnitude of effects required for foods/supplements the same as for drugs?
- What is a “gold standard” of evidence for probiotic foods/supplements?

Overview of the challenges of nutrition research: Establishing causality between foods and health benefits

Perspectives of a biostatistician on:

- Negative studies or conflicting results
- Statistical significance compared to biological meaningfulness
- The lack of the ideal human trial

What study populations are appropriate for food claims?

- Extrapolation from study populations to general population
- Population subgroups: elderly, infants, children, etc.,
- How might approaches need to adapt with new information from human microbiome project, individualized nutrition issues?

Guidelines for the design, conduct and reporting of human studies to evaluate the health benefits of foods

Wording of health claims

Probiotic/prebiotic research targets often are on endpoints that are not measurable with validated biomarkers and have no recognized risk factors that are intermediate measures of health responses. What are recommendations for research on probiotics/prebiotics for foods?

Clinical endpoints and biomarkers in probiotic research

- Present proposal to develop a position paper on biomarkers/risk factors with the following goals:
 - analyze all the markers used to assess health benefits in human studies with pro and prebiotics (we can start with ILSI guidelines and list all markers and benefits mentioned there)
 - estimate the relevance of using biomarkers compared to clinical outcomes and propose the best solution for each benefit
 - analyze each of the proposed biomarkers (method of assessment, levels in healthy individuals, increased risk levels, validation status...) drawing from available literature
 - propose what needs to be done to validate each biomarker
- Present example biomarkers (validated and non-validated)
- Is there consensus of value of proceeding with this? If so, than how to do it (ISAPP, ILSI, both or ?)

Perspectives on the problem of bioequivalency among different in vitro factors that might impact probiotic functionality in vivo

frameworks, whereas foods may be used to support or maintain normal body functions or reduce the risk of disease in the generally healthy population. However, the distinction between disease prevention and risk reduction is not clear scientifically. Furthermore, the growing body of scientific evidence demonstrates that some foods may be able to prevent or mitigate certain disease or illness. Rigorous scientific demonstration of this capability may be rendered meaningless by regulatory constraints on communicating these findings. Also, even if the regulatory environment is restrictive of claims, it is important that it be recognized that there is a difference between research and claims, and even if allowable claims are limited, the research on foods shouldn't be. The current interpretations of the border between foods and drugs perhaps made sense when less

information was available about the role of food and food ingredients in maintaining health and affecting the structure and function of the body, and fewer borderline products existed. However, both the science and the markets have progressed. If regulations were written de novo today, functional foods and medicines might be regulated under a common framework for various types of health-related claims and their substantiation. A complicating situation is that despite the regulatory categories, the difference between food and drugs is not always clear to the consumer.

There appears to be a similarly non-fluid regulatory view of health and disease in many countries.¹⁻⁴ A noteworthy exception exists in Japan, where Foods for Specialized Health Use (FOSHU) is targeted not only to healthy people, but also to people at the first stage of any illness

or borderline condition.⁵ Even though the medical community does not uniformly agree, people who may be experiencing suboptimal health, symptoms, syndromes or illness [defined as the subjective response of the patient to being unwell^{6,7}] are all viewed as having a “disease” by many regulatory interpretations. Under this interpretation, use of a “food” to help improve such health conditions would be viewed as a drug-use and would not be allowed. This is true even though in some cases, products commonly understood as foods may provide a safe and effective approach for the management of so-defined disease situations. For example, a food or dietary supplement shown to ameliorate the nausea that results from chemotherapy and thus help cancer patients reduce the inanition and wasting (but not treat the cancer) that often accompany the disease,

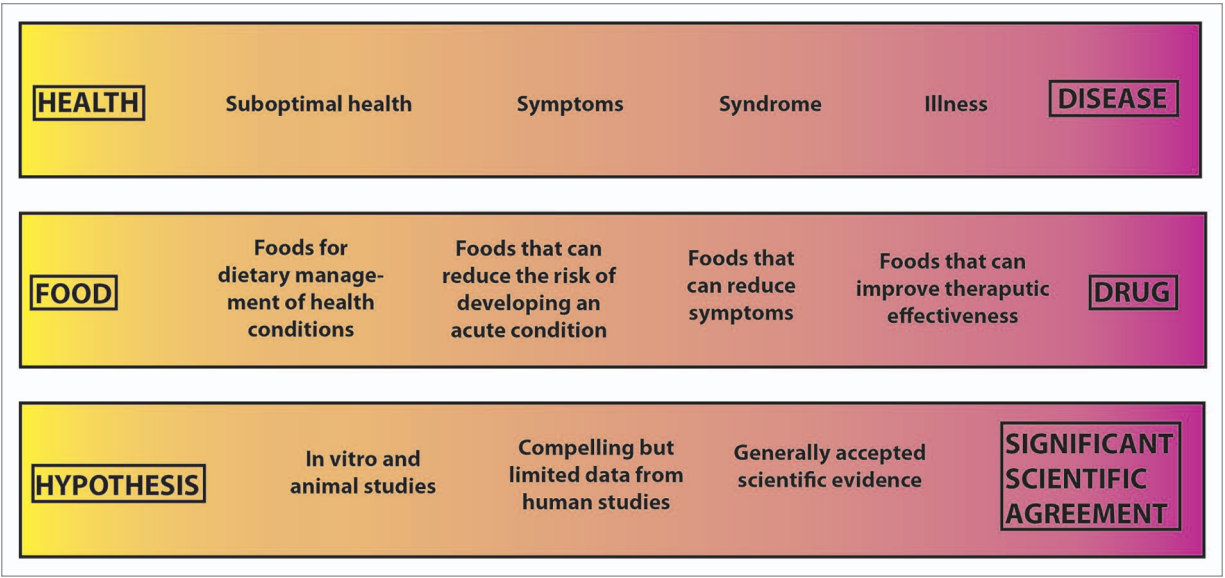


Figure 1. Regulatory compared to scientific understanding of terms found in food and drug law. In regulations, discrete distinctions are made between health and disease, food and drugs and acceptable and unacceptable levels of evidence to support claims. In scientific practice and clinical practice, these concepts are understood to span a continuum.

should not be treated as a drug. Children with ear infections (but with healthy guts) prescribed antibiotics should be able to eat a probiotic- or prebiotic-containing food demonstrated by rigorous research to help keep their guts healthy during therapy. Certain probiotics have been shown to reduce the infection rate with *Clostridium difficile*,⁸ reduce the risk, severity or duration of rotavirus-induced gastroenteritis,⁹ reduce the risk of developing atopic dermatitis,^{10,11} or reduce the incidence of common infectious diseases.^{12,13} Certain prebiotics have been shown to reduce the incidence of conditions such as travelers' diarrhea,¹⁴ antibiotic-associated diarrhea¹⁵ and infant diarrhea.¹⁶ Examples of such uses for foods are numerous. Although the number of studies required to constitute convincing evidence for these uses is a subject of much discussion, the important point is that if validated, such uses for foods would be useful for consumers but often precluded by regulatory authorities.

Another example where continua pose challenges for regulators lies in considering levels of evidence supporting health benefit claims. The strength of evidence on health benefits of foods can range from "emerging evidence" to "significant scientific agreement," and understandably, regulations favor the latter over the former. In the European Union, whereas

the review process is required to provide "scientific assessment of the highest possible standard," health claims are "based on and substantiated by generally accepted scientific evidence."¹⁷ However, it seems that in practice, the reviewers expect the *evidence* must meet the highest possible standard. In the United States the standard was "significant scientific agreement" until the Food and Drug Administration (FDA) was successfully sued on the basis that this standard unduly restricted commercial free speech.¹⁸ This ruling created "qualified health claims" in the US, a standard which acknowledges the continuum between emerging evidence and significant scientific agreement. Although claims now can be based on evidence that falls short of significant scientific agreement, the claim still requires pre-approval from the FDA. Such qualified health claims pose the challenge of accurately communicating the subtleties of limited scientific evidence to scientifically naïve consumers. This is no trivial undertaking, and those tasked with approval of claim language clearly have an underlying concern for protecting the consumer against misleading marketing messages. Although the scientific community would agree that evidence in support of health claims must be compelling, it also recognizes that all studies have limitations, and a standard

that requires a *reasonable level of evidence of substantiation* of a health benefit may serve all stakeholders better than a standard of the *highest possible evidence*. Finally, when considering the different standards of evidence required in different geographical regions, it becomes apparent that a harmonized approach to health benefit claims could provide clear benefits. Compliance with all regulations on substantiation and wording of health benefit claims in different regions of the world is a sizable challenge, and efforts to seek harmonization perhaps through Codex or other international collaborations could be worthwhile.

Foods vs. Drugs

Certain current regulatory frameworks require that food-form products that prevent or manage diseases be subjected to drug oversight. But important differences exist between scientific substantiation for foods and drugs, and these differences can make it difficult (and unnecessary) for foods to meet drug standards.¹⁹ Some of these differences that are relevant to food as a subject of interventional human studies are:

- Foods and food ingredients meet a higher standard of safety than do drugs: risk vs. benefit is generally not part of the assessment. History of safe use is often an important component of safety assessments.

- Foods are readily available to the total population, in non-limited amounts. Zero intake for a control group in a study may not be attainable.

- Foods must be considered as part of an overall healthy diet.

- Choice of a control product can be difficult when assessing functional ingredients in foods. The food without the functional ingredient is a likely choice for a control, but the control food itself may contribute to a physiological effect (e.g., conventional yogurt compared to a probiotic yogurt). The choice of a control product is driven in part by the research question being asked; however, to achieve blinding in a study on functional food, a control comprised of the food matrix must be used.

- Generally the anticipated magnitude of effect is smaller than for drugs.

- Unlike pills, food formulations can change frequently (new flavors, functional ingredients, levels of macronutrients, targeted formulations for different geographical regions). An important consideration for research on foods is determining when a new food formulation differs substantively from the researched food, requiring confirmatory efficacy studies.

- Profit margins are lower for foods than for drugs. This leads to a disparity with research investment possible by food compared to drug companies.

- Foods are most often natural rather than synthetic products, not produced under drug manufacturing practices, and are more likely to show batch-to-batch variability.

It should be noted that although dietary supplements are generally considered within food regulations, some of the differences highlighted above between foods and drugs do not pertain to dietary supplements. For example, formulation of an inert placebo for a dietary supplement is generally a straightforward choice, supplements do not contribute calorically to consumers' diet, matrix effects may not be as variable for supplement formulations and zero-intake may be easy to establish for subjects in studies.

Studies on foods should be of high-quality and well-controlled. But differences between foods and drugs compel recognition that the type of evidence

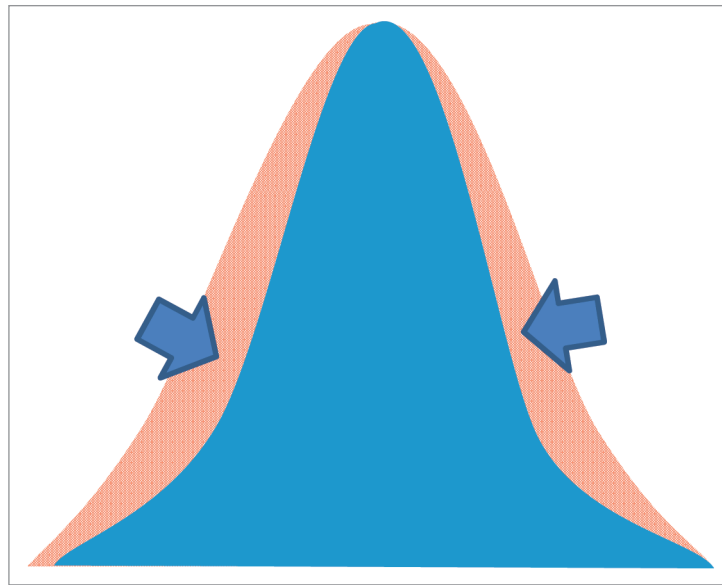


Figure 2. Visualization of the concept of improved homeostasis. An intervention able to minimize the variation around the mean for a specific measure, even in the absence of changing the mean, would be a demonstration of improved homeostasis.

required for efficacy may be different. For example, Blumberg et al.²⁰ recently questioned the appropriateness of randomized controlled trials for foods.

A regulatory framework that recognized the existence of the above-described continua would provide an environment where the full role of foods (including nutritional supplements) in promoting health, reducing the risk of disease and managing health conditions could be realized.

Implementing such a regulatory framework would present numerous challenges, but in the end consumers may benefit from such changes. However, one unintended consequence of this regulatory approach that would need to be considered is the risk of therapy substitution. Many health conditions require medical intervention, for which foods cannot substitute. Consumers are attracted to the ready availability, economy and lack of side effects from foods, but must be adequately informed by clear labeling when foods cannot substitute for needed medical intervention.

Homeostasis and Health: A Statistical Approach

One sizable challenge due to the current regulatory frameworks is how to conduct

meaningful studies on probiotics or prebiotics in healthy humans. How does one show that health is improved—or even more challenging, maintained—in a healthy person? What does “maintained” mean as a study outcome? One approach is demonstration of reduced incidence of disease or illness. Such a study would be conducted in healthy people, but it may be prohibitively expensive due to low incidence or long latency, depending on the endpoint being examined. Tracking the incidence of dental caries is an example of an endpoint that may be successfully undertaken with a manageable budget and time frame. But measuring the impact on immune function with concomitant demonstration of reduced common infectious diseases, for example, would be a much more expensive and lengthy study. Another approach, which would not require tracking a disease or illness endpoint, would entail measurement of homeostasis, as suggested by D. Tancredi. From a statistical point of view, if an intervention were able to minimize the variation around the mean for a specific measure (even in the absence of changing the mean; Fig. 2), 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

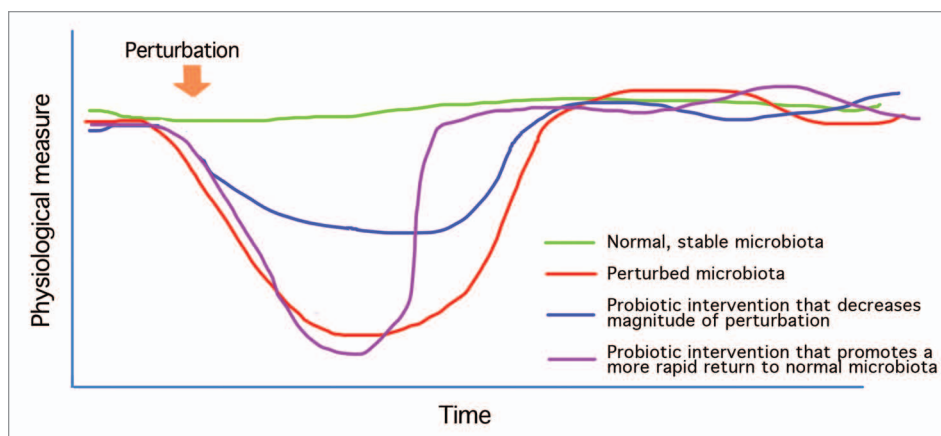


Figure 3. The concept of homeostasis as expressed by reducing the magnitude or duration of fluctuations. Such a study could be conducted in healthy people, by collecting repeated measures of the physiological measure and comparing intervention and control groups on summary measures of the amount of within-person fluctuation. The study design could also include a timed sequence of challenges designed to disturb the measure, allowing between-group comparisons on resistance to perturbation. Modified after Ger Rijkers, personal communication.

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 this.

One challenge to demonstrating the value of this approach is to identify appropriate biomarkers that could be studied. The following properties would be important to a biomarker:

- maintaining moderate levels of the biomarker is associated with good health;
- high or low values are associated with ill health;
- biomarker levels in the same person can fluctuate over time; and
- reducing the magnitude or duration of such fluctuations in healthy people is considered desirable (Fig. 3).

Such a biomarker could be an individual endpoint or be formed as a ratio of two other biomarkers, when maintaining the same relative amounts of the two component biomarkers would be desirable.

Assuming a biomarker with the above properties is available, it could be used as the outcome measure in a randomized controlled trial to provide evidence that the experimental food is able to improve the maintenance of health in humans. Statistically, the trial would be set up to address the hypothesis that the experimental substance is associated with lower variation in biomarker levels, compared to the control arm, in subjects who were healthy at baseline. Such a trial would be

able to use information on within-person variations in biomarker levels, even those who did not become ill. Partly as a result of the more efficient use of study data, such a trial would require far fewer subjects than an intervention that instead addressed the hypothesis that treatment is associated with fewer healthy persons becoming ill.

A mounting understanding of the value of stability of the colonizing microbial communities makes this endpoint an attractive one to consider. Perturbation of gut microbiota is associated with intestinal dysfunction, as illustrated during antibiotic treatment. Specific probiotics have been shown to promote a quicker rebound from antibiotic-induced microbiota disruption, including a study on *Lactobacillus rhamnosus* GG (LGG).²¹ This paper concludes "...that a key mechanism for the protective effect of LGG supplementation on the subsequent development of allergic disease is through the promotion of a stable, even and functionally redundant infant gastrointestinal community."

However, it would be useful to define additional biomarkers that would be appropriate targets for this type of investigation.

In pediatric nutrition, the measurement of metabolic homeostasis has become a standard approach when developing infant formulas.²² The concept of homeostasis as a model to distinguish between foods (including food supplements) and medicinal products was explored by the Council of Europe,²³ and is an interesting correlate to the above hypothesis.

Economic Impact

According to a 2006 World Bank report on health enhancing foods, "cost-effectiveness of functional foods in reducing disease burden and lost productivity is an important research gap."²⁴ While there is a growing interest in evidence-based health care, evidence on cost-effectiveness is often lacking. The pharmaceutical industry and the medical community have introduced science-based economic evaluation of health management programs and care protocols as well as standardized treatment protocols. These studies have established the principles of cost-benefit and cost-effectiveness assessments, evaluating not only the health spending but also the economic benefits.^{25,26} Such benefits could include, for example, the public health savings induced by health management programs. Approaches that establish procedures for the assessment of the role of food with particular beneficial effects on health, well-being and quality of life in our society are needed. Such assessment would provide important perspective on the economic impact of a regulatory framework that encourages research and communication on the health benefits of foods, and the subsequent broad implementation in the diet of target populations.

Conclusions

A reassessment of the regulatory approach to functional foods in general, and

probiotics and prebiotics in particular, is needed. Promulgated in the interest in protecting the consumer from fraudulent claims or from unsafe products, in some cases the regulatory standards being implemented have the unintended consequences of keeping valuable information from being communicated to consumers and healthcare providers, and perhaps more worrisome, may effectively discourage investment by food companies in research to explore the health benefits of their products. Success with research is never guaranteed, but companies seek clarity on a research path that at least should have the potential to result in a favorable assessment by regulators. Harmonization of different approaches globally would simplify requirements for industry, decrease consumer confusion and improve the scientific framework for the research community to set up appropriate research pathways. Conversations among all stakeholders to work toward regulatory frameworks more consistent with accepted scientific concepts of “continuum” and “suboptimal” are needed. The “continuum” approach does not seem fully possible without a change in law, as the current law clearly separates products, health conditions and evidence into discrete entities. A more flexible approach could contribute to better informed choices, increased consumer protection and encouragement of scientific innovation leading to improved health of the targeted populations. In addition, there are few endpoints for human studies that will satisfy the restrictive nature of endpoints that are physiologically meaningful but allowable in the current regulatory environment for probiotics and prebiotics. Development of new approaches for measuring health, such as the proposed assessment of homeostasis, is needed.

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