MORE THAN A GUT FEELING:

THE REGULATIONS ON USING PROBIOTICS TO BUILD A BETTER MICROBIOME

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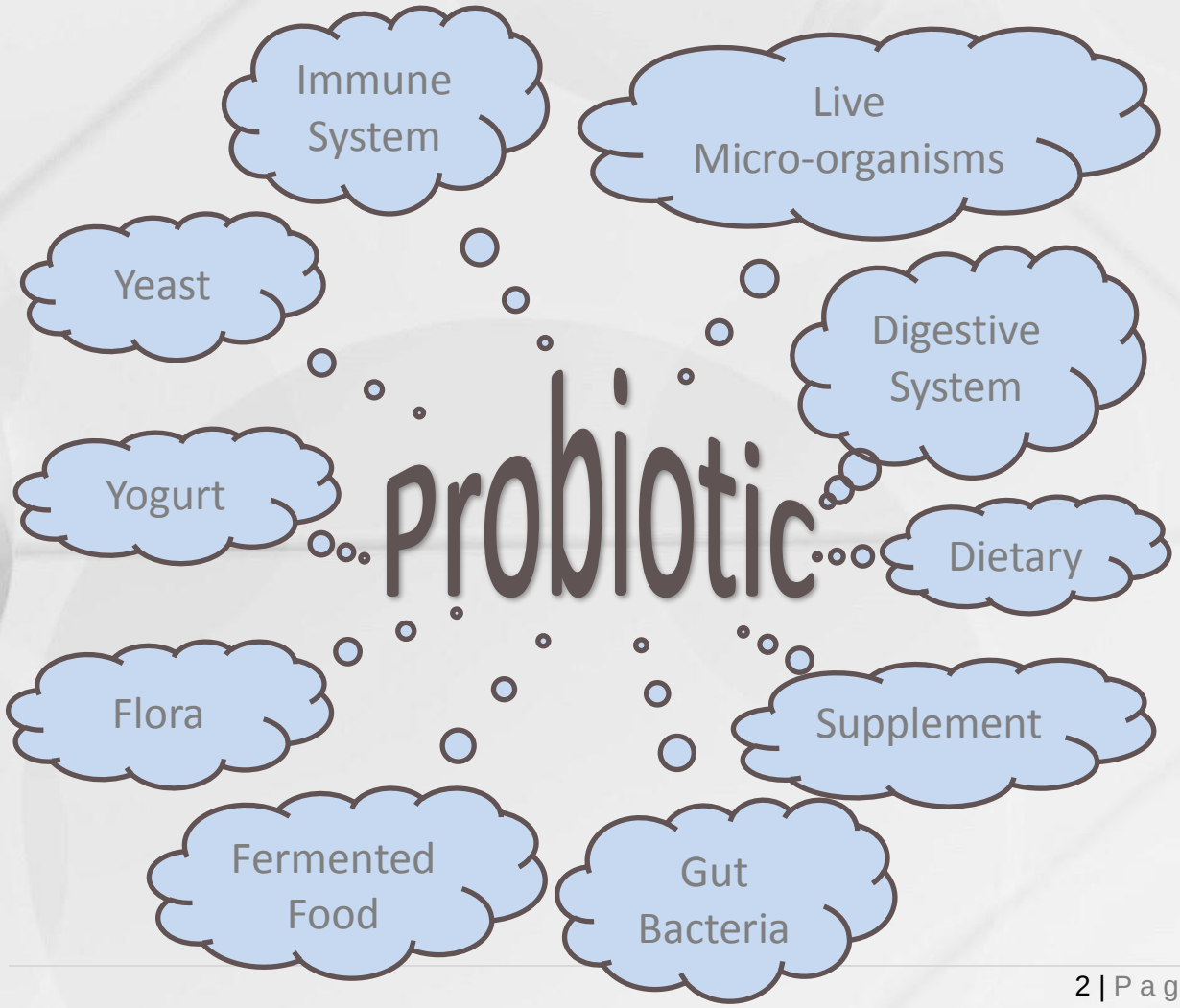
Overview: Gut Microbiome and the Marketplace

A vital organ made up of trillions of microbes that are invisible and completely alien to, not derived from and not part of our human cell lines, inhabits our gut (1). These microbes hold the potential to redefine how we understand our health, ourselves and disease(2). Research on the microbiome has exploded due to new techniques that enable identification of bacterial species without isolating and culturing – a process highly limited in its scope. Whole-metagenome shotgun analysis and sequencing of ribosomal 16S RNA strands, has expanded our knowledge moving us from a basic understanding of the microbiome to a place of awe at the enormity of this still untapped universe. These techniques now allow us to explore the sophisticated interplay between the microbiota and the human body. While probiotics have a long history of use in many countries around the globe, the North American market is consumer driven, putting more emphasis on the need for research. Tracking these market changes are regulators in the US, Europe and Canada.

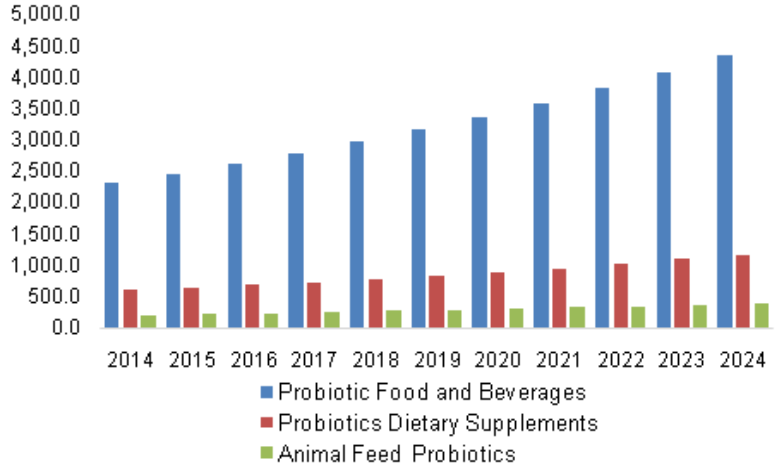
Beneficial microbes found in probiotic supplements are known to optimize a challenged microbiome. The term probiotic is derived from the Latin preposition “pro,” which means “for” and the Greek word “biotic” meaning “bios” or “life”. The joint FAO/WHO report defines probiotics as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.” (3).



The global probiotics market size exceeded 35 billion USD in 2015 and is expected to reach 74 billion by the year 2024 (Figure 1)(4). The food & beverages segment which is comprised of dairy and non-dairy products, cereals, baked foods, fermented products, and dry food probiotics accounted for more than 85% of the total revenue (4). Second were dietary supplement probiotics including food supplements, nutritional supplements, specialty nutrients and infant formula.

Species of *Lactobacillus* and *Bifidobacterium* bacteria are the most commonly used probiotics in products, such as starter cultures for the fermentation of yogurt and cheese, and animal products among others. Other species in the market include *Escherichia coli* Nissle, some *Enterococcus*, certain *Bacillus* species, and strains of yeasts such as *Saccharomyces cerevisiae* (baker's yeast)(5).

Figure 1. The U.S. Probiotics Market Revenue by Product, 2014 – '24 (USD Million)



Source: Grand View research Report ID: 978-1-68038-093-4 September 2016 | 85 Pages http://www.grandviewresearch.com/industry-analysis/probiotics-market

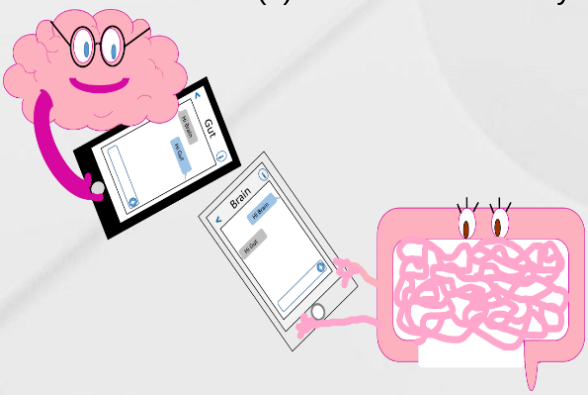
The complementary health questionnaire developed by NIH's National Center for Complementary and Integrative Health (NCCIH) and the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS) questionnaire identified that more consumers are not only looking for but are also purchasing products that have science to support their claims. A December 2015 poll by the Pew Research Center found that seven-in-ten adults (70%) said they were interested in "health and medicine", over local events in their community, science and technology, government and politics, religion and spirituality, entertainment and celebrities, sports, business and finance, or art and theater (6). Women are especially likely to express interest in health and medical topics. Approximately half of the women (52%) surveyed say health and medicine is among the top three topics of interest compared with less than a quarter (22%) among men (6). Furthermore, older adults (ages 50 to 64) were found to be more likely interested in health and medicine than younger adults (ages 18 to 29)(6).

Emerging Probiotic Research

The National Institutes of Health Roadmap 'Human Microbiome Project' and similar projects in other parts of the world, are studying how the microbiota might impact human health. Translating these findings into effective interventions that optimize health, is challenging (7).

Research on the human gut microbiome has revealed a sophisticated interplay between the microbiome and the host immune system and metabolism (8). It has been established that bacteria aid in many important metabolic pathways, including synthesis of essential compounds like secondary bile acids and short-chain fatty acids. The mechanisms whereby bacteria affect host physiology are being studied from a gene context and a functional perspective. Bacteria able to synthesize short chain fatty acids, including acetate, butyrate, and propionate, have been found to be critical for colonocyte homeostasis, and their imbalance has been documented in inflammatory bowel diseases and type II diabetes

Clinical studies have addressed probiotic foods and supplements and their potential beneficial effect on disease (9). Recent meta-analyses have demonstrated the efficacy of numerous probiotics, including; *E. faecium, S. thermophilus, L. rhamnosus,* and *L. reuteri*, at reducing cholesterol absorption. Furthermore, emerging evidence has indicated an anti-inflammatory effect for certain probiotics such as *L. reuteri,* which was shown to improve the inflammatory status in participants with rheumatoid arthritis (10-14). Interestingly, the microbiome has also been implicated in neurodevelopment and establishment of behavioral phenotypes. Researchers have shown that participants who consumed a multispecies probiotic supplement had significant impact on cognitive reactivity (15). In addition, administration of a probiotic mixture containing *L. acidophilus*, *L. casei* and *B. bifidum* was found to improve depression status and metabolic profile in patients with major depressive disorder (16).



Probiotics act by secreting substances that inhibit pathogenic bacteria, competing for nutrients, stimulating the body's immune system and interacting with nervous system receptors present in the gut. A United States government funded study with *Lactobacillus rhamnosus* GG showed that giving older, healthy individuals this probiotic supplement (10 billion CFU/day) appeared to modulate bacterial activity in ways which could promote interactions with the gut lining and anti-inflammatory pathways(17).

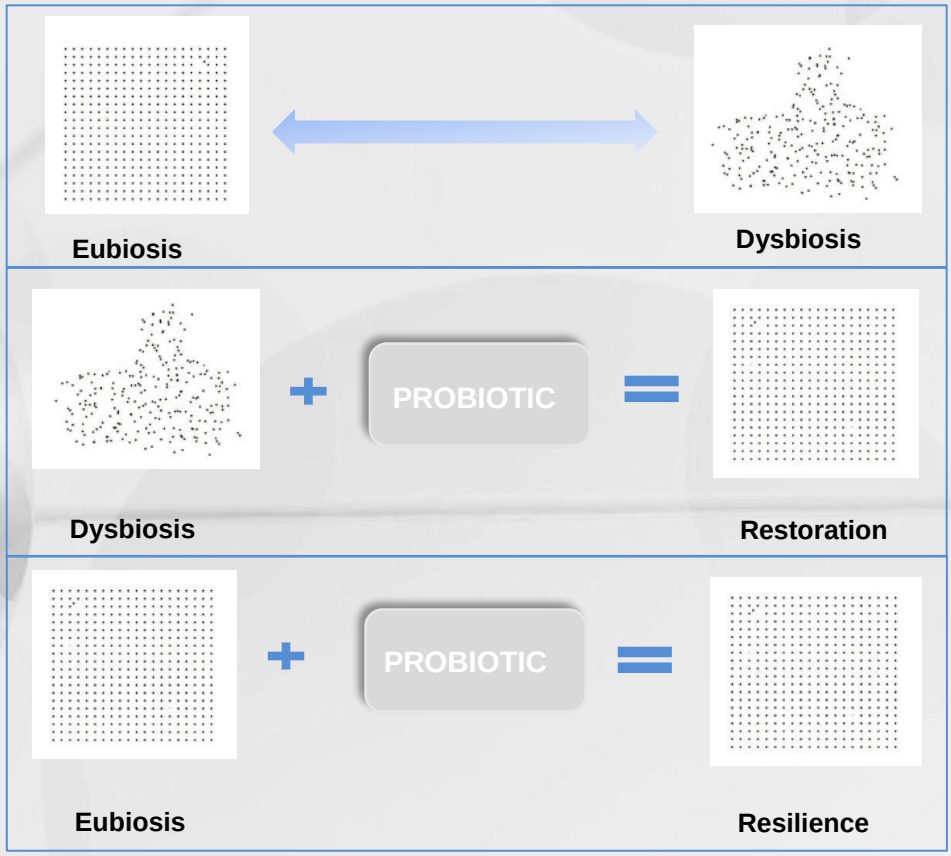
Research on probiotics encompasses investigations into their safety and tolerability, as well as potential roles in risk reduction and treatment of disease (18). A strong demand and large market opportunity exists for probiotic claim substantiation in healthy populations. Major challenges of conducting proper clinical trials with this population include: a lack of consistency in the design of clinical trials, the probiotic strains and concentrations utilized, and no standardized healthy phenotype for the intestinal microbiota. The multi-faceted effects of probiotics may require an

augmentation to the gold standard randomized controlled trial to better capture their efficacy. If guidance to assist claim substantiation is to exist, their needs to be boundaries around the design of studies to ensure safety as well as provide optimal conditions and surrogate biomarkers to capture the physiological effects of probiotics in healthy populations.

The Transitioning Microbiome: Healthy to Disease

The microbiota in the gastrointestinal tract, is composed of different cell types that communicate with each other and with their host and have defined functions, including; consuming, preserving and redistributing energy; operating physiologically important chemical transformations; and able to maintain and repair itself by self-replication (19). A healthy intestinal microbial ecosystem is balanced but flexible enough to withstand challenges and insults to the gut. The intestinal microbial ecosystem balance is termed, “eubiosis”, a state where beneficial species predominate (19). A deviation from healthy microbial compositions is termed “dysbiosis”, and has been linked with several disease states and inflammation-linked disorders such as allergies, cardiovascular disease, diabetes, cognition, obesity, and inflammatory bowel disease(19). Dietary choices, antibiotic treatment and pathogens can disturb eubiosis. For example, a consequence of antibiotic treatment may be the proliferation of opportunistic endogenous pathogens (e.g. *Clostridium difficile*) and exogenous pathogens due to conditions that better support their growth.

Figure 2: The Transitioning Microbiome



The Regulatory Landscape

Successful and responsible introduction of probiotic products into the global market requires labeling that provides realistic expectations of health benefits to the consumer and complies with regulatory requirements. Regulations for labeling claims differ among countries, but at their base is a requirement for scientific support for any statements regarding health benefits.

Probiotics have intrinsic and distinct characteristics that need to be considered when bringing products to market (20). Probiotics are live organisms, dynamic in nature and provide multi-faceted effects that are unlike pharmaceuticals which are designed to target a single function. Probiotics may degrade and lose their viability under certain circumstances. Because of this there are some unique questions regarding dosing, manufacture, storage, and shelf life.

United States

Under Dietary Supplement Health and Education Act (DSHEA), the Food and Drug Administration (FDA) and Federal Trade Commission (FTC) have shared jurisdiction over the substantiation of structure-function claims.

The FDA‘s Center for Food Safety and Applied Nutrition has primary responsibility for overseeing claims made on dietary supplement product labeling, including packaging, inserts and other promotional materials distributed at the point of sale. The FTC has primary responsibility for claims in advertising, including print and broadcast ads, infomercials, catalogues, and similar direct marketing materials. The FTC enforces laws that are designed to ensure that consumers get accurate information about dietary supplements so that they can make informed decisions about these products.

The FTC and FDA will often work together, under a long-standing liaison agreement governing the enforcement activities related to dietary supplements. Lawyers working in the industry have noted a growing increase in collaboration between the two agencies.

Probiotics are regulated by the FDA based on the product category into which they fall, i.e., food, food additive, cosmetic, dietary supplement, or drug (20). When questions arise regarding which category a probiotic belongs, the answer is determined on a case-by-case basis. Moreover, although many are sold as dietary supplements, probiotics are not specifically listed under the definition of dietary supplements.

Ingredients for which there is no proof of marketing in the US prior to 1994 are required to submit a New Dietary Ingredient (NDI) application to the FDA before sale as a dietary supplement. In examining whether a probiotic is a new ingredient; it must be compared to products previously available on the market or to previous NDI applications. The FDA has indicated that it may not be enough to have the same species of microorganism, the strain must also be considered. The degree of homology of the strain based on the genome may be considered by the FDA (21). However, this is currently being debated as the FDA has recently put forth a draft guidance on new dietary ingredient notifications and related issues.

FTC Regulation of Product and Labeling Claims

FTC assesses substantiation of claims from the point of view of a “reasonable consumer”. This is of importance when considering if a particular end-point may fall into the disease/drug category. For example, if a product “reduces pain” would a “reasonable consumer” consider using the product for any type of pain. The FTC requires that the claims be truthful and not misleading; and must have reasonable basis for substantiation based on sound scientific evidence. The FTC has increased its number of cases against dietary supplement companies from 120 in the 20 years between 1984 to 2003, to 100 in the two year span of 2014-2015 (22;23)

In 2010, the FTC alleged that Nestlé Healthcare Nutrition (HCN) made misleading claims in television, magazine, and print ads about its probiotic product BOOST Kid Essentials.(24). The FTC found that there was a lack of clinical studies to support these statements and led to the FTC prohibiting Nestlé HCN from making these claims unless they were accompanied by significant scientific agreement (25).

The FTC charged The Dannon Company with misleading advertising in allegedly exaggerated health benefits of its DanActive dairy drink and Activia yogurt (26). Per the FTC’s complaint, Dannon represented, expressly or by implication, that drinking DanActive reduces the likelihood of getting a cold or the flu. Dannon agreed to a settlement with the FTC that limited these health statements but allowed for Activia to be marketed to “relieve temporary irregularity or help with slow intestinal transit time” if consumed at 3 servings per day (27). The FTC reiterated a “two well designed human clinical studies” claim substantiation standard expressed in earlier settlements.

The regulatory body (CFIA) in Canada also examined Dannon’s advertising and the company agreed to make changes to the labeling and advertising of Activia and DanActive by increasing visibility of the scientific names of the “probiotic” cultures in the yogurts, and rewording health statements to be less misleading, court documents said (28).

In September of 2014 the FTC filed a motion holding Bayer in contempt of a 2007 consent order that required Bayer to possess “competent and reliable scientific evidence” for dietary supplement claims (29). The case regarded claims made for a probiotic dietary supplement called Phillip’s Colon Health for prevention of constipation, diarrhea, gas and bloating. The Justice Department attorneys argued that the claims imply that the product can prevent, cure or treat symptoms of gastrointestinal distress. The Feds maintained that, given the claims made for Phillips’ Colon Health, Bayer should have conducted randomized, placebo-controlled clinical trials. Bayer disputed the notion that Phillips’ Colon Health should be used to mitigate, prevent or treat any disease; that clinical trials are needed to substantiate any claims since these are “generally required for drugs” and not for dietary supplements.

Interestingly, in 2015, the US District Court for New Jersey rebuffed the FTC’s argument (30). The Court rejected the FTC’s attempt to argue that the use of the phrase, “prevention of occasional digestive upsets” in a single store advertisement was a "disease" claim, justifying the requirement of clinical trials as substantiation. The Court stated that merely using the word "prevention" does not automatically mean prevention of disease. The use of the terms “occasional” and the described symptom, “digestive upsets,” indicate structure-function

claims. Per guidance in the Federal Register, the term “promotes digestion” does not refer explicitly or implicitly to an effect on a disease state.

The Court observed that the FTC Advertising Guide establishes that the standard applied by FDA for the approval of drug products, two long term double blinded placebo controlled clinical trials, is not what is required to support claims for dietary supplements, rather: "Randomized clinical trials are not required. Instead the Court found that, "competent and reliable scientific evidence" is a 'flexible" standard, and there is no fixed formula for the number or type of studies required. Although well controlled human clinical studies are the most reliable form of evidence, they are not necessary.

However, the FTC standard has not changed and the current regulatory landscape requires scientific evidence for claims substantiation.

Canada

Canada is arguably at the forefront of regulating probiotics having already permitted certain non-strain specific claims (31). Health Canada regulates probiotics as Food Ingredients and as Natural Health Products (NHP). Live bacterial cultures, including those represented as "probiotics", are food ingredients and can be added to food products under the food provisions of the Food and Drug Regulations. At present, probiotics are primarily found in dairy products such as yogurts, cheeses, and milk-based beverages (32).

Probiotics sold in pharmaceutical dosage forms (e.g. tablets, capsules) are considered NHPs. Health Canada developed a Probiotics Monograph that includes detailed information on acceptable health claims, associated doses, source materials and required risk information (33). All probiotic natural health products are subject to pre-market assessment and licensing which requires the manufacturer to provide evidence of safety and efficacy under the product’s recommended conditions of use. If a product complies with the monograph requirements, it is eligible for expedited review of its marketing application.

To be considered a probiotic as per Health Canada regulations, the product must fulfill two eligibility components. First, the strain(s) must be present on the list of accepted bacterial species. The Canadian probiotics monograph specifies which probiotics strains are eligible and those that are excluded from a general claim of “contains probiotics” (See reference below Table 1). Secondly, there must be minimum of 1 billion CFU (colony forming units) of the eligible microorganism(s). When marketing this health claim, the non-strain specific claim can only describe the nature of probiotics as they exist naturally as part of human gut flora. The claim cannot be extended to any specific health benefit and must remain general as is adhered to by the expression of “optimizing intestinal flora health”.

Health Canada’s non-strain specific monograph allows for generalized health claims to be made for a list of approved strains of live microorganisms when present in adequate amounts (1 billion^{+} CFU) (See reference below Table 1). These regulations also allow for additional strain-specific claims not specified in the monograph, but a manufacturer wishing to use such claims must provide additional evidence to Health. To market a product under these regulations, manufacturers must attest to strain-specific evidence regarding the identity, safety and efficacy of

the probiotic. Lastly, Health Canada requires that all probiotic strains used are adequately identified and quantified on the label and that the level of microorganisms listed must be present at the quantities stated throughout the products shelf life. All NHPs sold in Canada require pre-market approval from Health Canada before sale in the country (34). These products must obtain product licenses corresponding to Natural Product Numbers (NPN) and the sites which manufacture, package, label and/or import them must have site licenses indicating good manufacturing processes (34).

Table 1: The Canadian Advantage

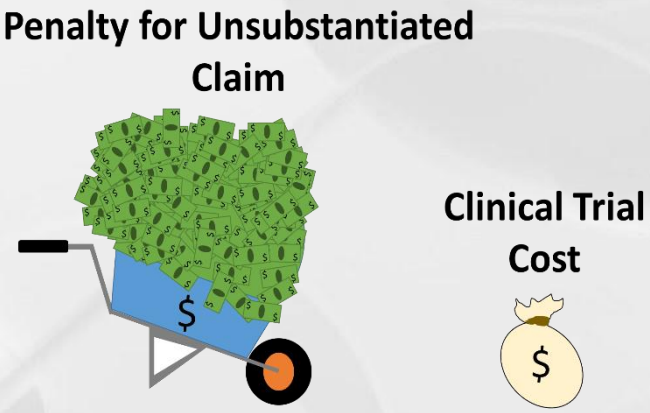
Health Canada established the Natural and Non-Prescription Health Products Directorate in 2013 and recognizes the importance of natural health products in medical practice and has evolved to:
Permit risk-reduction claims
Permit claims in disease indications including asthma, depression, cancer, diabetes, hypertension, obesity, etc.
Allow health claims on foods
Recognize diverse product types (ie. Synthetic duplicates, probiotics, enzymes, etc.)
Review clinical trial applications for scientific merit

See http://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq.do?atid=probio&lang=eng for more information regarding the species approved for non-strain specific claims.

European Union (EU)

The agency charged with regulation of probiotic foods and food supplements is the European Food Safety Authority (EFSA). EFSA requires that for a claim to be approved the company should clearly define their product, include specific statements on what exactly the microorganism affects, and provide scientific substantiation of the health claim based on the targeted population (i.e. It needs to include a human trial). As of 2010, EFSA had rejected more than 800 health claims related to probiotics (20). According to the panel, claims that various probiotics could strengthen the body's defenses, improve immune function and reduce gut problems were either so general as to be inadmissible or could not be shown to have the claimed effect. To date, EFSA has found that the specific applications for health claims have not provided sufficient evidence for that specific microorganism in the context of the claim made (35). However, they have approved a claim regarding live yogurt cultures (*Lactobacillus delbrueckii, Lactobacillus bulgaricus* and *Streptococcus spp)* and improved lactose digestion (20). Highlighting the success that food has enjoyed in this respect over probiotic supplements.

Scientific Studies for Claim Substantiation.



As the probiotic market becomes more competitive clinical trials are a necessary and routine part of product development and marketing. The FDA uses an evidence based review system to evaluate the strength of the scientific evidence supporting a proposed claim. The FTC assesses substantiation of claims from the point of view of a "reasonable consumer". This is of importance when considering if an endpoint may fall into the disease / drug claim category. For example, if a product 'reduces pain' then would a 'reasonable consumer' consider using the product for 'any type of pain'. As well, in this instance, the use of the word *pain* would classify the product as a disease and it would therefore become a drug claim. An FTC attorney will look at a claim to assess if the claim is "truthful", "non-misleading", "suggestive", "implied" or "straight". Furthermore, when making claims based on scientific evidence one should not confuse the fact that the greater the observed effects does not mean the greater the strength of the claim.

Table 2:

Important questions to consider in the design of your clinical study:
Are you interested in demonstrating efficacy, safety or bioavailability?
Do you want to start with a pilot study (using small number of participants) or conduct a larger, more definitive trial?
What are the desired claim statements for the product? Express the claim within a natural body process and explore the upper or lower limits of normal.
What is the target population for this product? Consider a healthy population within which the normal state is challenged and needs help to return to homeostasis.
How many participants should be in the study to prove efficacy? To prove safety? For dose tolerance?
Will the duration of the study be sufficient to move the chosen end points?
Will the product be stable for the duration of the study?
What is the best study design? Examples include double-blind, randomized, placebo control, parallel and open label,
Will the study need a run-in period to establish a baseline before it starts?
What is the appropriate control? How can the placebo be made similar enough to the test product to ensure blinding?

It is important to define scientific and marketing goals prior to designing the clinical trial. Defining the intended use for the product, along with the target population and the claim statements used to reach a population are beneficial to ensuring the right type of study design is implemented.

Conducting a clinical trial in the health nutrition industry can be an intimidating process. In an extremely competitive market, the company and the products must be able to withstand the heightened scrutiny that accompanies this industry. Clinical research must be conducted to substantiate product claims and gain consumer confidence. Where to go? What to expect? How much will it cost? How long before one sees results? What happens if the results are not favorable? are some of the questions which should be addressed when considering a clinical trial for a product. In particular, the adequacy of delivery systems and stability of the investigational product over the course of the trial are important considerations.

The single most important aspect to consider is clinical study design. Clinical trials in this industry differ from those of pharmaceutical trials, as these products have multi-faceted effects, outcomes and bio-markers. The optimal study should be designed in such a way as to eliminate bias on the part of the researchers and the participants.

The gold standard for claim substantiation is the randomized double-blind placebo-controlled study. These studies can be conducted in a parallel fashion or using a cross-over design. However, cross-over designs are plagued with challenges associated with the inability to define reasonable wash-out periods and issues such as “drifting baselines” and as such are not ideal. In the double-blind study model, neither the participants nor the researchers know which participants belong to the control group or the test group. Other study designs, can play role in providing additional information to the totality of the evidence. Randomized single-blind studies are those in which the participants are blinded to test product but the researcher are not. An open-label trial or open trial is one in which both the researchers and participants know which treatment is being administered. Observational studies, follow a cohort of participants through a set time, observing and measuring outcomes. Retrospective studies will examine data from studies that have already been done for further analysis and information.

Study Protocol

The clinical protocol should be written per guidelines provided by the ICH (The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) for the design, conduct, safety, and reporting of clinical trials.

Study Populations

Target populations for dietary supplements wanting to make a structure-function claim are those who are looking to improve some aspect of their health but are otherwise healthy. By definition, dietary supplements are not intended to mitigate, treat, diagnose, prevent, or cure a disease or its symptoms. Dietary supplements are intended to improve health but not treat disease; except in Canada where disease populations can be studied for structure-function claims.

When choosing study participants, it is important to limit confounding factors that can influence results, to ask the appropriate questions to disclose pertinent health issues and to have clear inclusion and exclusion criteria.

Test Product

The probiotic test product needs to be clearly defined as to the taxonomic identity of the strain, the potency (number of viable organisms) and the minimum dose required to produce a benefit

(20). If the beneficial dose is unknown, then dose-ranging studies may be indicated. If administered orally, the study product must be able to survive transit through the stomach to reach the intestines and adhere to the intestinal epithelium for colonization. Furthermore, the probiotic product must have an adequate shelf life, in food or powdered form, to be able to deliver a consistent quantity of viable microorganisms throughout the duration of the study.

Table 3: Points to Consider in a Clinical Trial

Study Design parameters
Study design appropriate for the test product • Controls in place for potentially confounding factors • Randomization of subjects to treatment and control • Blinding (similarity of test product and control)
Population relevant to the indication of the test product • Selected inclusion & exclusion criteria • Sample size sufficient to show comparative differences
Duration of the study appropriate to move endpoints
Endpoints selected with consideration of marketing claims
Safety parameters included
Data collection techniques
Detailed statistical analysis plan
Results analysis
Final report / publication

Study Endpoints / Biomarkers

In a clinical research trial, a clinical endpoint generally refers to the occurrence of a disease, symptom, sign or laboratory test result that constitutes one of the target outcomes of the study. A clinical trial will usually define or specify a primary endpoint as a measure that will be considered success of the therapy (e.g. in justifying a marketing approval). The study may have several endpoints, including a primary endpoint which is the main target result, secondary endpoints which are supportive in nature and exploratory endpoints that are experimental in nature. A surrogate endpoint (or marker) is a measure of effect of a certain treatment that may correlate with a real clinical endpoint and is intended to substitute for a clinical endpoint.

In designing a trial to demonstrate effectiveness of a dietary supplement it is important not to select a primary outcome/endpoint that could be construed as drug-related. Use of a disease endpoint has two important consequences: First, the research becomes drug research and is therefore subject to higher levels of scrutiny and greater protection for the human subjects than research on non-drug substances. Second, the research cannot be used to support product claims for foods and dietary supplements (which are not permitted to make drug claims).

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

It is challenging to measure health improvement and/or health maintenance in a healthy person. Some researchers have suggested that the focus of probiotic studies could be in measurement of homeostasis. From a statistical point of view, if a study could minimize the variation around the mean for a specific measure (even in the absence of changing the mean), it could reflect improved health. For example, rather than chronic constipation the study might measure bowel irregularity via frequency of bowel movements and colonic transit time (20).

Sample Size and Statistical Analysis Plan

The number of subjects needed in a clinical study should be determined using statistical analysis based upon the primary endpoint. The analysis should determine the number of subjects likely to produce a statistically significant effect based upon the expected effect of the test product. This information is best gained from previous studies on this product. If no previous studies are available, an educated guess can usually be made based in previously reported studies using similar agents. The number of participants in the study should be a large enough so that they could be expected to represent the target population.

Safety

Prior to moving into the human clinical study arena, the probiotic must go through several processes for: identification of the strain by molecular techniques, transferable antibiotic resistance, as well, in the absence of prior knowledge on the species, toxicology studies may be indicated to prove product safety. Safety parameters in human studies should include blood chemistry and hematology profiles such as blood cell counts, electrolytes, and measures of kidney and liver function. Adverse event recording is a crucial part of proving safety.

Safety is a top concern for regulators and the consumer. Therefore, having monitored safety parameters in your clinical study will ease acceptance of a product in the marketplace and allow you to claim that your product is safe.

Adverse event recording is a crucial part of proving safety. The US FDA, EFSA and Health Canada require the mandatory coding of safety data using MedRA recording– a clinically validated medical terminology coding dictionary for all clinical trials.

Table 4: Writing a Study Report that Meets Regulatory Approval

ICH-GCP Checklist for Clinical Study Protocol
✓ Introduction/ overview and Rationale for the conduct of the study
✓ Background Information
✓ Trial Objectives
✓ Trial Design
✓ Eligibility criteria, well defined Inclusion/Exclusion criteria
✓
✓ Account of all subjects that entered the study and their progression through the study
✓ Treatments administration and timing of

- ✓ Sample size calculation and literature used for the calculation
- ✓ Clear Description of Randomization Process
- ✓ Assessment of Efficacy
- ✓ Statistical Analysis Plan outlining sample size calculation and all statistical procedures for the comparison of the primary, secondary and exploratory analysis. Should include methods on the handling of drop outs and missing data, as well as any additional analysis plan that may be considered.
- ✓ Direct Access to Source data / Documents
- ✓ Quality Control & Quality Assurance
- ✓ Ethics
- ✓ Data Handling & Recordkeeping
- ✓ Financing & Insurance
- ✓ Publication Policy

Challenges with Studying Probiotics

The general structure-function claim for probiotic products is that they help "optimize intestinal flora health", which is a non-strain specific health claim for probiotics. The purpose of non-strain specific claims is to allow new products to remain marketable until a certain point when manufacturers can develop strain-specific evidence. Currently, there are no available health claims for probiotics in the US.

The study of the microbiome across different cultures has revealed that environmental differences play a role in shaping the human microbiome, requiring the healthy human microbiome be characterized across life spans, ethnicities, nationalities, cultures, and geographic locales (36).

A challenge with conducting clinical trials on probiotics is that each person in the study already has a unique microflora and that the investigational probiotic, when added to this, will elicit unique levels of response. The variability of the established biome, among other factors, may determine whether the participant responds to treatment in a measurable manner. The existing microflora may determine whether the participant is a responder or a non-responder – thus highlighting the importance of choosing the correct study population. The generalizability of the research must also be a consideration in choosing populations for study. Studying healthy populations that are either vulnerable or experiencing stress should be considered for structure function claims purposes.

Choosing your Contract Research Organization

Choosing a contract research organization (CRO) to conduct your clinical trial is a daunting task. This is particularly true when comparing organizations that offer similar services. Some of the factors to consider in your choice are (37):

Company Structure and Reputation: Whether considering a global or local CRO, it is important to learn about their financial stability, partnerships and success stories and metrics, focusing particularly on their recent track record (past 2 years) as well as their ability to meet timelines and budgets.

Experience and Service Portfolio: Depending on the study needs, specialized CROs or CROs with experience in several therapeutics areas might be chosen. Identification of core capabilities and new areas of expansion should also be taken into consideration.

Adaptability and Flexibility with Sponsor/Study Requirements: A CRO should have processes in place that will allow the company to accommodate the specific needs of its customers. The organization should also be able to identify and quickly manage emerging study challenges.

Efficiencies: Dedicated project managers that are accessible and knowledgeable and have experience in the indications to be studied are a must. Responsiveness, overall study oversight, facilitation of cross-communication among all the players in the study and a clear understanding of the customer's requirements are important factors that will ensure consistency and adherence to timelines while minimizing duplication of efforts and extraneous costs. The ability to select sites that can achieve enrollment goals in a timely manner is key to the success of any clinical trial.

Quality Assurance and Transparency: Overall quality assurance processes should be in place; this is particularly important if the CRO utilizes subcontractors. Transparency and good communication are crucial when outsourcing clinical trials. Data accuracy, confidentiality and security are of paramount importance. A description of the systems in place to manage data, oversight and quality assurance processes should be made available to you and incorporated into the data management plan.

In addition to being able to study populations in the USA, conducting a clinical trial in a regulatory environment like Canada which allows for disease populations to be studied, provides the opportunity to extrapolate results into healthy populations. Thereby allowing one to navigate diseased versus healthy population claims when a product may have indications for conditions like OA, CVD, diabetes, etc. Thus, conducting a study in Canada, a country with diverse populations, opens doors for product application and marketing opportunities globally.

A good study design and an experienced research partner are the keys to providing sound results. As the health and nutrition market becomes more competitive, clinical trials will become an absolute necessity and a routine part of product development and marketing. It is important that the dietary supplement industry choose their research partner carefully to achieve the maximum return on investment.

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