Probiotics-Regulatory Overview (USFDA, EU, Canada and India)



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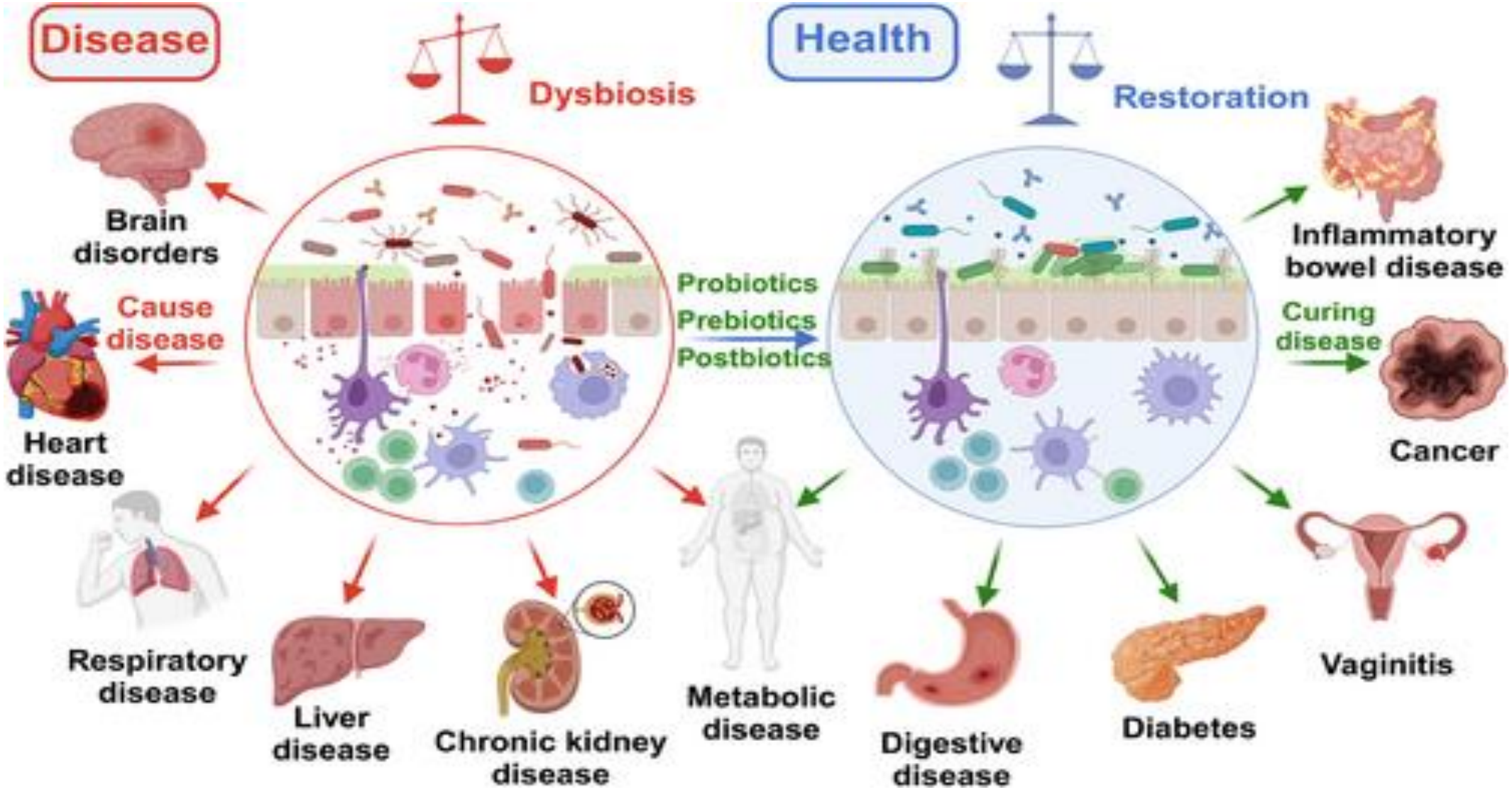
Introduction to Probiotics (1/3)

- The gut microbiota and its homeostasis play a crucial role in human health. Probiotics are live microorganisms thought to be healthy for the host organism. According to the currently adopted definition by FAO/WHO, probiotics are: "Live microorganisms which when administered in adequate amounts confer a health benefit on the host"
- The human gut microbiota is an intricate ecosystem comprising trillions of microorganisms, including bacteria, viruses, fungi, and other microbial entities. This dense and diverse microbiome has coevolved with humans, shaping and being shaped by our physiology, diet, and lifestyle.
- This vast microbial community plays a multifaceted role in our gut, and its homeostasis has emerged as an indispensable aspect of human health. Recent scientific explorations have revealed that gut microbiota homeostasis is critical for regulating intestinal inflammation, maintaining human metabolic homeostasis, and maturation and regulation of the immune system.
- The health-beneficial bacteria in probiotics could compete with pathogens and modulate the gut microbiota, and exhibit immunomodulatory, anti-obesity, anti-diabetic, and anti-cancer activities. Moreover, recent studies showed that probiotics could neutralize COVID-19 infections.
- However, disruptions in gut microbiota homeostasis, known as dysbiosis, may contribute to the development of a variety of diseases. For instance, inflammatory bowel disease (IBD), obesity, type 2 diabetes, and even distant systemic diseases, including cardiovascular diseases, certain cancers, and neurodegenerative disorders have been attributed to dysbiosis.
- Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are the most common disorders of gut brain interactions (DGBIs) attributed to systemic inflammation leading to disruption of the gut-brain axis. On the other hand, emotional disorders have also been demonstrated as DGBIs.

Introduction to Probiotics (2/3)

- Increasing clinical studies and evidences have demonstrated that probiotics, prebiotics, and postbiotics can prevent and treat various diseases, but currently they can only be used as dietary supplements rather than medicines, which restricts the application of probiotics in the field of medicine.
- In recent years, an increasing number of studies have reported the application of probiotics and postbiotics produced by their metabolism in the treatment of various animal disease models, the efficacy of probiotics, with its varying functions in treating corresponding diseases, has demonstrated the potential of probiotics, prebiotics, and postbiotics as medicine.
- In gastrointestinal diseases, probiotics such as *Bifidobacterium longum* and *Limosilactobacillus fermentum* KBL374, have been shown to alleviate symptoms of IBS and dextran sulfate sodium (DSS)-induced IBD in mice by modulating the gut microbiota, immune response, and improving intestinal mucosal barrier function. In cancer prevention and treatment, Bender *et al*. found that *Lactobacillus reuteri* can stimulate cytotoxic $CD8^+$ T cells by secreting postbiotics indole-3-aldehyde (I3A). When mice were fed a tryptophan-rich diet and metabolized by *L. reuteri* into I3A, it enhanced the effectiveness of immune checkpoint inhibitor (ICI) treatment, suppressed melanoma size, and prolonged survival.
- The regulatory challenges in development include safety of strains, determination of precise mechanisms, interactions with other medications, interpretation & extrapolation of animal model data to impact in human, limited clinical evidence, and inconclusive or contradictory finding.
- Addressing the challenges and limitations will be essential for the successful clinical application of probiotics, prebiotics, and postbiotics, including conducting more extensive research, optimizing strain selection, ensuring quality control, and regulatory compliance.
- Regulatory concerns arise due to the varying classification of probiotics, prebiotics, postbiotics as dietary supplements, food additives, or medicines among countries, leading to differing regulatory standards and approval processes.

Diseases associated with gut microbiota dysbiosis, and probiotics, prebiotics, and postbiotics to alleviate or treat disease by restoring gut microbiota homeostasis.



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Introduction to probiotics (3/3)

- The global probiotics market has experienced significant growth and is projected to continue expanding. As of 2023, the market size was valued at USD 87.70 billion in 2023 and is expected to grow at a CAGR of 14.1% from 2024 to 2030.
- The global population is aging, and there is a growing interest in healthy aging and age-related health concerns.
  - Probiotics have the potential to support healthy aging by promoting gut health, immune function, and cognitive well-being.
- Two drugs targeting the gut microbiome have received FDA approval in the past year
  - New Jersey-based Ferring Pharmaceuticals received FDA-approved for its drug Rebyota, which treats recurrent Clostridioides difficile, or C. diff, infection.
  - Seres Therapeutics, based in Massachusetts, received the FDA approval for its microbiome drug SER-109, which also treats recurrent C. diff infection.
- Market activities:
  - In 2018, Genentech partnered with biotech company Microbiotica to develop inflammatory bowel disease (IBD) drugs
  - In 2019, Merck teamed up with biotech business 4D Pharma to develop vaccines based on the microbiome.
  - In 2020, Gilead collaborated with microbiome company Second Genome to develop IBD drugs
  - In March 2023, J&J began working with biotech company Holobiome to develop prebiotics and probiotics for infant and maternal immune health.
- As per global data, most of the research in microbiome therapeutics focuses on infectious diseases, gastrointestinal diseases, dermatology, and oncology.
- In this presentation we cover the regulatory requirements with respect to probiotics basis the current regulations in force across major markets like US, Europe and also cover regulations in force in India.

Executive Summary (2/3)

- Food and Agriculture Organization (FAO) of the United Nations / WHO definition of probiotics – Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host – is acceptable globally.
- **US**
  - Depending on a probiotic product's intended use, the FDA regulates it as a dietary supplement, a food ingredient, or a drug. FDA approval is not required if probiotics to be marketed as food or dietary supplements.
  - They are regulated by FDA's CFSAN division under a regulation called DSHEA. According to DSHEA, the manufacturer is responsible for safety and efficacy and labelling of food and dietary supplements. FDA does not approve dietary supplements for safety and effectiveness.
  - If safety of the product is not maintained and if FDA receives reports of serious adverse events associated with use of their products and if FDA finds the product is adulterated, FDA issues warning letter and prohibits entry of product in the market.
  - If a dietary supplement contains a new dietary ingredient (NDI), then the manufacturer is required to submit NDIN to FDA and demonstrate safety of the ingredient to be used in the dietary supplement before marketing.
  - If probiotic is to be used as a drug intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, a BLA is to be submitted, and FDA approval is mandatory before the product goes to the market.
- **EU**
  - Foods are regulated by EFSA. EU Regulation 1924/2006 – NHCR – is available for nutrition and health claims to be made on foods. However, the term 'probiotic' is an unauthorised Health Claim in EU because according to the Commission if the product provides health benefit, indicates functionality then it should be scientifically substantiated.
  - Similar to nutritional claim, indications of – contains probiotics – is acceptable. This creates confusion to the consumers and leads to divergent interpretations in EU Member States on the use of the term 'probiotic' in labeling of food products. Member states like France, Italy, Denmark, Spain agrees to use the term 'probiotic' as a category name.

Executive Summary (2/3)

- However Czech Republic uses the term "contains probiotics" as a nutrition claim. Portugal goes for the mutual recognition procedure (MRP) and claim approved in MRP country to be approved in Portugal. Lack of harmonization on probiotic regulation is a major issue in EU. In general, to sell or import food supplements in the EU, the product needs to undergo a notification procedure with the national authority of a member state. Novel foods should require prior authorization at the EU level.

- **Canada**
  - Probiotics are considered as food ingredients and are added to food products. Similar to US, in Canada also, manufacturers and importers of foods are responsible for the safety and labelling of food products they produce and sell. Health claim and functional claim i.e. physiological effects of probiotic microorganisms in food should be supported by acceptable scientific evidence.
  - CFIA is responsible for enforcing all provisions with respect to food. Bacterial cultures that are not novel food do not require premarket safety review by Health Canada. However, novel foods, would require premarket notification and need to demonstrate the safety of the novel food.
  - When the food product is represented as having a therapeutic use or purpose (e.g. carrying claims about disease risk reduction or treatment), the product is classified as a natural health product (NHP) and are regulated by NHPD.
  - All NHPs must have product licences and the Canadian sites which manufacture, package, label and/or import NHPs must have site licences. Health Canada has developed Probiotic Monograph to assist industry stakeholders in obtaining product licences for NHPs.
- **India**
  - ICMR along with DBT has finalized the guidelines for evaluation of probiotics in food. The guidance is based on international guideline and defines the steps to be followed and set of parameters required for a product / strain to be termed as 'probiotic'.
  - Overall, clarity regarding probiotics is well defined in US and Canada. Harmonization is not seen in case of EU. In case of India, as the guidance is based on International Guidance, in case of any doubt, international guidance can be referred.

Probiotics – US Overview (1/3)

- According to U.S. Department of Health and Human Services, National Institute of Health (NIH), probiotics are live microorganisms that are intended to have health benefits when consumed or applied to the body in adequate amounts. They can be found in food e.g. yogurt and other fermented foods; dietary supplements; and beauty products.
- Probiotics mainly contain bacteria and yeasts.
- Probiotics are identified by their specific strain, which includes the genus, the species, the subspecies, and an alphanumeric strain designation.
- The seven core genera of microbial organisms most often used in probiotic products are *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, Escherichia,* and *Bacillus*.
- Examples of the nomenclature used for several commercial strains of probiotic organisms –

Genus	Species	Subspecies	Strain Designation	Strain Nickname
Lactobacillus	*rhamnosus*	none	GG	LGG
Bifidobacterium	*animalis*	*lactis*	DN-173 010	*Bifidus regularis*
Bifidobacterium	*longum*	*longum*	35624	Bifantis

- Probiotics exert health effects by nonspecific, species-specific, and strain-specific mechanisms.

Nonspecific mechanisms	Species-specific mechanisms	Strain-specific mechanisms
i. inhibition of the growth of pathogenic microorganisms in the gastrointestinal tract (by fostering colonization resistance, improving intestinal transit, or helping normalize a perturbed microbiota), ii. production of bioactive metabolites (e.g., short-chain fatty acids), and iii. reduction of luminal pH in the colon.	i. vitamin synthesis, ii. gut barrier reinforcement, iii. bile salt metabolism, iv. enzymatic activity, and v. toxin neutralization.	i. cytokine production, ii. immunomodulation, and iii. effects on the endocrine and nervous systems

Probiotics – US Overview (2/3)

- Depending on a probiotic product's intended use, the FDA regulates it as a dietary supplement, a food ingredient, or a drug.
- Many probiotics are sold as dietary supplements, which don't require FDA approval before they are marketed.
- The FDA requires dietary supplements should be
  i. Must adhere to high standards of quality
  ii. free of contaminants or impurities, and
  iii. accurately labelled.
- Probiotics which are intended to use as food or dietary supplement cannot lawfully be marketed to cure, mitigate, treat, or prevent any diseases.
- If a probiotic or Live Biotherapeutic Product (LBP) is to be used as a drug intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, a Biologics License Application (BLA) is to be submitted.
- The applicant or the manufacturer should
  i. Submit BLA – Biologics License Application
  ii. Prove that the product is safe and effective for its intended use through clinical trials and
  iii. Have FDA approval before it can be sold.
- In the absence of an approved product, healthcare providers who administer products containing live bacteria or yeast to treat, mitigate, cure or prevent a disease or condition should submit an Investigational New Drug Application (IND) to the agency to ensure the investigational use of an unapproved product is conducted with the appropriate safeguards.
- USP has developed 14 monographs specific to probiotic ingredients, including representatives from the Genera *Lactobacillus, Bacillus, Streptococcus, and Bifidobacterium*.
- These monographs contain definition of the article, tests for identification, quantification assays (enumeration in the case of probiotics), limits for contaminants, and other quality parameters. USP also considers the safety of probiotics for monograph development.
- A new "live biotherapeutic products" (LBP) category falls under these pharmaceutical expectations. These LBPs will have to be registered as medicinal products to prevent or treat diseases.

Probiotics – US Overview (3/3)

- Probiotics are effective in preventing and treatment of –

  i. antibiotic-associated diarrhea (including diarrhea caused by *Clostridium difficile*),
  ii. necrotizing enterocolitis and sepsis in premature infants,
  iii. treatment of infant colic,
  iv. treatment of periodontal disease, and
  v. induction or maintenance of remission in ulcerative colitis
  vi. Atopic dermatitis
  vii. Pediatric acute infectious diarrhea
  viii. Inflammatory bowel disease
  ix. Irritable bowel syndrome
  x. Hypercholesterolemia
  xi. Obesity

- Probiotics could -
  i. cause infections,
  ii. produce harmful substances
  iii. transfer antibiotic resistance genes from probiotic microorganisms to other microorganisms in the digestive tract
  iv. be harmful to people with compromised immune systems or high-risk individuals, e.g. premature infants or seriously ill hospital patients,
- NCCIH (National Center for Complementary and Integrative Health) of US Government agency sponsors research related to
  i. Diet-microbiome interactions in the digestive tract
  ii. The mechanisms by which probiotics may help to reduce postmenopausal bone loss
  iii. Engineering probiotics to synthesize natural substances for microbiome-brain research
  iv. The mechanisms by which certain probiotics may relieve chronic pelvic pain

First BLA – 351(a) – innovator biologics – to treat the microbiome approved in 2023



- Applicant - Seres Therapeutics, Inc.;
- Proprietary Name - Fecal Microbiota Spores;
- Strength - 1X10 LOG 6 AND 3X10 LOG 7CFU/TAB;
- Approval Date - April 26, 2023;
- Ref. Product Excl. Exp. Date - April 26, 2035;
- Orphan Exclusivity Expiration Date - April 26, 2030

- The product contains a cocktail of bacteria to prevent recurring infections of *C. difficile* bacteria in people who have had previous episodes and help them maintain healthy levels of gut bacteria.
- It is made from donated fecal material that is sterilized and processed in spore form to contain a combination of bacteria that only activate one can reach the gut. The recipe features bacteria from the Firmicute phylum, one of the dominant populations of human gut bacteria.
- Clinical trials were conducted in nearly 200 people who had had recurring *C. diffcle* infections.
- According to the U.S. Centers for Disease Control and Prevention (CDC), about one in six people who have had a *C. difficile* infection will have another one in two to eight weeks.
- In studies on which the approval was based, people took four capsules daily by mouth for three days to try to prevent recurrence of the infections. 88% of the participants did not have another infection eight weeks after a single course of treatment—the time period during which many infections come back—compared to 60% of those who received a placebo. Six months later, 79% of those who took the product remained free of re-infections, while only 53% getting placebos did.
- The pills are given after patients finish a course of antibiotics to first kill as many of the *C. diffciile* bacteria as possible; the microbiotic therapy then helps to restore the beneficial bacteria.

Warning Letters issued by FDA in recent times for Probiotics

- Letter issued in - Sept 2023
- Company - Infinant Health, Inc (formerly Evolve BioSystems Inc.)
- Name of probiotic product - Evivo with MCT Oil
- Reason –
  i. A preterm infant, birth weight <1000g, was administered this probiotic, as part of in-hospital care, developed sepsis caused by the bacterium Bifidobacterium longum and subsequently died.
  ii. Evivo with MCT Oil is a probiotic formulated to contain the live bacterium, Bifidobacterium longum subsp. infantis.
  iii. Genomic sequencing data demonstrate the bacterium that caused sepsis in this infant was a genetic match to the bacteria contained in this probiotic.
- FDA's claim –
  i. An unapproved and unlicensed product sold for use in treating or preventing or reducing the risk of necrotizing enterocolitis (NEC) disease in preterm infants, in violation of the FD&C Act and the Public Health Service Act.
  ii. The product was intended to be added to food for preterm infants and as such was also found to be an adulterated food under the FD&C Act.
  iii. This product has not undergone the FDA's rigorous premarket review evaluation for safety and effectiveness, nor has been evaluated for compliance with the agency's rigorous manufacturing and testing standards for drugs and biological products, including testing for extraneous organisms.
- This product has since been voluntarily recalled and is no longer available in the U.S.

- Letter issued in - Oct 2023
- Company - Abbott Laboratories
- Product - Similac Probiotic Tri-Blend, which contains *B. infantis* (Bb-02), *S. thermophilus* (TH-4) and *B. lactis* (BB-12).
- Claim in the letter –
  i. This product is not an infant formula.
  ii. It contains *B. infantis* (Bb-02), an unsafe food additive.
  iii. It also contains *S. thermophilus* (TH-4®), 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, when used in preterm infants.
  iv. The product is intended for use in the mitigation, treatment, or prevention of disease, meaning it's a drug as per FD&C Act.
- Abbott has agreed to discontinue sales of Similac Probiotic Tri-Blend product and is working with the FDA to take additional corrective actions.

Probiotics as Dietary Supplement

- If a probiotic is intended for use as a dietary supplement, it is placed under the umbrella of "foods," and is regulated by FDA's Center for Food Safety and Applied Nutrition (CFSAN).
- FDA regulates dietary supplements under a regulation called DSHEA - Dietary Supplement Health and Education Act of 1994 (DSHEA).
- According to DSHEA, the manufacturer is responsible for determining that the dietary supplements that it manufactures or distributes are safe and that any representations or claims made about them are substantiated by adequate evidence to show that they are not false or misleading.
- The manufacturers need not provide FDA with evidence that substantiates the safety or purported benefits of their products, either before or after marketing.
- Manufacturers and distributors of dietary supplements and dietary ingredients are responsible for evaluating the safety and labeling of their products before marketing.
- Manufacturers and distributors should not market adulterated or misbranded dietary supplements and dietary ingredients.
- **FDA does not approve dietary supplements for safety and effectiveness.**
- Manufacturers and distributors of dietary supplements have been required to record and forward to FDA any directly received reports of serious adverse events associated with use of their products.
- If a dietary supplement contains a new dietary ingredient that was not sold before October 15, 1994, then the manufacturer is required to notify FDA and demonstrate to FDA before marketing why the ingredient is reasonably expected to be safe for use in a dietary supplement.

New Dietary Ingredient Notification (NDIN) Process

The manufacturer or distributor of an NDI or of the dietary supplement that contains the NDI to submit NDIN to CFSAN **75 days before** introducing the product into interstate commerce.

After receipt of an NDIN, FDA to send an acknowledgement of receipt to the notifier stating
1. the date of receipt of the notification
2. the NDIN number assigned to the notification.

In case of questions during review process, FDA to contact the applicant. After reviewing a submission of additional information, FDA to determine the submission as a substantive amendment and reset the filing date.
75-day review period to be reset and provide the new filing date as a date of receipt by FDA.

After finishing the review, FDA to send the response letter to the notifier by sending

i. Letter of acknowledgingredient,tion; or

ii. Letter listing deficiencies that make the NDIN incomplete.

iii. Objection letter raising concerns with the adequacy of the identity information or safety information (e.g., identifying gaps in the history of use or that the safety information on the NDI does not support the conditions of use); and

iv. Letter raising other regulatory issues with the ingredient or product (e.g., the ingredient is not a dietary ingredient or the product does not satisfy all parts of the dietary supplement definition)

After the 90th day, the entire notification, except trade secrets and confidential commercial information, to be placed on public display by FDA

If the required premarket notification is not submitted to FDA, then the dietary supplement containing the NDI is considered to be adulterated.

Content of NDIN

- NDIN describing the NDI should:
  - (1) specify which of the dietary ingredient categories the NDI belongs to and explain the basis for conclusion;
  - (2) describe the manufacturing process used to make the NDI, including process controls;
  - (3) describe the physical properties and chemical or molecular composition and structure of the NDI; and
  - (4) include a specification sheet describing the critical identity and safety attributes of the NDI, including the purity and strength of the NDI and the identities and levels of any impurities and contaminants.
- The NDIN should contain a description of the dietary supplement in which the NDI will be used, including:
  - (1) the level of the NDI in the dietary supplement per serving;
  - (2) the identity and level of any other dietary ingredients and non-dietary ingredients (e.g., binders and fillers) in the dietary supplement per serving;
  - (3) a description of the manufacturing process of the dietary supplement, including process controls;
  - (4) a specification sheet for the dietary supplement that describes its critical safety attributes; and
  - (5) the conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, a discussion of the ordinary conditions of use of the dietary supplement.
  - (6) The conditions of use should include the serving form (e.g., tablet, capsule, powder, liquid), serving size (e.g., weight or volumetric measure per serving), frequency of use (e.g., number of servings per day and interval between servings), duration of use, instructions for use, target population, excluded populations (if any), and any other restrictions on use.
  - (7) safety narrative containing objective evaluation of the history of use or other evidence of safety cited in the notification, along with an explanation of how the evidence of safety provides a basis to conclude that the dietary supplement containing the NDI, when used under the conditions described in the NDIN, will reasonably be expected to be safe.

Concept of NDIN Master File

- Notification should contain NDIN Master File containing information about an NDI, a dietary supplement containing an NDI, or both.
- The NDIN should provides the basis on which the manufacturer or distributor of the NDI or dietary supplement has concluded that the dietary supplement containing the NDI will reasonably be expected to be safe including citation to published articles.
- An NDIN Master File should contain identity, manufacturing, and/or safety information relating to an NDI.
- The Master File owner can grant written authorization to other parties to reference information from the NDIN Master File through a Letter of Authorization.
- The Letter of Authorization should describe the specific sections of the NDIN Master File to which the Master File owner is authorizing a right of reference.
- If the authorization does not extend to the entire Master File, the Letter of Authorization should specify the part(s) of the NDIN Master File each authorized party is authorized to use.
- When FDA receives an NDIN that relies on information in an NDIN Master File to which the notifier has a right of reference, FDA reviews the referenced information in the NDIN Master File as part of FDA's standard review of the NDIN.
- FDA does not intend to conduct a scientific review of an NDIN Master File without a corresponding NDIN.
- If questions arise during the review of the NDIN, FDA to contact the notifier, except that if the questions relate to the content of the Master File, FDA to contact the Master File owner directly for clarification.

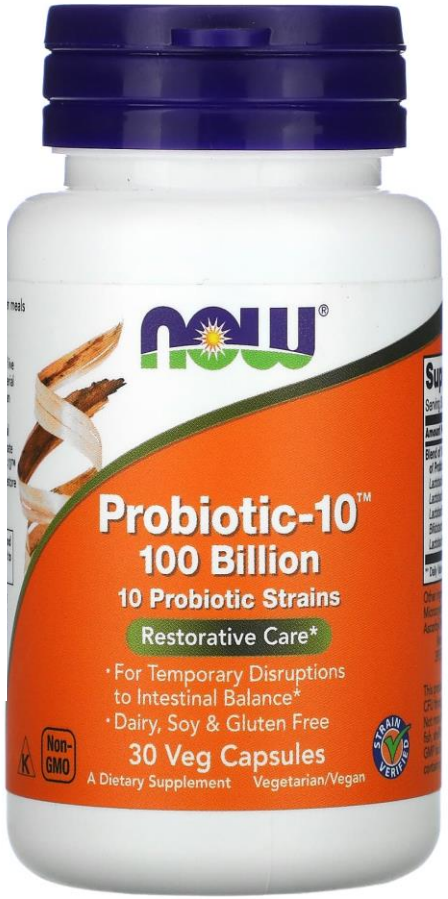
Labelling Requirements

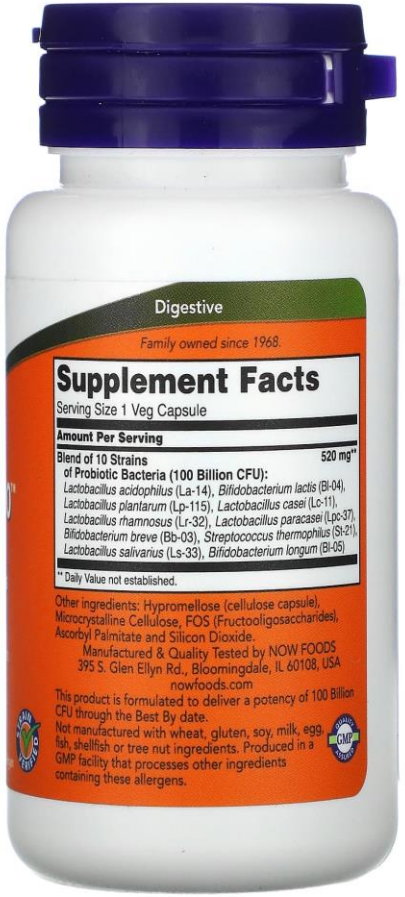
- The quantity in terms of weight of the microorganisms on probiotic products.
- The quantity in colony forming units (CFUs) clearly separate and readily distinguishable from the weight, e.g., 10 billion CFU or 300 million or billion.
- The declaration of quantity in CFUs is accurate and not misleading.
- The declaration of quantity in CFUs measures only live microbial ingredients and does not include inactive, dead, or nonviable organisms.
- Live microbial dietary ingredients in a proprietary blend to be listed in descending order of predominance by weight.
- Categories of claims
    i. Health claims (claims about relationship between a dietary ingredient/other food substance and reduced risk of a disease/health-related condition),
    ii. Structure/function claims (claims about effects on a structure or function of the human body), and
    iii. Nutrient content claims (claims characterizing the level of a nutrient or other dietary ingredient in a dietary supplement).
- The label should identify the genus, species, and strain for each microorganism in the product.
- For a product containing only one strain: Declare the quantity of the strain in CFUs. If multiple strains: Declare the total count of the blend in CFUs.
- Genuinely Recognized as Safe (GRAS) mark.
- Disclaimer – These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease – should be available on the label.

Examples of Probiotics in US Market

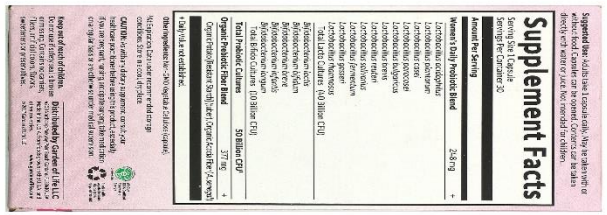












Probiotics – EU Overview

- In the European Union, foods are regulated by the European Food Safety Authority (EFSA) and drugs by the European Medicines Agency (EMA).
- EU Regulation (EC) 1924/2006 – Nutrition and Health Claims Regulation (NHCR) - is available for nutrition and health claims to be made on foods. However, products claiming to be probiotics or to have specific health effects cannot be sold in the EU, as use of the term 'probiotic' is considered to be an unauthorised health claim. According to the Commission, the term implies that a product provides a health benefit, which could be misleading to consumers unless it can be scientifically substantiated.
- EU Regulation 1924/2006 clarifies the distinction between nutrition claims and health claims made on foods:
  i. A claim is a nutrition claim if in the naming of the substance or category of substances, there is only factual information (examples: Contains lycopene; Contains lutein; Contains low fat; source of omega-3 fatty acids; high in fibre etc.)
  ii. A claim is a health claim if in the naming of the substance, or category of substances, there is a description or indication of a functionality or an implied effect on health (examples : Vitamin D is needed for the normal growth and development of bone in children; Live cultures in yogurt improve lactose digestion of the product in individuals who have difficulty digesting lactose).
- Many applications have been submitted to EFSA for health claims for probiotics. However none of them are approved, except one related to live yoghurt cultures and improved lactose digestion (ID 1143, 2976) - an article 13.1 claim on live yoghurt and improved lactose digestion for the microorganisms *L. delbrueckii subsp. bulgaricus* and *Streptococcus thermophilus* (minimum 10^8 CFU/g). The target population is individuals with lactose maldigestion.
- On the scientific level in EU, probiotics as one of the categories of food is negatively impacted because 'health claim' on probiotics in food is not received positive assessment by EFSA and indications such as 'contains probiotics' should therefore be regarded as health claims when considering new applications.
- Therefore on the label Latin term for a particular strain of bacteria is available which is not easily understood and creates confusion rather than clarity to the consumers.
- This leads to divergent interpretations in EU Member States on the use of the term 'probiotic' in labeling of food products.
- EP also has developed monographs for LBPs and these LBPs will have to be registered as medicinal products to prevent or treat diseases.

Different Approaches in European Countries on Probiotics

Portugal (PT)

As per Feb 2024 updates, if the probiotic food supplements are already marketed in at least one European Union (EU) Member State (MS) and if is not yet in PT market, then the notification to be submitted to the DGAV confirming that it complies with the requirements for mutual recognition DGAV notification procedure.

France (FR)

According to DGCCRF, as per Jan 2023 updates, in the case of food supplements, the term 'probiotic' can be used as a category name to characterize the nature of the substances used in the product, providing that specific conditions are met and can be used on the labelling if 10^7 to 10^9 live cells of a strain per day reach the gastrointestinal tract and develop there and only claims - balance of the intestinal flora.

Denmark (DK)

As per May 2021 new guidance on labelling, the term 'probiotic' can be used on food supplements.

Italy (IT)

As per Mar 2018 revised guidance, the term 'probiotic' can be used as category of product for the balance of the intestinal microflora.

Czech Republic (CZ)

CZ has issued National Guidelines allowing the use of the term "contains probiotics" as a nutrition claim, subject to the fulfilment of the conditions of use for nutrition claims defined in the nutrition and health claims (Regulation (CE) n°1924/2006) NHCR.

The Netherlands (NL)

As per NVWA Mar 2021 updates, clear indications are available on the use of the term 'probiotics' to identify the categories of micronutrients or substances that characterize the product in food supplements.

Spain (ES)

As per AESAN Oct 2020 updates, use of the term "probiotic" on the labels of food and food supplements produced and commercialized in the country is acceptable.

United Kingdom (UK)

As per Nov 2021 updates, non- specific health claim when accompanied by specific authorized health claim is acceptable.

Notification Process for Food Supplements

- To sell or import food supplements in the EU, the product needs to undergo a notification procedure with the national authority of a member state.
- Upon completion, the product is included in a specific list with a unique registration code, verifying formula and label compliance.
- Nutrients used in food must have a History of Safe Use (HoSU) within the EU to be considered for use. Otherwise, they may be classified as "novel foods" requiring prior authorization at the EU level.
- For non-EU registered companies, establishing a legal entity in an EU member state or appointing a third-party Legal Representative (LR) is necessary. The representative will be mentioned on the label and act as the point of contact for the national authority.
- Novel foods are defined as food products or ingredients that have not been consumed to a significant degree within the EU before May 15, 1997.
- Novel food registration in Europe is governed by Regulation (EU) 2015/2283.
- An applicant who intends to place on the EU market a novel food should submit an application to the European Commission (EC).
- The EC makes it available to the Member States and mandates EFSA for a scientific assessment. EFSA conducts a thorough evaluation of the novel food's safety and potential risks to human health and adopt its opinion within 9 months from the date of receipt of a valid application from the EC.

Scientific Data Requirements for Novel Food Registration

- A comprehensive risk assessment of the novel food.
- The documentation on the procedure and strategy followed when gathering the data.
- A description of the safety evaluation strategy and the corresponding toxicological testing strategy and justification the inclusion or exclusion of specific studies or information.
- The raw data for the individual studies, published and unpublished, undertaken by the applicant, or on their behalf, to support the application. This information includes data used to generate the conclusions of the individual studies and results of examinations.
- Safety data for all groups who would be consuming novel food.
- For each biological or toxicological study, the applicant should clarify whether the test material conforms to the proposed or existing specification. Where the test material differs from that specification, the applicant should demonstrate the relevance of those data to the novel food under consideration.
- Toxicological studies should be conducted in facilities which comply with the requirements of Directive 2004/10/EC or, if they are carried out outside the territory of the Union, they shall follow the OECD Principles of Good Laboratory Practice. The applicant should provide evidence of compliance with those requirements and should justify any deviation from the standard protocols.
- Overall conclusion on the safety of the proposed uses of the novel food. The overall evaluation of potential risk to human health should be made in the context of known or likely human exposure.

Examples of Probiotics in EU Market









Probiotics – Canada Overview (1/2)

- Live bacterial cultures, including those represented as "probiotics", are food ingredients and can be added to food products.
- Manufacturers and importers of foods are responsible for the safety of food products they produce and sell.
- All product representations (including claims) should be truthful and not misleading, deceptive, or likely to create an erroneous impression regarding the character, value, quantity, composition, merit, or safety of a product.
- Health claim and functional claim i.e. physiological effects of probiotic microorganisms in food should be supported by acceptable scientific evidence.
- The Canadian Food Inspection Agency (CFIA) is responsible for enforcing all provisions with respect to food.
- Common "probiotic" bacteria (primarily lactobacilli and bifidobacteria) added to foods have a history of safe use in food products. Bacterial cultures that are not novel food do not require premarket safety review by Health Canada.
- If the culture(s) meets the definition of novel food, as, in cases where there is no history of safe use in foods or the strain is genetically modified, then it would require premarket notification and need to demonstrate the safety of the novel food.
- Where a health claim is made, the Latin name (i.e., genus and species) and the strain of the probiotic microorganism or mixed culture that is the subject of the claim should be declared.
- The level of the probiotic strain expressed in colony forming units (cfu) in a serving of stated size of the food should be declared; and if more than one probiotic strain is added to a food, the above recommendations to be applied to the mixed culture.
- The food manufacturer is responsible for the stability and viability of the probiotic strain or mixed-culture in the food product so that the product delivers the declared level in a serving of stated size throughout product shelf life. Documentation to support these quality aspects of the product should be maintained.

Probiotics – Canada Overview (2/2)

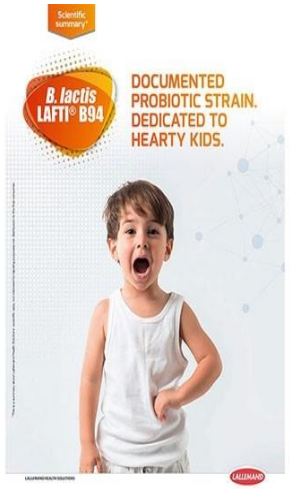
- To ensure the safety of probiotic food, the manufacturer should ensure that –

  No person shall sell an article of food that
  (a) has in or on it any poisonous or harmful substance;
  (b) is unfit for human consumption;
  (c) consists in whole or in part of any filthy, putrid, disgusting, rotten, decomposed or diseased animal or vegetable substance;
  (d) is adulterated; or
  (e) was manufactured, prepared, preserved, packaged or stored under unsanitary conditions.
- Where a food product is represented as having a **therapeutic use** or purpose (e.g. carrying claims about disease risk reduction or treatment), the product is classified as a **natural health product (NHP)**, depending on the nature of and risks associated with the microorganism and taking into consideration the product's represented therapeutic use, as well as the history of use and public perception of the product's intended use.
- Probiotics can be sold in pharmaceutical dosage forms (e.g. tablets, capsules) as NHPs and are regulated by Health Canada's Natural Health Products Directorate (NHPD).
- To be sold in Canada, all NHPs must have product licences and the Canadian sites which manufacture, package, label and/or import NHPs must have site licences.
- Health Canada has developed **Probiotic Monograph** to assist industry stakeholders in obtaining product licences for NHPs.
- The monograph has details about acceptable health claims, associated doses, source materials and required risk information.
- Claims about the diagnosis, treatment or mitigation or prevention of a disease, disorder or abnormal physical state or its symptoms in humans, or restoring, correcting, or modifying body functions in humans are representations about the therapeutic use of a product and are classified as NHPs.

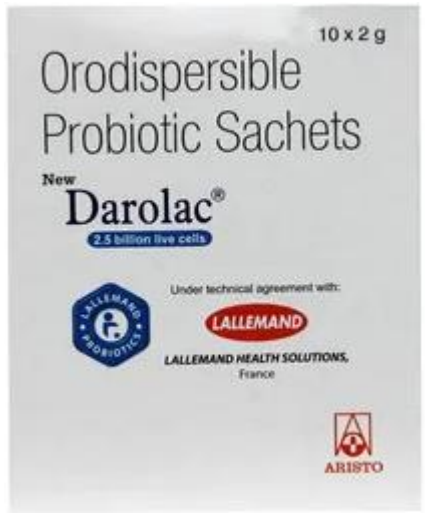


Probiotic Monograph

Examples of Probiotics in Canada Market







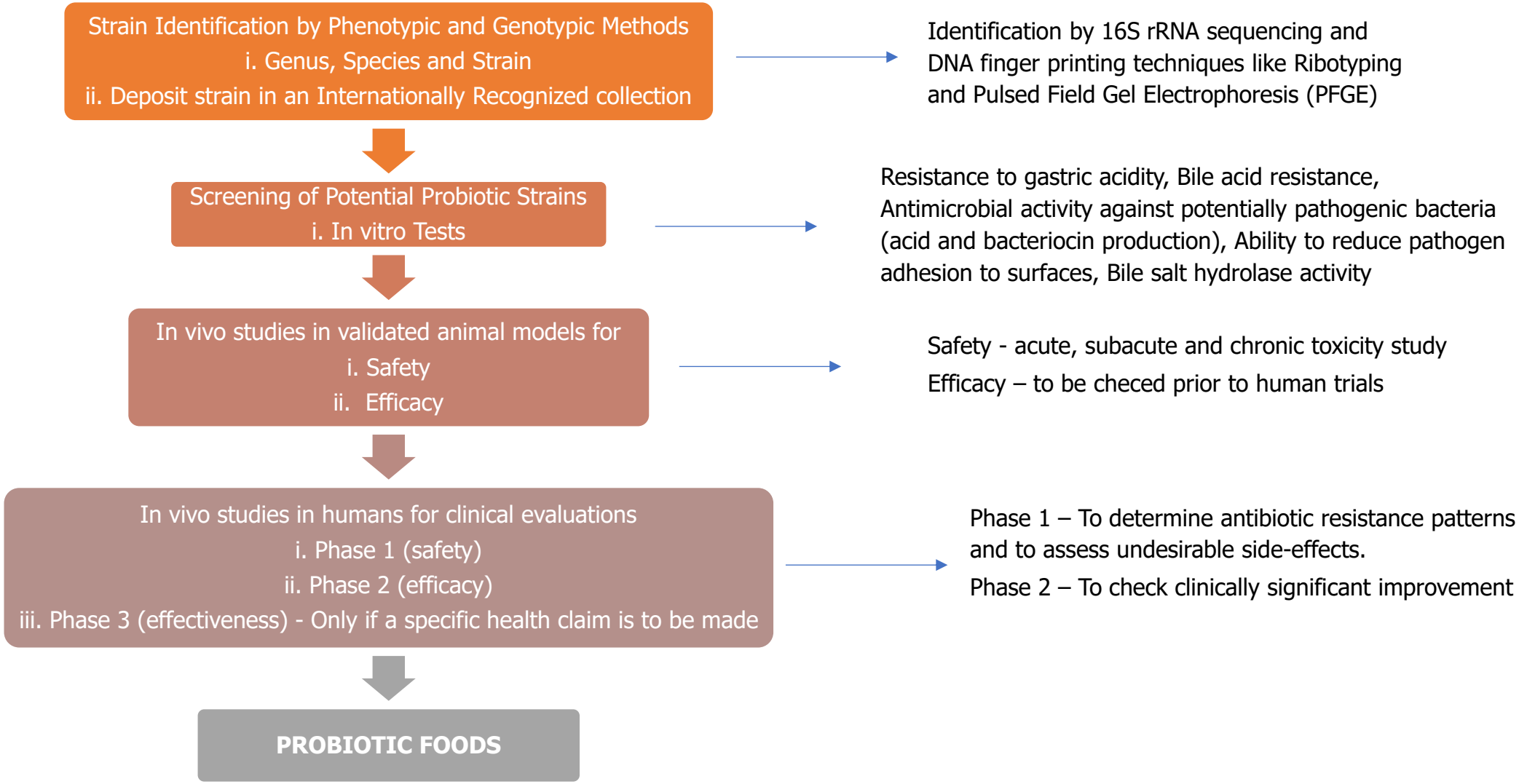






Probiotics – India Overview (1/2)

Indian Council of Medical Research (ICMR) along with Department of Biotechnology (DBT) formulated the guidelines for evaluation of probiotics in food. This guideline defines the steps to be followed and set of parameters required for a product / strain to be termed as 'probiotic'.



Probiotics – India Overview (2/2)

Labeling Requirements:

The following information should be mentioned on the label :

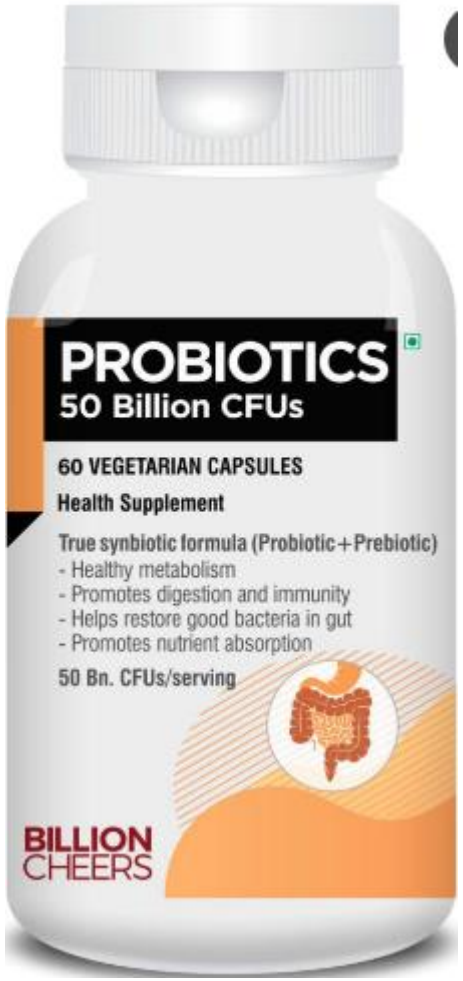
- Genus, species and strain designation following the standard international nomenclature.
- The minimum viable numbers of each probiotic strain should be specified at the level at which efficacy is claimed and at the end of shelf-life.
- Evidence-based health claim(s) should be clearly stated.
- The suggested serving size to deliver the minimum effective quantity of the probiotic related to the health claim.
- Proper storage conditions to be mentioned.

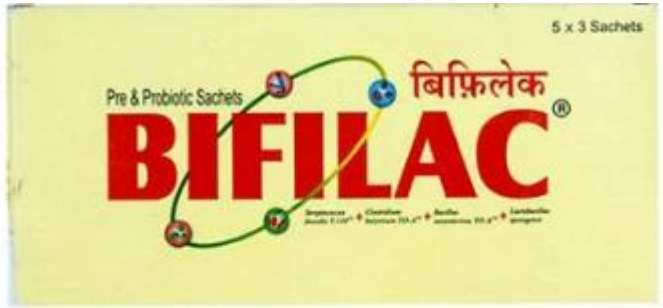
Manufacturing and handling procedures:

- Adequate quality assurance program should be followed.
- Good Manufacturing Practices should be followed.
- The Codex General Principles of Food Hygiene and Guidelines for Application of Hazard Analysis and Critical Control Point (HACCP) should be followed.

Examples of Probiotics in India Market















References (1/2)

1. https://www.fda.gov/food/guidance-documents-regulatory-information-topic-food-and-dietary-supplements/dietary-supplements-guidance-documents-regulatory-information
2. https://www.fda.gov/food/dietary-supplements
3. https://www.fda.gov/food/information-consumers-using-dietary-supplements/questions-and-answers-dietary-supplements
4. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-new-dietary-ingredient-notification-procedures-and-timeframes-dietary-supplements
5. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-industry-new-dietary-ingredient-notification-master-files-dietary-supplements
6. https://www.fda.gov/files/food/published/Draft-Guidance-for-Industry--Policy-Regarding-Quantitative-Labeling-of-Dietary-Supplements-Containing-Live-Microbials-PDF.pdf
7. https://www.efsa.europa.eu/en/topics/topic/food-supplements
8. https://www.ipaeurope.org/legal-framework/european-legal-framework/
9. https://www.canada.ca/en/health-canada/services/food-nutrition/food-labelling/health-claims/questions-answers-probiotics.html
10. https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/guidance-document-use-probiotic-microorganisms-food-2009.html
11. https://webprod.hc-sc.gc.ca/nhpid-bdipsn/atReq?atid=probio&lang=eng – probiotics monograph developed by Health Canada
12. https://www.indiascienceandtechnology.gov.in/sites/default/files/file-uploads/guidelineregulations/1527507721_PROBIOTICS_GUIDELINES.pdf
13. https://www.sciencedirect.com/science/article/pii/S2772502222001457#:~:text=These%20health%2Dbenefici%20%20al%20bacteria%20could,could%20neutralize%20COVID%2D19%20infections

References (2/2)

14. https://www.mdpi.com/2077-0383/11/17/5155
15. https://onlinelibrary.wiley.com/doi/10.1002/mco2.420
16. https://www.cell.com/trends/microbiology/fulltext/S0966-842X(21)00005-6
17. https://www.mdpi.com/2076-2607/12/2/234
18. https://www.mdpi.com/2036-7422/15/1/16
19. https://www.cureus.com/articles/111413-role-of-probiotics-in-human-health#!/

Thank You!

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