

# Comparative Insight of Regulatory Guidelines for Probiotics in USA, India and Malaysia: A Critical Review

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**Abstract:** Probiotics have always been a unique category of natural products due to established evidences of their applications in wellness of human beings. In spite of being based on live microorganisms, commercial exploration of probiotics as biologics, pharmaceuticals, food and nutritional supplements has witnessed a tremendous increase due to their potential of providing health benefits. Currently different regulatory bodies across the globe consider probiotics under several categories depending upon their intended use. In order to clear the ambiguity related to regulatory specifications, assurance of quality and premarketing safety assessment for drafting of comprehensive guidelines with global acceptance is need of the hour. The aim of this paper is to compare existing regulations in countries like United States, India and Malaysia to develop harmonized guidelines for approval of probiotics.

**Keywords:** Dietary supplements, Functional food, *Lactobacillus*, Probiotics, Regulatory guidelines, FDA.

## 1. INTRODUCTION

During past decade, nonpathogenic microbes have been included in various food stuffs especially fermented foods and beneficial roles of these microbes were evidenced. These health benefits escalated the research to support the concept that there are clinical health benefits to ingest these micro-organisms [1]. According to recent advent, utilization of microbes as food stuffs or as pharmaceuticals made the basis of the probiotics. Probiotics are live microorganisms used either as pure homogeneous or mixed heterogeneous culture which exhibit beneficial effect on health of host [2]. Probiotics now become a commercial commodity because of its much widespread healthcare settings and global market for these functional foods is growing at a very fast pace. Probiotics are not considered as single category rather subcategorized under different categories as per existing regulations of countries around the globe [3] as given in Table 1.

Today, most probiotic bacteria are sold over-the-counter as dietary supplements or in food products such as yogurt, with ambiguous benefits. Probiotics are subcategorized into different categories according to their intended use in different countries as probiotic drugs, probiotic foods (e.g., foods, food ingredients, and dietary supplements), probiotics for animal use and genetically modified probiotics [4]. In the United States, probiotic products are marketed as both foods and biologic drugs and as functional foods in Malaysia. In India, probiotics comes in two forms, milk and fermented milk but major pharmaceuticals companies

have become active in this space and are devising newer drugs and products as well. Some of the definitions related to probiotic subcategories used in USA, India and Malaysia are as follows:

According to FAO/WHO, **probiotics** are defined as live microorganisms which when administered in adequate amounts confer a health benefit on the host.

**Functional foods** are defined as products that are similar in appearance to conventional foods that are consumed as part of a normal diet and have demonstrated physiological benefits, and/or have the potential to reduce the risk of chronic disease beyond nutritive function, i.e. they contain bioactive compounds.

**Medical food** are the products intended for external use in the dietary management of a disease or condition for which distinctive nutritional requirements have been established by medical evaluation and is formulated to be administered under the supervision of a physician.

**Dietary supplement** is defined as as a product which is taken by mouth that is intended to supplement the basic diet and that contains a dietary ingredient in the form of vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances and concentrates, metabolites, constituents, extracts, combinations of the preceding types of ingredients which may be available in tablets, capsules, softgels, liquids, or powdered form.

**Drug** is an article intended for the cure, mitigation, treatment, diagnosis, or prevention of disease.

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**Table 1: Probiotic Subcategories in Different Countries**

Serial No.	Country	Category
1.	Denmark/Sweden/Finland	Food Supplements
2.	Canada	Natural health products
3.	Italy	Dietary food
4.	European countries/Belgium/Germany	Biotherapeutic agent
5.	Japan/India/China/Malaysia	Functional food
6.	USA	Dietary Supplements /Drugs/Live Biotherapeutic agents/Medical food

**Biological product** is defined as a product containing a virus, serum, or toxin applicable to the prevention, treatment, or cure of a disease [5].

Probiotic consumption exerts myriad of beneficial effects which are evidenced by rigorous scientific evaluation in recent years. Probiotic therapy have been advocated for enhanced immune response, restoration of our gut microbiota, improvement of barrier function of gut epithelium, modified inflammatory response, treatment of diarrhea originated due to traveling or antibiotic course or upsetness of gastrointestinal tract, prevention of ulcers related to *helicobacter pylori* etc. [6, 7]. Therapeutic benefits by using different probiotic strains are summarized as Table 2.

## 2. PROBIOTIC MARKET: OUTLOOK ACROSS THE GLOBE

Probiotic is a new buzz in human dietary portfolio. 'Let food be thy medicine and medicine be thy food', the age-old quote by Hippocrates, is evidently proved in today's life because the market for probiotics is flourishing. The concept of live microbial ingredients, with a positive effect on human health, emerged in the early 1900s. The increasing trend for probiotics was first observed in Japan in late 1980. This concept became popular and has quickly spread to the other areas like Asia Pacific, as well as the European Union and the United States because of a heightened awareness of the link between health, nutrition, and diet. It is a major focus of attention of scientists across the world due to their promising health benefits and their applications offers an innovative approach for development of novel probiotic formulations. The probiotic market has shown spectacular growth till date and will grow infinitely as consumers become more familiar with probiotics. According to current business scenario, Japan accounts for about one-half of this market, and United States is expected to be the other fastest growing country for probiotic market and experienced a rapid growth especially of dairy products in Europe [55].

The review of market for functional foods in the United Kingdom, France, Germany, Spain, Belgium, Netherlands, Denmark, Finland, and Sweden showed that the probiotic yogurt market in these 9 countries totaled >250 million kg [56]. France represented the largest market, having sales of ≈90 million kg, valued at US \$219 million. Denmark has achieved highest proportion (20%) of probiotic yogurts, followed by Germany and the United Kingdom (both at 13%) and then France (11%). As per new market research report, 'Probiotics Market' (2009-2014), published by Markets and Markets, the global probiotics market will expected to expand by 2014 to \$32.6 billion, whereas with the Europe and Asia, nearly 42 and 30% of the total revenues are accounting respectively. Europe will attain largest market for probiotics with an estimated \$13.5 billion by 2014 as per the business reports. Asia will be the second player and fulfill the largest segment, growing at with an estimated CAGR of 11.2% to reach \$9.0 billion by 2014 [57].

In USA, probiotics are considered to be "complementary" or "alternative" medicine. USA market has grown slowly but surely opened up to these products in the recent past and expected to grow at a CAGR of 17% from 2009 to 2014. The probiotic cultured drinks and probiotic yogurts are the major products of the market. Though the market base of probiotic products is comparatively lesser in the USA the market is expected to grow at an astounding rate of almost 14% in the same period driven by the large scale acceptance of the probiotic yogurts in spoonable single serve packs, probiotic cultured drinks in single shot packaging form and probiotic dietary supplements. In USA sale of probiotic supplements was nearly \$770 million in 2010, which was up about 22% from the previous year, according to Euromonitor International, a market research firm.

Indian probiotic industry is evolving at a steady pace. India at present accounts for less than 1% of the total world market turnover, but it will show tremendous

Table 2: Therapeutic Claims Associated with Different Probiotic Strains

Serial No.	Probiotic microbe(s)	Disease	Reference
1.	Lactic acid bacteria and <i>Streptococcus salivarius</i> subsp. <i>Thermophilus</i>	Lactose maldigestion	[8-11]
2.	Lactic acid bacteria, <i>Bifidobacterium</i> species, or <i>Saccharomyces boulardii</i>	Gastroenteritis acute diarrhea	[12-23]
3.	Lactic acid bacteria or <i>S. boulardii</i>	Antibiotic-associated diarrhea	[24-30]
4.	Lactic acid bacteria	Traveler's diarrhea	[31-32]
5.		Allergies	[33-37]
6.		Dental caries	[38-40]
7.		<i>Clostridium difficile</i> -induced colitis	[41]
8.		Intestinal inflammation in children with cystic fibrosis	[42]
9.		Respiratory infection in children	[43]
10.		Nasal colonization with pathogens	[44]
11.	Lactic acid bacteria and <i>Bifidobacterium</i> species, <i>S. boulardii</i> and drug, <i>S. boulardii</i> alone, or Lactic acid bacteria alone	Inflammatory bowel disease or irritable bowel syndrome	[45-49]
12.	Lactic acid bacteria specifically <i>L. rhamnosus</i>	Acute infectious diarrhea in children	[50]
13.	<i>L. casei</i> , <i>L. bulgaricus</i> , <i>S. thermophilus</i> , <i>L. acidophilus</i>	Rotavirus nosocomial infection in children	[51]
14.	<i>L. rhamnosus</i>	<i>Helicobacter pylori</i> eradication	[52]
15.	<i>B. longum</i> , <i>B. infantis</i> , <i>B. breve</i> , <i>L. acidophilus</i> , <i>L. casei</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i> , <i>L. plantarum</i> , <i>S. salivarius</i> subsp. <i>thermophilus</i>	Pouchitis	[53]
16.	<i>B. infantis</i> , <i>S. salivarius</i> subsp. <i>thermophilus</i> , <i>B. bifidum</i>	Necrotizing enterocolitis	[54]

growth in near future in the probiotic industry because India has a distinct advantage of having highest cattle population and India being the world's highest milk producer. Indian probiotic industry is valued more than \$2 million at present and supposed to be around \$10 million in coming 2- 3 years. Major pharmaceuticals companies have become active and are trying to formulate newer drugs and products, and packaged products like probiotic-based nutritional supplements with special needs such as lactation, pregnancy, immunodeficiency etc and products especially for pediatric and geriatric patients. In India Amul, Nestle and Motherdairy are contributing a lot to probiotics dairy products and urban population acceptance to these products is helping to increase companies focus to produce more and more probiotic products [58]. Above all Indian market also has some probiotic based pharmaceutical formulations named as Sporolac, ViBact, Darolac, Biglac, Bifilac etc.

Malaysia is as an upper middle income country by the World Bank. Its current GDP per capita is about C\$

7,605 (current price basis) or C\$ 13,850 (purchasing power parity basis). The situation of Malaysia's economic status is very much similar to Eastern European countries, e.g. Russia and Turkey, and its achievements are well comparable that achieved by China and India. The increased health concerns and various health threats amongst the better informed Malaysian population have been genuine and major contributors of the increased purchase of functional foods, nutraceuticals and organic foods. Malaysia functional food and drink market, is now valued at more than RM 30 billion (about C\$ 11.5 billion). Unfortunately, no information is readily available on the total size of the functional food market today. Functional food and drink production was expanded in the market in the 1990s in Malaysia. The major portion of the market constitutes dairy processed goods and baked goods. The companies involved in the production of functional / enriched food products in Malaysia are: Nestlé Malaysia, F&N (Fraser & Neave), Mamee Double Decker (MDD) group of companies and Kraft, which are Malaysia's largest food and drink

companies supplying a range of functional / enriched food products [58].

### 3. REGULATORY GUIDELINES FOR PROBIOTICS

#### 3.1. USA

In USA, probiotics are regulated as a variety of products and dealing bodies are named as: Dietary Supplement Health and Education Act (DSHEA) and Food and Drug administration (FDA). Such food products i.e. dietary supplements will be regulated by FDA's Center for Food Safety and Applied Nutrition [59]. In contrast to drugs, dietary supplements and food ingredients do not need FDA approval before being marketed. As per existing guidelines in USA,

- If a probiotic is intended for use as a dietary supplement, it will be considered as "foods," and such products are regulated by DSHEA.
- If a dietary supplement contains a new dietary ingredient that was not sold earlier, then the manufacturer is required to notify FDA [60].
- If the probiotics are considered to be the probiotic drugs as per their intended use then probiotic drug must be proven safe and effective for its intended use before marketing and then it will be regulated by FDA [61].
- In case of biologics, one needs to have an approval *via* Biologic Licence Application (BLA). Determination of a biological product can be more complex because a biological product can be a virus, therapeutic serum, toxin, anti-toxin, vaccine, blood, blood component or derivative, allergenic product, or protein (except any chemically synthesized polypeptide) or analogous product applicable to the prevention, treatment, or cure of a disease condition. The definitions of drug, new drug, and biological product are not different rather a product can be any of these categories, depending on its composition and intended use(s). FDA applies the current good manufacturing practices (cGMP) and investigational new drug (IND) approval process to new drugs as well as live biotherapeutic agents and biological products [62].

#### 3.1.1. Claims for Dietary Supplements

According to DSHEA, nutrient content claims, structure/function or health claims for the products is

responsibility of the manufacturers of dietary supplements [63]. Structure/function claim, given by manufacturers is reviewed and accepted by experts in the field by FDA to prove that the claim is not misleading. A dietary supplement need not to have the premarket approval, as a necessary requirement for drugs if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose. When a structure/function is claimed by the manufacturer then it must be stated that FDA has not evaluated the claim and that the product is not intended to "diagnose, treat, cure, or prevent any disease"; such as a drug [64, 65]. Clinical studies are then rated on the basis of quality and strength of evidence. FDA in 2007 had announced a final rule establishing cGMP requirements for dietary supplements to ensure the identity, purity, quality, strength, and composition of dietary supplements [66]. According to Nonprescription Drug Consumer Protection Act (2006), serious adverse events associated with use of dietary supplements must be recorded and forwarded to FDA by either manufacturers or distributors.

#### 3.1.2. Claims for Live Biotherapeutic Agents as Drugs

If a dietary supplement contains a new dietary ingredient that was not sold, then the manufacturer is required to notify FDA. A LBP (Live Biotherapeutic Product), is a biological product that: 1) contains live organisms, such as bacteria; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine. An example of an LBP would be one or more strains of Lactobacilli administered orally to treat patients with ulcerative colitis, or administered vaginally to prevent bacterial vaginosis. For live biotherapeutic agents, FDA issued guidelines entitled, "CGMP for phase I investigational drugs" in July 2008 [62]. These regulations include manufacturing controls and are necessary to achieve appropriate product quality. According to these guidelines, biological products are subject to section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and the IND regulations at 21 CFR Part 312. These regulations include identification and control of the raw materials and the drug substance, stability assurance, and, where appropriate, nonclinical safety assessments (21 CFR 312.23(a)(8)). Quality control and quality assurance should be refined as product development proceeds.

Following are the mandatory points to be disclosed while using a live biotherapeutic agent or a biological product as a drug substance:

### 3.1.2.1. Description

- Including physical, chemical, or biological characteristics.
- Biological name and strain designations.
- Original source of cells from which the drug substance was derived.
- Culture/passage history of the strains.
- If cells were obtained from a clinical specimen, a description of the clinical health of the donor(s).
- Summary of the phenotype and genotype of the product strains, with special attention to biological activity or genetic loci that may indicate activity or potency; Documentation and summary of modifications, if any, to the LBP, e.g., intentional introduction of foreign genes or mutations, along with details of the genetic construction.

### 3.1.2.2. Characterization

- Characterization of an LBP must include a description of the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance (21 CFR 312.23(a)(7)(iv)(a)).
- Identification of the cells up to species and strain level at least proved by two complementary methods of identification, e.g., biochemical identification and genetic identification.
- Minimum inhibitory or minimum bactericidal concentrations for a panel of antibiotics proposed by the investigator and assessment whether the product strains are sensitive or resistant to each of the antibiotics in the panel.
- Assay determining whether or to what extent antibiotic resistance is transferable from a product strain to relevant microbial flora.
- Need for such a gene or alternative approaches, if antibiotic resistant gene has been intentionally introduced in the product strain(s).
- Methods used to attenuate an otherwise virulent strain, as well as documentation addressing the stability of such attenuation.
- Product's mechanism(s) of action(s).

### 3.1.2.3. Manufacturer

- Name and address of the manufacturer(s) of the drug along with other pertinent organizational information.
- List of all additional products that are manufactured or manipulated in the same or adjacent areas used to produce the drug substance.
- Whether the production of other products will utilize the same product contact equipment and, if so, how that equipment will be cleaned between operations for the manufacturing of different products.
- A floor diagram which enable visualization of the production flow and to identify adjacent operations that may create particular concerns, such as contamination by extraneous microorganisms.

### 3.1.2.4. Method of Manufacture

#### a. Raw materials

- List of all materials (e.g., culture media, buffers, etc.) used in the manufacture of the drug substance, and their tests and specifications, or reference(s) to official compendia.
- Representative certificates of analysis from the supplier(s) for purchased materials.
- Manufacturer's acceptance criteria.
- The source and quality of materials and appropriate documentation.

#### b. Flow charts

#### c. Cell bank system

- Detailed description of the cell banking procedures
- The banking system.
- The size of the cell banks.
- The methods, reagents, and media used for preparation of the cell banks.
- The conditions employed for cryopreservation and storage.

- In-process controls; and storage conditions.
- Description of the procedures used to avoid extraneous microbial contamination.
- Precautions (e.g., storage of cell banks in multiple freezers or at different sites) taken to prevent any event that could render the cell banks unusable.

d. Cell growth and harvesting

- Steps in propagation, from retrieval of the cell bank to culture harvest (stages of growth).
- The media used at each step (including water quality), with details of their preparation and sterilization.
- The inoculation and growth of initial and sub-cultures, including volumes, time and temperature of incubation(s).
- Precautions taken and in-process testing conducted to control contamination.
- The nature of the main culture system, including operating conditions and control parameters, (e.g., temperature of incubation, static vs. agitated, aerobic vs. anaerobic, culture vessels vs. fermenter, volume of fermenter, or number and volume of culture vessels).
- The use of antibiotics in the medium and rationale, if applicable.
- The methods and the criteria used for harvesting and determining yields, and the criteria for pooling more than one harvest, if applicable.

e. Purification and downstream processing

- Methods and materials of separation and/or concentrate intermediate forms and the final bulk of whole cells.
- Analytical tests developed or adopted by the manufacturer to show identity, purity, and concentration, and the levels of product related and non-product related impurities.

f. In-process testing

- Specify the criteria for accepting or rejecting an in-process batch.

### 3.1.2.5. Drug Substance Specifications

- The identity of each microbial strain present in the drug substance.
- Testing may be based upon biochemical methods such as fermentation profile or genotypic methods, including such as ribotyping, restriction fragment length polymorphism (RFLP), or both.
- Potency of live microbial products is generally a measure of viable cells per unit or dose, i.e., colony-forming units (CFUs).
- Purity tests of a LBP may include assessment of endotoxin content, residual antibiotics, and/or the quantification of residual toxic components or contaminants introduced during manufacture.

However, manufacturers need to notify FDA guidance to industry before marketing a product. FDA has described only the manufacturing guidelines. Only manufacturing guidelines are not sufficient for the safe use of probiotics and hence must be harmonized with respect to each and every aspect.

## 3.2. India

In India, sporulating *Lactobacilli* are sold in market with some of the antibiotic preparations mainly to prevent antibiotic induced diarrhea especially for pediatric patients. Indian government has Food Safety and Standard Act (FSSA) to address the quality safety and efficacy related issues of nutraceutical, functional food, and dietary supplements [67]. The FSSA was created in 2005 to draft rules and regulations in food sector by categorizing the foods for special dietary uses or functional foods, nutraceuticals or health supplements respectively [68]. Foods and drugs are regulated by PFA (Prevention of Food Adulteration Act) and FDA respectively. Initiatives were taken by Indian Council of Medical Research (ICMR) /Department of Biotechnology (DBT) for the formulation of guidelines for regulation of probiotic foods. ICMR formulated the guidelines which deal with the use of probiotics in food and provide requirements for assessment of safety and efficacy of the probiotic strain and health claims and labeling of products with probiotics [69].

Guidelines recommended by ICMR for evaluation of probiotics in food are as follows:

1. Genus, species and strain identification
  - Phenotypic identification

- Genotypic identification
2. *In vitro* tests to screen potential probiotic strains
    - Resistance to gastric acidity.
    - Bile acid resistance.
    - Antimicrobial activity against potentially pathogenic bacteria (acid and bacteriocin production).
    - Ability to reduce pathogen adhesion to surfaces.
    - Bile salt hydrolase activity.
  3. *In vivo* safety studies in animal models
  4. *In vivo* efficacy studies in animal models
  5. Evaluation of safety of probiotics for human use
    - Determination of antibiotic resistance patterns.
    - Assessment of undesirable side-effects.
    - Tests for toxin production and hemolytic activity respectively if strain belongs to similar category.
  6. Evaluation of efficacy studies in humans
  7. Effective dosage of probiotic strain / strains
  8. Labeling requirements
    - 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.
  9. Good Manufacturing Practices

- Hazard analysis
- Critical control point

These guidelines have a provision to access the efficacy, safety and health benefits of probiotic food ingredients and fulfill some essential prerequisite conditions before being used for the internal use by humans [70].

### 3.3. Malaysia

There is currently no official definition of functional food products in Malaysia. Functional foods are classified as food and must comply with the food regulations. All food and drugs that are either locally produced or imported products are conducted by a sophisticated legal system in Malaysia. The main government departments and agencies that implement and enforce these regulations are the Food Safety and Quality Division (FSQD), the Drug Control Authority, the National Pharmaceutical Control Bureau (NPCB), and the Committee for the Classification of Food-Drug Interface Products.

- An official body named as the “Committee for the Classification of Food-Drug Interface Products” in Malaysia interacts with nutraceuticals and certain functional foods and concludes the category whether a product is a food or a drug.
- A product will be regulated by FSQD (Food Safety and Quality Division), if a product contains 80% or more of food ingredients, either singly or in combination, and with equal to or less than 20% of biologically active ingredients of natural products with pharmacological and/or therapeutic properties, the product is regarded as a food product.
- A product will be regulated by NPCB (National Pharmaceutical Control Bureau), if a product contains less than 80% of food-based ingredients and more than 20% of the active ingredients or if the product is a ‘pure’ form (close to 100%) of active ingredients, e.g. vitamins, minerals, amino acids, fatty acids, fiber, enzymes, etc, or products containing solely natural ingredients that are not traditionally used as food and possess medicinal value, when there is greater uncertainty about the efficacy and safety of a product.
- For functional foods, regulations are under the authorized division (FSQD) and its purpose is to

ensure the protection of public from fraud and wrong manufactured products. In Malaysia, continuous revision and updating of the regulations are conducted by the various Ministries.

As Malaysia's regulations are locally developed with reference to CODEX, these are complex regulatory guidelines for the functional foods but no separate guidelines are entitled for the probiotic category, which seems to be a necessity in the future because of the well entrenched minds of the majority of the Malaysians regarding the concept of maintaining their healthy nutrition [58].

### 3.4. Other Attempts

#### 3.4.1. FAO/WHO

An attempt was made by the Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert (FAO/WHO) Consultation to standardize the requirements needed to make health claims regarding probiotic agents, evaluation of health and nutritional properties of probiotics and presented some guidelines for evaluating probiotics in food that could lead to the substantiation of health claims in 2001.

Guidelines recommend by FAO/WHO for evaluation of probiotics in food are based on following points:

1. Identification of the genus and species of the probiotic strain by using a combination of phenotypic and genotypic test.
2. *In vitro* testing to demonstrate the mechanism of the probiotic effect.
3. Safety assessment and *in vivo* studies of the probiotics strain
  - Patterns of antimicrobial drug resistance,
  - Metabolic activities,
  - Side effects noted in humans during clinical trials and after marketing,
  - Toxin production and hemolytic potential if the probiotic strain is known to possess those properties,
  - Lack of infectivity in animal studies.
4. *In vivo* studies using animals and humans.

#### 5. Health claims and labeling

- Genus, species and strain designation.
- Minimum viable numbers of each probiotic strain at the end of the shelf-life.
- The suggested serving size.
- Health claim(s).
- Proper storage conditions.
- Corporate contact details for consumer information.

The consultation recommends that specific health claims on labeling material on probiotic food items must be presented and available to the consumer and it should be the responsibility of product manufacturer for ensuring particular material is safe enough to use directly [71,72].

#### 3.4.2. WGO

An attempt has also been made by World Gastroenterology Organization (WGO) for demonstrating global guidelines for probiotics and prebiotics. WGO has presented the points described by The Council for Agricultural Science and Technology. Other than the points discussed in FAO/WHO, these guidelines are focused on the genus, species, and strain for each probiotic in a product, along with the number of viable cells of each probiotics strain that will remain up to the end of shelf-life [73].

#### 3.4.3. ILSI

International Life Science Institute (ILSI) has also given guidelines for evaluation of probiotics in food products demonstrating *In vivo* tests to correlate *in vitro* tests for evaluation of safety of probiotics to humans and also had given essential requirements of infant food formula. Under the part of efficacy evaluation demonstration of dose or CFU ingested per day, period of use and scientific substantiation of health claims are included in these guidelines [74].

### 4. NEED OF HARMONIZED REGULATIONS FOR PROBIOTICS

At present, various regulatory agencies across the globe consider probiotics under several categories (e.g. biologics, drugs, foods, nutritional supplements etc.). Therefore probiotics are regulated by different guidelines depending upon their regulatory category.

An effective regulatory framework in operation and harmonization of guidelines is required to maintain high quality, safety, stability and efficacy of probiotic formulations during the entire processing, production and storage chain along with post marketing surveillance. As no proper standardization parameters are present for the probiotics, lack of standardization is becoming a major challenge to establish the credibility of health promoting functions of probiotics. Probiotic products which claim specific nutritional, functional or therapeutic characteristics are present on the boundaries of being food, dietary supplement or medicine, posing challenges for regulators. So, taking into consideration the rapid growth in probiotics worldwide, there is an urgent need of globally accepted uniform regulatory guidelines. These harmonized guidelines are important to:

- bring harmonization of standards for global acceptance,
- strictly regulated probiotic based products with quality control and assurance,
- increase customer acceptance, which ultimately leads to increase in probiotic market value,
- put no false claiming on probiotic products will be there,
- probiotics as a better choice than other alternatives such as antibiotics as they are the nature's truest form of antibiotics; and
- provide less expensive alternative of many medicines with negligible or no side effects.

Information provided by labeling claims will help the consumers to understand the features, contents and usage of particular foods and to choose the proper foods. With more public information available, consumer can better decide about the purchase and this factor will lead to decide quality and quantity of purchase. Information provided by labeling claims will also help the manufacturers because they will be benefitted by promoting the sale if characteristics of their products and proper labels are correct. So there is urgent need to review the terms probiotic, prebiotic, and biotherapeutic along with regulatory definition of drug, biologic, dietary supplement and GRAS. This Discussion also need to focus on the regulatory difference between a dietary supplement and a drug/biologic as well as to design the regulation of probiotics as biologics. As laws and regulations

improve and research continues to separate facts from fiction, functional foods and natural health products are likely to play an increasingly important role in health maintenance and disease prevention in coming years. But for proper regulatory framework and harmonization, development of probiotics should be according to their clinical indications. Taking all the above said points into consideration, there is a need of comprehensive guidelines and regulations globally for judicious and effective use of probiotics and safety of whole of the populations using probiotics based product. The harmonized guidelines for regulation of probiotics may be framed by common point selection of existing guidelines and inclusion of comparison based recommendations. Such comparative insights on existing regulatory guidelines in USA, India, and Malaysia with suggestive recommendations are given as Table 3.

#### 4.1. Recommendations for Dossier Development of Probiotics

General points to be considered in a probiotic dossier should be as follows.

1. Description of strain isolation.
2. Strain identification: genus, species identification considering phenotypic as well as genotypic DNA based techniques.
3. Physiological and metabolic characteristics of the strain determined through *in vitro* analysis.
4. Proposed mechanism of action and definition of active principle.
5. Technological characteristics specifically including genetic stability which is required during growth and its ability to remain viable while shipping, preservation and storage.
6. Safety
  - Recommended consumption level.
  - Contraindications, if any.
  - Virulence, if any.
  - History of consumption.
  - Mutagenicity, if any.
  - Acute and chronic toxicity.
  - Post marketing surveillance.

**Table 3: Comparison of Regulatory Guidelines for Probiotics in USA, India and Malaysia**

Serial No.	Parameter	USA	India	Malaysia
1.	Regulatory category of probiotics	Drugs/biologics/dietary supplements or food ingredient/live biotherapeutic products.	Drugs and functional foods.	Functional foods.
2.	Regulatory authority for approval	1. Drugs/ biologics/live biotherapeutic agents need approval from FDA 2. Dietary supplements and food ingredients are approved by Dietary Supplement Health and Education Act (DSHEA).	1. Functional food are regulated by regulated by PFA (Prevention of Food Adulteration Act) as per The Food Safety and Standards Act of (FSSA). 2. Drugs are regulated by FDA.	1. Functional foods regulated by i)FSQD (Food Safety and Quality Division), if functional food consists 80% food ingredient and 20% biologically active component. 2) NPCB (National Pharmaceutical Control Bureau) if biologically active component is more than 20%
3.	Premarket Approval	Required for drugs, biologics and live biotherapeutic agents. Not required for dietary supplements and food ingredients.	Required for both drugs and functional foods.	Required for functional foods by FSQD.
4.	Recommended regulatory guidelines	Guidelines are different for dietary supplements and drugs based on their intended use. For LBP's, major stress is on manufacturing controls and the extent of such manufacturing controls.	Guidelines are recommended for probiotics in food and major stress is on identification and evaluation of probiotic strain along with health claims and labeling claims.	No official definition and exclusive guidelines for functional foods. They comply with food regulations only which include nutrition labeling and covering claims.
5.	Therapeutic claims	Allowed but not used for drug substances rather used only for dietary supplements.	Allowed but not used for drug substances rather used only for food ingredients.	Nutrition claims are allowed for food and followed very strictly under Food Regulation Act.
6.	Structure/function claim	Allowed only for functional foods but not for the drug products.	Not allowed.	Nutritional/function claim referring physiological role can be mentioned on food products.
7.	Assessment of safety parameters	USFDA is responsible for the safety of drugs, LBPs, biological products. Food safety is responsibility of DSHEA.	FDA is responsible for the safety of drugs and food safety is responsibility of FSSA. ICMR guidelines can also be used to identify and evaluate safety.	FSQD is responsible for the safety of functional food products.
8.	Requirements for approval	Drugs/Biologics: 1. Clinical data 2. Data to support study of products in humans: CMC, Stability, Pharmacology/ toxicology Dietary supplements and food ingredients: 1. Health claims 2. Structure/ function claims	Drugs: 1. Clinical data 2. Data to support study of products in humans: CMC, Stability, Pharmacology/ toxicology Functional foods: 1. Strain identification 2. Functional characterization 3. Safety assessment 4. Labeling requirement	Not available
9.	Available probiotic products	Florastor, Dietary products.	Sporolac, Yogurt, Darolac, Biglac, Bifilac etc.	Enriched drinks, functional foods, Tiger branded children's biscuits with probiotics.

(Table 3). Continued.

Serial No.	Parameter	USA	India	Malaysia
10.	Recommendations	A) Adoption of the definition of probiotics B) Use and adoption of the guidelines C) Regulatory framework to allow specific health claims on probiotic food and drug products. D) Promotion of these guidelines E) Evaluation, identification, labeling, health claims and safety related guidelines must be applied.	A) Adoption of the definition of probiotics B) Use and adoption of the guidelines C) Promotion of these guidelines D) Good manufacturing practices (GMP) must be applied E) Quality assurance and shelf life of probiotics should be established F) Further development of methods (in vitro and in vivo) to evaluate the safety along with already Prescribed guidelines G) Further development of guidelines for approval process.	A) Framing official definition of functional food and specifically the probiotics. B) Strict guidelines should be maintained for probiotic drug as well as probiotic food categories covering all the aspects including identification, evaluation, labeling and health claims, good manufacturing practices and approval process.

## 5. CONCLUSION

Probiotics are advocated by many health care professionals because of their evidence based health benefits in specific clinical scenarios. Probiotic therapy has already made its way in the treatment of number of diseases and hence the global market of these products is achieving a rapid pace but still the rational usage, selection and design of probiotics remain important challenges for the scientific community in concern with their safety factors. There is an urgent need to address the quality, safety and efficacy issues of probiotics. Some countries are regulating probiotics under the category of functional foods and drugs, whereas most of the countries consider them as functional foods, medical food, biological product, dietary supplements or natural health products. So a careful risk assessment for patients and proper handling of the probiotic during administration need to be conducted before using probiotics as drugs. It becomes evident from the careful analysis of regulatory aspects in different countries that all the leading nations worldwide are now recognizing the importance of probiotics and their beneficial impact on human beings. Each country is in process of addressing the problematic issues and regulating proper regulatory structure for the functional foods. Despite of this, due to separate regulations in different countries, there are certain considerable confusions and challenges ahead for the regulatory bodies, food scientists, manufacturers and even consumers about the claims associated with probiotics, which needs to be addressed for the successful marketing and usage of functional foods. To resolve all the issues related to probiotics, a common regulatory framework is required which will allow free exchange of products and will minimize confusion of different regulations. Thus a

comparative study is helpful to develop a harmonized guideline for these products which can be internationally accepted. In absence of any regulatory standards or even if these standards are not up to the mark, there would always be a possibility of marketing of ineffective products with false claims. In conclusion there is need for proper regulatory framework and harmonization of regulations on probiotics with international standards to ensure the quality and safety for active utilization of probiotics across the globe.

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