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An Overview of Regulatory Considerations for Probiotics in Various Countries

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ABSTRACT

Probiotics, which are stared as live microorganisms administered orally leading to health benefits, and are used widely in control and treatment of diseases, remarkably against bacterial diseases. Since probiotics having potential to cure, treat or mitigate diseases particularly in critically ill patients they considered as a drug. Depending upon their anticipated use regulatory requirements vary significantly across the globe. Earlier there was no much stringent marketing regulation for probiotics as a dietary supplements, only a premarket notification was required, but recently use of probiotic as a drug put forth to prove safe and effective for its intended use before marketing in different countries across the globe. The future of probiotic foods is even more promising, as modern users are bothered to keep their individual health and think the food that they eat to be healthy and capable of inhibiting infection. This article summarizes the regulatory guidelines for probiotics in different countries.

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ABBREVIATIONS

1. FAO/WHO: Food and Agricultural Organization/World Health Organization.
2. MHLW: Ministry of Health and Welfare.
3. FOSHU: Food for Specified Health Use.
4. FDA: Food and Drug Administration.
5. FUFOSE: Functional Food Science in Europe.
6. NMPA: National Medical Products Administration.
7. ANVISA: National Health Surveillance Agency Brazil.
8. FSANZ: Food Standards Australia and New Zealand.
9. DSHEA: Dietary Supplement Health and Education Act.
10. BLA: Biologic License Application.
11. PFA: Prevention of Food Adulteration Act
12. FSQD: Food Safety and Quality Division
13. NPCB: National Pharmaceutical Control Bureau

INTRODUCTION

As per FAQ/ WHO probiotics are live microorganisms that when administered in adequate amounts confer a health benefit on the host.[1] Probiotics are again sub classified as probiotic foods, probiotic drugs, dietary supplements, Functional foods, live biotherapeutic agents.

Probiotics considered as food supplements which are generally safe to consume by improving or restoring gut flora in healthy population. Certain probiotics are lactobacillus acidophilus, saccharomyces boulardiilyo, bifidobacterium infantis.

Drugs available in market are Spermophilus, provella, primadophilus Bifidus, Novaflor, Intestinex, Floragen3, Acidophilus, Philips colon health etc.

Probiotics compete with bad microorganisms and colonize our gut flora. They have proved that they cure some Diarrheal diseases, Helicobacter pylori infection, Irritable bowel syndrome, lactose intolerance, inflammatory bowel diseases, urinary tract infection, etc. Besides this, they are having some side effects. Headache, Allergy symptoms, Bloating and gas, constipation and increased thirst are the causes.[2]

Table No. 1: Probiotic classification across the globe

COUNTRY	CATEGORY	DEFINITION AS PER COUNTRY	REGULATORY BODY
	Probiotics	The live micro-organisms which when given in adequate amounts confer a health benefit	FAQ/WHO
INDIA	Functional foods and drugs	Natural food has physiological functions which regulates the biorhythms, the nervous system, the immune.	FSSAI, PFA, FDA
JAPAN	Functional foods and nutraceuticals	As per Japanese system, these products are in diverse category named as Food for special health use, with a specific regulatory approval process isolated from food fortified with vitamins, minerals, and dietary supplements not carrying FOSHU claims, Nutraceuticals are defined as chunks of food or whole food quantity that have some medical or health benefits, containing the prevention and treatment of disease. Certain compounds and molecules also comes under this are Vitamins, minerals and herbal supplements.	MHLW,FOSHU
EUROPE	Functional foods	A natural food that constructively alters one or more important functions of the body beyond sufficient nourishing effects which is relevant to either a better state of health and well-being and/or decrease of risk of disease. Intake as part of a normal food pattern. It is neither tablet, a capsule nor any form of dietary supplement.	FUFOSE
CHINA	Functional foods	Functional food is defined as a food that has distinctive health benefits or is able to supply vitamins or minerals and has the competency to	NMPA

		control human body functions.	
BRAZIL	Functional foods	Functional foods constitute products to which contain health ingredients due to which have precise physiological effects and/or are boosted with other ingredients added not normally found in the product, providing health benefits beyond their nutritional value.	ANVISA
NEW-ZEALAND &AUSTRALIA FOODS	Functional	Functional foods are products which are supposed to serve physiological functions beyond the provision of simple nutrient requirements.	FSANZ
USA	Dietary supplements	Dietary supplements are mainly used as a supplement to the diet; consisting one or more nutritive components (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents and also can be taken orally as a pill, capsule, tablet, or liquid; and is labeled on the front panel as a dietary supplement.	DSHEA
	Drugs	Drug is an article proposed for the cure, mitigation, treatment, diagnosis, or prevention of disease	FDA
	Biological products	Biological product is a product containing a virus, serum, or toxin applicable to the prevention, treatment, or cure of a disease.	BLA
	Medical food	Some medical food are also products used for external application in controlling of diet in a disease or condition for which typical nutritional requirements established by medical assessment and is formulated and given under the supervision of a physician	FDA
	Live biotherapeutic agent	Live biotherapeutic agent is a biological product (1) contains live micro-organisms, such as bacteria; (2) is used in prevention, treatment, or cure of a disease or condition of human beings and (3) is not a vaccine.	FDA
MALAYSIA	Functional Foods	Currently no official definition	FSQD, the Drug

		available for functional food products in Malaysia.	Control Authority, NPCB and the Committee for the Classification of Food-Drug Interface Products.
CANADA	Natural health products	It is defined as a ingredient, or a combination of ingredients, a homeopathic medicine or a traditional medicine, that is intended to deliver a pharmacological or functional activity or other direct effect in Diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physiological state or its symptoms in humans; Restoring or correcting organ functions in humans; or Modifying organ functions in humans, such as modifying those functions in a manner that maintains or promotes health.	Natural Health Products Directorate

INDIA

In India, former there were no specific regulatory guidelines and efficient methodology for probiotic products as well, so in the lack of any such standards and procedures, there was excessive scope of deceitful statements being promoted. So a method was hence required for framing guiding principle and rules for assessing the safety and efficacy of probiotics in India. Taking in sight the above, a Task Force was established by Indian Council of Medical Research (ICMR) along with the Department of Biotechnology (DBT), constituting specialists from various fields to structure regulatory guidelines for assessment of probiotics in food in India. These guidelines have set of guidelines to define a product/ strain as actual probiotic.[3]

Lately, probiotics are taken as food and therapeutic as well in the country but since changing classes, probiotics are regulated in a different way as per their proposed use. In India, presently food and drugs are regulated by Prevention of Food Adulteration Act (PFA) and FDA, correspondingly. The Food Safety and Standards Act of 2005 (FSSA) describes the foods for distinct dietary uses or functional foods, nutraceuticals or health supplements

(IMNA, 2010). FSSA was passed by the Indian government with the determination to control different ranges of eatables regulations covering nutraceuticals, foods and dietary supplements. Minimum criteria associated to quality and composition of the products are established by currently imposed PFA Rules. PFA regulates labelling and packaging of food products to maximize the components, nutritional information, expiration date, company and details of manufacturing and country of origin and importer with respect to the food product must be revealed to customer.

JAPAN

Products that are marketed or used as items are advantageous for maintenance and improvement of health are generally referred to as "health foods" in Japan. There is no clear definition for the term from the legal side, however other than "foods with health claims" that is defined under Health Promotion Law.

Applicable laws and regulations [8]

- Food Sanitation Act
- Food Safety Basic Law
- Japanese Agricultural Standards Law
- Health Promotion Law
- Pharmaceutical Affairs Law

Foods for Specified Health Uses (FOSHU)

Products for specific health uses contains functional health ingredients with biological and physiological function on body.

When some products are marketed as foods for indicated health benefits, an evaluation by the national government must be undertaken to prove the efficacy and safety of each physiological functions and specified health functions etc. and must obtain approval for the same.

Ordinary FOSHU: Detailed review has to be done with scientific proof for each application. [10]

Standardized FOSHU:

- No prerequisite of detailed assessment for food products meeting the standard, limit and specifications
- Must contain sufficient scientific evidence.
- For efficiency: Few process for products whose safety has already proved and approved.[10]

Reduction of disease risk FOSHU:

- Requires detailed review process with scientific evidence for each application.
- Allowed for products whose ingredients clinically and nutritionally produced to reduce a risk of certain disease (i.e., Calcium for Osteoporosis and Folic acid for neural tube defects).[10]

Qualified FOSHU:

- Requires detailed review process with scientific evidence for each application
- Permitted for products with ingredients showing certain health effects but not reaching the standards for FOSHU approval
- Labeled as "Qualified Food for Specified Health Uses"[10]

FOSHU approval

General procedure for approval of FOSHU

FOSHU labelling requirements:

Table No. 2: Approval procedure in Japan [8]

Sample of the entire package with labels and health claims
Evidence to prove that the functional component is effective in maintenance of health
Dosage instruction and nutritional information.
Human study reports to prove safety of the product.
Stability studies of the product and functional component.
Description about the physical and biological characters of the final product and the core component
Qualitative and quantitative methods to determine functional component and report of analytical assay.
Nutrient constituent analysis report and energy content of the product.
Method of production, list of equipment and details of Quality control system.

Mandated FOSHU documentation can be summarized into 3 essential requirements for FOSHU approval:

1) Scientific evidence like clinical studies to show effectiveness.

2) Data from the historical consumption pattern and the human clinical studies to prove safety of the product; and

3) Analytical determination of the functional component responsible for the beneficial physiological action.

EUROPE

Europe was second for launching explanation of functional foods and applying a regulatory commission on functional food science in Europe (FUFOSE) in 1995. Europe has an advanced market for probiotics by rapid progress as functional foods, whose biggest sector is composed of probiotic food products, especially dairy products such as yogurts and fermented milks. According to European laws, even microbial cultures existing in food essentials to fulfill the permissible requirements. European food safety authority hosted qualified presumption of safety (QPS) for the first time for safeguarding the premarket safety evaluation in foods and food supplements.

European guiding principle have been studied by many employees and collaborators and therefore a comprehensive explanation of European guidelines has been defined. Which finally accomplish that probiotics are not having any lawful description and definite regulations rather they fit the class of functional foods. European regulatory structure is yet not synchronized as probiotics are controlled by the Food Products Directive and Regulation if to be marketed as food supplement (Regulation 178/2002/EC; Directive 2000/13/EU) and under Herbal Medicinal Products Directive (2004/24/EC) if promoted as traditional herbal products. For the use of probiotic product as herbal medicinal product, it is suggested to apply and get a drug registration, or they will be reassigned to the class of food supplements. Ultimately, registered drugs are enclosed under the Drug Law (65/65/EC, amended).[4]

CHINA

China is well-known for its extensive traditional Chinese medicine history. At present, China has a well-developed market for functional foods, which are founded on traditional nutritive culture and has intense principles of performance along with fast economic development.Primarily, China has implemented Food and Hygiene Law, which has defined nutrients as 'any finished product or raw material proposed for the individuals to consume, as well as any product that has conventionally aided as both food and medication'. But recently, State Food and Drug Administration (SFDA) are regulating all health foods which contain all type of functional foods and nutraceuticals in China. The functional foods are defined as a food that has distinct health functions or is able to source vitamins or minerals. It is appropriate for consumption by distinct clusters of individuals and has the role of regulating human body functions.[9]

BRAZIL

In American nations, Brazil is invented to be first country to issue law concerning functional food. In Brazil, probiotics are reflected as functional foods and deliberated to be different from food. But regulation asks for safety and efficacy demonstration of food products and therefore all these products essential to be registered and approved by regulatory authority called National Health Surveillance Agency Brazil (ANVISA).[1]

NEW ZEALAND AND AUSTRALIA

New Zealand and Australia have united framework organization called Food Standards Australia and New Zealand (FSANZ).Former by, functional foods were well-defined as the foods, which are comparable in appearance to conventional foods and are proposed to be consumed as part of a regular diet; but as per latest rules, these are made-up to function physiological roles beyond the provision of simple nutrient supplies.[9]

USA

Presently US is regulating functional foods as a range of products as per their proposed use and regulating bodies are Dietary Supplement Health and Education Act (DSHEA) and Food and Drug Administration (FDA). Such sustenance products, i.e., dietary supplements are regulated by FDA's Center for Food Safety and Applied Nutrition. And food constituents does not require FDA approval prior marketed. As per standing guiding principle in USA,

- If a probiotic is used in the formula of dietary supplement, then are reflected as 'foods', and are regulated by DSHEA. [3]

- If a dietary supplement consists of an innovative nutritive component and do not have a promotion history previously, then the company is prerequisite to notify US Regulatory body.

If the probiotics are reflected to be the probiotic medicines for therapeutic determinations then probiotic medication must be demonstrated safe and effective for its intended usage prior marketing and then it will be regulated by FDA.

- In case of biological product, individual needs to get approval via BLA. Identifying a biological product shall be more intricate because a biological product may be a virus, therapeutic serum, toxin, anti-toxin, vaccine, blood, blood component or imitative, allergenic product, or protein (except any chemically produced polypeptide) or corresponding product appropriate to the anticipation, treatment, or cure of a disorder. The definitions of drug, new drug and biological product are not diverse slightly a product can be any of these classes, dependent on its composition and proposed use (s). FDA put on the cGMP and IND approval process to new drugs as well as live biotherapeutic agents and biological products.[5]

MALAYSIA

Malaysia is one among the important markets of concern for nutraceuticals business in Southeast Asia. Drug Control Authority (DCA) regulates these products as pharmaceutical products in Malaysia. Pre-marketing approval process is considered for health supplement products. Depending upon the type and dosage of the components used in the formulation, product is classified as dietary supplement or traditional medicine.

In Malaysia, health supplements are classified as 'dietary supplement' when it contains vitamins and minerals, amino acids, natural substances from plants/animals, enzymes and probiotics which the Malaysian DCA has recognized as safe and are not in the list of prohibited ingredients. Some dietary supplement ingredients are prohibited like vitamin K and caffeine.[3]

Some natural ingredients such as alfafa and spirulina are considered as traditional medicine when they are incorporated in certain health supplements which are not traditionally used as food and have medicinal value. Certain prohibited herbs are ephedra, valerian extract and other botanicals which contain aristolochic acid. During formulating the health supplement for Malaysia one has to check and ensure that they are free from the prohibited ingredients.

One major thing one has to note is, the products containing both dietary supplement and traditional medicine ingredients are not allowed to register in Malaysia.

But, the Malaysian regulatory body recently come up to agree combination products that contain vitamins and traditional herbal ingredients which are safe to take as food, for example, ginseng.[3]

The use of statements for both dietary supplements and traditional medicines are restricted. Dietary supplements are only allowed to make nutrient function statement and/or other function statement that are on the list. For example 'Vitamin A helps to maintain growth, vision and tissue development'.

Claims has to be made for traditional medicines according to the list of predefined statements which covers general maintenance of health, blood and body fluid and women's health.

In Malaysia, as dietary supplements regulated under the pharmaceutical category they have to comply with quality and safety requirements of the pharmaceutical products.

Though, applicant does not require to submit a full drug registration dossier like controlled drugs. General information and documents such as product formula, certificate of analysis, GMP certification, and stability study reports are required.

Only list of probiotic microorganism listed in the Schedule 12A of the Regulations are permitted - Mainly Bifidobacterium spp and Lactobacillus spp.

• The viable probiotic count must not be less than 106 cfu/ml or cfu/g during the shelf life of the food.

• The probiotic cultures must not contain transmissible antibiotic resistant genes.

• Companies may apply for inclusion of new probiotic into Schedule 12A.

CANADA

To market the product in Canada, **natural health products** required to be registered by Health Canada. This means that prior a natural health product can sale, an applicant has to submit documents to Health Canada for assessment to confirm that the product is safe and effective, while the level of evidence required can differ. Non-scientific data is accepted to establish effectiveness, for instance texts establishing ancient usage of the product. Additional details are provided on this fact later in the document. If the regulatory body of Canada finds that this data meets the requirements as per the guidelines, it will issue a "product license". One can find licensed natural health products by viewing for the eight-digit natural product number (NPN), or in the case of a homeopathic product, a homeopathic medicine number (DIN-HM). These numbers are created on the product label. In count, Canadian industries that manufacture, package, label and import natural health products needs to have "site licenses" to be able to carry out these events. To get a site license from regulatory body, the firm should submit documents to demonstrate they are capable of undertaking the activities based on certain criteria.[7]

CRITERIA FOR ASSESSMENT OF PROBIOTICS[9]

1) Genus and species identification of the probiotic strain by using a mixture of phenotypic and genotypic tests as clinical proof saying that the health profits of probiotics may be strain specific.

2) In vitro analysis to outline the action of the probiotic effect, and

3) Demonstration of the clinical health benefit of probiotic agents with human trials.

Additionally, safety assessment of the probiotic strain should at a minimum determine

1) Patterns of antimicrobial drug resistance.

2) Metabolic actions.

3) Adverse events noted in humans during clinical trials and after putting in marketing.

4) Toxicity production and hemolytic potential if the probiotic strain is identified to possess those properties, and

5) Deficiency of contamination in animal studies.

CONCLUSION

The recent increase in occurrence and severity of disease has encouraged some physician to suggest probiotics in combination with antimicrobial drug therapy as drugs.

Commercialization of probiotic products made their importance within past 50 years. The term probiotics should be used properly, it should be corrected since lack of alertness and the integrity of health claims related with probiotic products are posing a foremost threat to probiotic manufacturer and its buyers.

All the developing and developed nations worldwide are now identifying the significance of probiotics as a drug and their advantageous effect on human beings. Every single country is in progression of figure out the issues and monitor appropriate regulatory guideline for the probiotic drugs, but due to distinct regulations in different countries, there are some significant misperceptions and challenging tasks ahead for the regulatory agencies, food experts, companies and also customers about the statements related with probiotics, which requires to address for the successful promotion and use of functional foods. Undoubtedly, the regulatory guiding principles are frequently altering as a consequence of ongoing progresses in different countries and hereafter the regulatory status of probiotics must be described by a certain point of harmonization across the world. A common regulatory structure is required to overcome all the issues associated to probiotics, which will open

access for exchange of prebiotic drugs and will reduce complexity in different regulatory guiding principles.

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REFERENCES

1. Guidelines for evaluation of probiotics in food. Report of a Joint ICMR/DBT 2011. Available from: http://icmr.nic.in/ guide/PROBIOTICS_GUIDELINES.pdf [accessed 28 October2019].
2. Joint Food and Agriculture Organization of the United Nations/World Health Organization Working Group report on drafting guidelines for the evaluation of probiotics in food, London, Ontario, Canada, April 30 and May, 2002. [Accessed 25 October 2019]. ftp://ftp.fao.org/es/esn/food/wgreport2.pdf
3. Arora M, Sharma S, Baldi A. Comparative insight of regulatory guidelines for probiotics in USA, India and Malaysia: A critical review. Int J Biotechnol Wellness Ind 2013;2:51-64.
4. Saxelin M. Probiotic formulations and applications, the current probiotics market, and changes in the marketplace: A European perspective. Clin Infect Dis 2008;46:S76-9.
5. Food and Drug Administration Overview of dietary supplements [updated 2009 Oct 14] Available at: http://www.fda.gov/Food/DietarySupplements/ConsumerInformation/ucm110417.htm[accessed 29 October 2019].
6. Guidelines for evaluation of probiotics in food. Report of a Joint ICMR/DBT 2011.] Available at: http://icmr.nic.in/guide/PROBIOTICS_GUI DELINES.pdf. [accessed 15 September 2019
7. Canadian natural health product registry.
8. Health food regulatory system in Japan
9. FAO/WHO. Report of a Joint FAO/WHO expert consultation on guidelines for the evaluation of probiotics in food. London, Ontario, Canada: World Health Organization and Food Agriculture Organization of the United Nations; 2002
10. MHLW. Ministry of Health, Labour and Welfare: Food for Specified Health Uses (FOSHU). Available at: http:// www.mhlw.go.jp/english/topics/foodsafety/fhc/02.html. [Accessed 17 October 2019].