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Overview of Regulatory Oversight and Evaluation of Probiotics in the United States, and India

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ABSTRACT: Live microorganisms known as "probiotics" are marketed with the promise that, when taken orally, they will improve or restore the gut microbiota's health. The first probiotic was named Lactobacillus bulgaricus, a bacillus strain discovered in Bulgarian yogurt. Bulgarian physician and microbiologist Stamen Grigorov discovered the finding in 1905. The contemporary notion is typically credited to Russian Nobel winner Élie Metchnikoff, who proposed in 1907 that Bulgarian peasants who consumed yogurt lived longer. The U.S. Food and Drug Administration (FDA) may regulate a probiotic product as a dietary supplement, a component of food, or a medication, depending on its intended purpose. Several probiotics are offered as dietary supplements that can be marketed without first receiving FDA approval. When probiotics first became popular in India, no rules existed. Hence, the Indian Council of Medical Research (ICMR) in conjunction with the Department of Biotechnology (DBT) formed a task force to create the regulatory rules for probiotic manufacturing in India to assess the safety and prevent the popularisation of probiotic products with misleading claims. Regulation, health claims, research and evidence, consumer awareness, and education are issues in the United States as a result of the usage of probiotics, whereas quality control, a lack of regulatory framework, low awareness, and accessibility are challenges in India. The fundamental purpose of this project is to compare the regulations and registration requirements required for probiotic approval in the US and India. The research was conducted to gather information from numerous marketing websites and official websites like the FDA, FSSAI, ICMR-DBT, and CDSCO. My research revealed that many people nowadays mostly depend on controlling their dietary habits to maintain their health, such as by including probiotics in their diet. Hence, there is an increase in the number of probiotic product regulations and approvals globally to maintain safety.

Keywords: Probiotic, Lactobacillus bulgaricus, Dietary supplement, Regulations, Indian Council of Medical Research (ICMR), Department of Biotechnology (DBT).

INTRODUCTION

Live microorganisms known as "probiotics" are marketed with the promise that, when taken orally, they will improve or restore the gut microbiota's health. Probiotics are generally regarded as safe to consume; however, there is a slight possibility that they could cause undesirable host-bacteria interactions. According to some research, probiotics may be beneficial for certain diseases; nevertheless, many of their claimed health benefits lack enough evidence. The first probiotic was named Lactobacillus bulgaricus, a bacillus strain discovered in Bulgarian yogurt. Bulgarian physician and microbiologist Stamen Grigorov discovered the finding in 1905. The contemporary notion is typically credited to Russian Nobel winner Élie Metchnikoff, who proposed in 1907 that Bulgarian peasants who consumed yogurt lived longer.

World Health Organization (WHO) report from October 2001 defines probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. [Cleveland Clinic (2023) Probiotics. Available at: https://my.clevelandclinic.org/health/articles/14598-probiotics].

What are Probiotics?

The healthy bacteria in probiotics contribute to the maintenance of the body's functionality and wellness. Benefit from these beneficial bacteria in numerous ways, including how they help you feel better and fight off bad bacteria when there is an overgrowth. There are trillions of microorganisms on and in each person's body. These microorganisms are made up of:

- Bacteria.
- Fungi (including yeasts).
- Viruses.
- Protozoa.

Everybody has a different microbiome. Even twins have unique microbial cells. No two humans are alike.

A bacterium must possess several qualities to be referred to as a probiotic:

• Survive after being ingested in your intestine (being eaten).
• Possess a tangible benefit
• Consumed without risk.

What role do probiotics perform?

Probiotics, often known as beneficial bacteria, are primarily responsible for preserving the body's healthy equilibrium. It mainly neutralizes the body. Healthy bacteria help the immune system work properly and reduce inflammation, which keeps the body healthy. Several varieties of beneficial bacteria can also:

• Aid in food digestion.
• Produce vitamins.
• Support the gut's lining cells to stop harmful germs from entering the blood.

Everyday consumption of a fiber-rich, well-balanced diet contributes to maintaining healthy levels of beneficial bacteria.

Where in the body do beneficial microbes (Probiotics) reside?

Although the gut, particularly the large intestines, is frequently associated with helpful microorganisms, the body has numerous other places where they can be found. These locations are in contact with the "outside world" and include:

1. Gut.
2. Mouth.
3. Vagina.
4. Urinary tract.
5. Skin.
6. Lungs.

Common Probiotic bacterial species:

Even though a wide variety of bacteria can be categorized as probiotics, two bacteria are the most widely available in stores as probiotics:

1. Lactobacillus.
2. Bifidobacterium.

Probiotics are also made up of good yeast. Saccharomyces boulardii is the type of yeast that is most frequently seen in probiotics.

Probiotics from food: Diet is the body's primary source of healthy microbes. Particularly in fermented foods like yogurt and pickles, the body can find a variety of healthy bacteria. Moreover, fermented beverages like kombucha (fermented tea) and kefir (fermented dairy drink) can boost the diet's probiotic intake.

A few examples of foods high in probiotics that can be added to the diet and when to try them are as follows:

Table 1: Appropriate probiotics that are recommended at a particular time in the Day [Walker R (2006) Probiotic Microbes: The Scientific Basis. American Society of Microbiology].

Time	Probiotic recommended
Breakfast	Yogurt, Buttermilk, Sourdough bread.
Lunch	Cottage cheese, Tempeh, Kombucha.
Snack	Fermented Pickle
Dinner	Kimchi, Miso Soup, Fermented Sauerkraut.

Criteria to be a Probiotic:

Despite the various definitions given for probiotics, there must be a set of unchanging requirements before the microbial suspension may be considered a probiotic. They consist of:

• Probiotics should be non-toxic and stable.
• Probiotics should be lactic-acid powder.
• Should be stable in the food matrix.
• The ability to attach to epithelial cells and tissue is necessary.
•Pancreatic secretions and stomach acids need to be resistant.

When provided along with antibiotics, ought to be able to increase the likelihood of eradication and minimize the negative effects [CDSCO (2017) or AMRI Available at: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MTQ2MQ==].

Overview of the Probiotic Market in the US:

As consumers' awareness of their health has grown, the COVID-19 pandemic has had a stronger impact on their shifting consumption habits. In the US, consumers began to keep away from processed or junk food in favor of wholesome, nutritional goods. Since the epidemic, probiotic product sales have grown in the US as consumers turn to nutrient boosters to strengthen their immunity. Since then, there has been a dramatic increase in consumer appetite for probiotics in the US. Manufacturers are creating probiotic products that can be useful for every person because the virus can affect people of various ages.

Rising health consciousness and customer desire for nutritious products are expected to drive the market in the medium term. People of all ages are using probiotics, which are the main ingredient in the expanding digestive health supplement market. Yet, the millennial generation is the one who consumes the most due to a growing awareness of health and well-being thanks to multi-channel advertising, which has significantly changed their consumption, habits [WHO FAO (2006) Probiotics in Food. Available at: https://www.fao.org/3/a0512e/a0512e.pdf].

Can Probiotics be harmful?

Probiotics have a long history of use and appear to be safe, especially in healthy individuals. There is, however, a shortage of reliable data on the incidence and seriousness of adverse effects because there has not been much research that has examined the safety of probiotics. Probiotics carry a higher risk of negative side effects for those with serious illnesses or weakened immune systems. Probiotics should be carefully balanced against any potential dangers before being prescribed to high-risk patients, such as preterm infants or very ill hospital patients.

Probiotics may have negative side effects, such as infections, the creation of toxic compounds, and the spread of antibiotic-resistance genes from probiotic organisms to other microbes in the digestive tract. It has been noted that some probiotic products contain bacteria other than those indicated on the label. These pollutants may occasionally present serious health hazards [NIH (2019) Probiotics: You need to Know. Available at: https://www.nccih.nih.gov/health/probiotics-what-you-need-to-know (accessed August 2019).].

Categorization of Probiotics: In multiple countries, probiotics fall under various classifications. They fall under a variety of classifications, including:

Table 2: Categorization of Probiotics in Different States [Suhani Sharma (2013) Probiotics in India: Current Status and Future Prospects. Drug Therapy/ Medical Updates].

Country	Probiotic Category
Canada	Natural Health Products
USA	Dietary Supplements, Drugs, Medical Food, live Bacteriotherapeutic agents, biological agent
Japan, China, Malaysia, and India	Functional Food
Sweden, Denmark, and Finland	Food Supplement
European Countries like Belgium and Germany	Biotherapeutic/Pharmaceuticals

Regulations of probiotics in the US: The U.S. Food and Drug Administration (FDA) may regulate a probiotic product as a dietary supplement, a component of food, or a medication, depending on its intended purpose. Several probiotics are offered as dietary supplements that can be marketed without first receiving FDA approval. While dietary supplement labels are permitted to make statements about how the product affects the body's structure or function without FDA approval, they are not permitted to make any health-related claims, such as that the supplement lowers your risk of contracting a disease. A probiotic must adhere to more stringent prerequisites to be sold as a medication for the treatment of a disease or ailment. Before it can be sold, it must undergo clinical trials to demonstrate that it is secure and useful for the purpose for which it is being used [US FDA (2022) New Drug Application (NDA). Available at: https://www.fda.gov/drugs/types-applications/new-drug-application-nda].

Overview of the Indian market for Probiotics: The growing customer awareness about the prevalence of many gastrointestinal illnesses is driving the probiotics market in India. Furthermore, the country's probiotic market is expanding as more people become aware of the multiple benefits, they have for boosting immunity and gut health. A big growth-inducing aspect is also the growing senior population, which is more likely to suffer from chronic gastrointestinal diseases. The demand for probiotics is also being increased by consumers' shifting tastes away from high-calorie diets and towards functional foods and beverages. Also, the growing number of working women and the increased focus on enhancing female health have accelerated the acceptance of specialised probiotics like L. acidophilus, L. rhamnosus, Bifidobacterium, etc.

In addition, the popularity of ready-to-eat product options is expanding as a result of consumers' busy schedules and sedentary lifestyles, which is increasing demand for probiotic curd, yogurt, and drinks in convenient, flexible packaging. Also, several dairy, allergen, and sugar-free formulations, as well as the developing nutraceutical industry, are having a favourable impact on the probiotics market in India. In addition, consumers are becoming more interested in immunity boosters, nutritional supplements, and fortified food items as a result of the expansion of coronavirus disease. In the upcoming years, this is also anticipated to drive the probiotics market in India. [Impactful Insights. India Probiotics Market: Industry Trends, Share, Size, Growth, Opportunity and Forecast 2023-2028. Available at: https://www.imarcgroup.com/india-probiotics-market#:~:text=Market%20Overview%3A,20.50%25%20during%202022%2D2027].

Regulations of Probiotics in India: Since people in India are becoming more health-conscious and knowledgeable about the advantages of a balanced diet, probiotics have become more and more popular. Live bacteria called probiotics can be taken through food or supplements and can assist in strengthening the immune system and gut flora. When fermented foods like curd, buttermilk, and pickles were commonly consumed in the past, probiotics were first used in India. Yet, the popularity of these conventional fermented foods decreased as modern processed foods and lifestyle modifications proliferated. Many domestic and foreign businesses have recently brought probiotic meals and supplements to the Indian market. They include probiotic supplements, beverages, yogurt, kefir, and kombucha. Probiotics have potential, and the Indian government has begun several programmes to encourage their use. When probiotics first became popular in India, no rules existed. Hence, the Indian Council of Medical Research (ICMR) in conjunction with the Department of Biotechnology (DBT) formed a task force to create the regulatory rules for probiotic manufacturing in India,assess the safety, and prevent the popularisation of probiotic products with misleading claims [CDSCO (2017) or AMRI Available at: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MTQ2MQ==].

What is the difference between probiotics and prebiotics?

Probiotics are meals or supplements that contain living microorganisms to preserve or enhance the "good" bacteria (typical microflora) in the body. Prebiotics are diets that feed the human microbiota, usually high-fiber meals [Mayo Clinic (2022) Prebiotics and Probiotics. Available at: https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/expert-answers/probiotics/faq-20058065].

MATERIAL AND METHODS

In this study, an effort has been made to explore how probiotics are governed, assessed, and approved in the US and India, as well as to provide patient safety and regulatory framework harmonization for the study.

Primary and secondary data sources used in this comparative study are as follows:

• Websites of several organizations and regulatory bodies.

• Journal Articles that have been published in peer-reviewed journals.

• Regulations and guidelines published by the regulatory bodies of the study's participating nations.
• Databases and documents from several regulatory bodies.

There are four primary comparison stages:

a) General regulatory requirements
b) Approval Criteria
c) Evaluation Parameters
d) Safety Data

Aim and Objectives

Aim: The main goal and purpose of this project are to compare the complete regulatory overview of probiotics in two different countries, namely the United States and India, which includes complete data that includes its applications to the regulatory submission and evaluation procedures required for market approval.

Objectives:

• To emphasize the full regulatory considerations of probiotics.
• To describe in detail the prerequisites for obtaining marketing authorization as well as the approval procedures necessary in two different countries.
• To go into the current situation's probiotic utilization and safety.
• Additionally, to understand the grounds for acceptance or rejection of probiotics before their release on the market.

RESULTS AND DISCUSSION

United States: If a probiotic was not sold in the US before October 15, 1994, it would need to go through the new dietary ingredient process to be used in a dietary supplement. This is known as "Generally Recognized As Safe" (GRAS) status in the US. For probiotics used in meals or supplements, there is no need for premarket approval of safety; it is up to the manufacturer to adhere to regulations.

Regulations that are not always present in the health food industry must be considered when using probiotics for the prevention or treatment of diseases. These factors were discussed by Jennifer Ross of the U.S. FDA in a presentation to the colloquium participants, and are outlined below:

• The U.S. FDA regulates substances by their intended purpose. The FDA mostly regulates probiotic-like items as foods or biological products.
• The FDA's Centre for Food Safety and Applied Nutrition (CFSAN) regulates probiotic items as food, which also covers dietary supplements. Products that are regulated as foods, including dietary supplements, may make limited labelling claims (Dietary Supplement Health and Education Act).
• Most probiotic-like products have been subject to regulatory oversight by CBER's Office of Vaccines Research and Review (OVRR). The term Live Biotherapeutic Product (LBP) is used to describe products containing whole, live microorganisms (e.g., bacteria, yeast) with an intended therapeutic effect (e.g., cure, treat, prevent, mitigate, or diagnose a disease or condition) in humans, regardless of the route of administration, to avoid confusion with and distinguish from the numerous definitions of "probiotic." LBPs may comprise recombinant microorganisms or commensal microorganisms that have been isolated from a healthy human host.
• When permission to commercialize a biological product, such as an LBP, in the US for a specific illness claim is needed, a Biologics Licencing Application (BLA) is submitted. Data from numerous clinical trials that were carried out by an Investigational New Drug Application (IND)are typically included in a BLA. Clinical trials were often planned prospectively to assess a product's safety and effectiveness for a particular clinical indication. Often, an illness or condition as well as a population are used to define a clinical indication (i.e., children or adults).

An IND consists of the following:

(i) Cover Sheet
(ii) Table of Contents
(iii) Introduction and General Investigational Plan
(iv) A description of the composition, manufacturing process, and control testing of the drug substance and drug product.
(v) Pharmacological and toxicological studies of the drug conducted in vitro or using animal models to support the proposed clinical investigation;
(vi) Any prior human experience

A proposed clinical trial protocol. It is important to highlight that current good manufacturing practices (cGMPs) for biological products are distinct from those for foods and dietary supplements. It must be demonstrated that a biological product is pure, effective, safe, and consistently produced from lot to lot.

Before applying formally, plans for submitting an IND can be addressed with the FDA. It is recommended that anyone considering doing clinical research contact the FDA beforehand to find out whether the IND regulations apply in a specific circumstance. Several clinical investigations that are carried out just for research objectives and not for licensure or marketing approval demand an IND as well. Before spending the time and resources necessary to file an IND, it may be necessary to request a pre-IND meeting to facilitate compliance with the rules and identify regulatory obstacles [NIH (2019) Probiotics: You need to Know. Available at: https://www.nccih.nih.gov/health/probiotics-what-you-need-to-know]

Regulations based on the use of Probiotics:

1. Level – 1: Basic Level: May not be Probiotic depending on the definition
2. Level – 2: Safe but not clinically proven Probiotic
3. Level – 3: Clinically Documented Probiotic
4. Level – 4: Specific Probiotic Health Benefit
5. Level – 5: Narrow Use

Level 1: Microorganisms that are utilized as starting cultures in preparations like Dahi/Yogurt and whose purpose is to ferment food before they perish in the stomach or after contact with bile.

Level 2: Despite not having been specifically clinically tested, certain products (or the microbial species they contain) have a long history of safe use. Additionally, there may be more of those species in the stool as evidence.

Level 3: Microorganisms whose utilization (by mouth, skin, vaginal, or another target site), and delivery (dairy, powder, food, cream, medical device, or other) confer a fundamental effect that benefits health, as shown in human studies.

Level 4: Microbial strain(s) that can be used by all consumers without risk, but may or may not be beneficial to all, and for whose mechanisms of action are partially recognized and proven. These strain(s) also have an additional special function not conveyed by all organisms.

Level 5: Microorganism(s) that are specifically used (e.g., elevating certain neurochemical levels in the brain to relieve stress). Not for everyone, and not in the drug category.

Regulations of Probiotics based on their intended purpose:

The intended purpose of the product is a major factor in current probiotics regulations in the United States. Typically, probiotics are classified as nutritional supplements and food additives. Probiotics, however, can also be applied to pharmacological treatments.

1. Regulation of Probiotics as Food Ingredients: The Generally Recognized as Safe (GRAS) program provides an exemption from the definition of a food additive and the related exemption from premarket approval by the U.S. Food and Drug Administration (FDA).

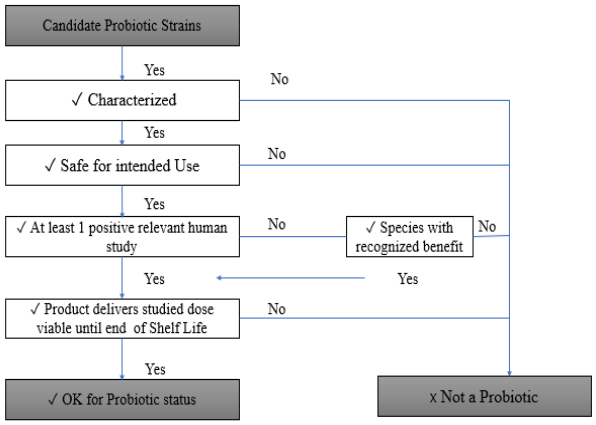
Through the program, GRAS status may be gained by one of two methods:

a) History of Use (a drug used in food before January 1, 1958)

b) Scientific processes (consensus among certified experts)

2. Regulation of Probiotics as Dietary Supplement: The CRN-prepared Old Dietary Ingredient (ODI) list does not list the strains of each species of bacteria. Recently discovered new strains might not qualify for the DSHEA's grandfather clause and might be categorized as a new dietary ingredient (NDI).

3. Regulation of Probiotics as Pharmaceuticals: Probiotics are supposed to promote health rather than treat illness, an expert panel was opposed to their regulation as biologics. As of right now, probiotics used in foods and dietary supplements cannot be used to claim that they prevent or treat disease.



Before being sold, probiotics must comply with FDA biological criteria and undergo clinical trials to demonstrate their efficacy and safety [FSSAI (2011) Food Safety and Standards (Licensing and Registration of Food Businesses) Regulations 2011. Available at: https://www.fssai.gov.in/upload/uploadfiles/files/Licensing_Regulations.pdf].

Characterization of Probiotic. According to generally recognized scientific standards, the probiotic is supported by at least one human clinical trial. Probiotic is active in the product at an effective dosage during the complete shelf life of the product.

Evaluation of Probiotics: Probiotic products are subject to US Food and Drug Administration regulation (FDA). Most probiotic products do not need FDA premarket approval, but makers are still required to follow certain rules and regulations. They consist of:

i. Generally Recognized As Safe (GRAS) status: Ingredients for probiotics must be GRAS-certified, which signifies that authorized professionals typically consider them to be secure for usage as intended.

ii. Labelling: According to FDA rules, the product labeling must provide a comprehensive list of components, the number of live microorganisms in each dose, and the suggested dosage.

iii. Good Manufacturing Practices (GMPs): Manufacturers of probiotics are required to adhere to GMPs, which contain specifications for production, testing, and quality assurance.

iv. Post-market surveillance: The FDA keeps an eye on probiotic products to guarantee their efficacy and safety. If there are any safety issues, the FDA may decide to take the product off the market or demand more testing.

• Overall, the evaluation processes and tests necessary for probiotic product approval in India and the US emphasize guaranteeing the product's efficacy and safety as well as correct labeling and production protocols [ICMR-DBT (2011) Guidelines for Evaluation of Probiotics in Food. Available at: https://dbtindia.gov.in/sites/default/files/PROBIOTICS-GUIDELINES-PDF_0.pdf].

Administrative and Regulatory Procedures:

Pre-IND Advice and Meetings and Drug Master Files

An IND requires certain data, such as product characterization, final and in-process testing, animal data, and the proposed clinical procedure, which are all evaluated during a pre-IND conference. An IND sponsor that does not produce the tested product may ask the manufacturer to deliver a Drug Master File (DMF). DMFs are examined by the CBER rather than the CDER and can be utilized by a commercial business to allow an IND sponsor to refer to the data in the DMF in support of the IND without exposing the DMF's contents to the IND sponsor. If a DMF will be filed or substantially changed, the DMF holder must inform the relevant IND sponsors and the appropriate review division.

Chemistry, Manufacturing, and Control (CMC) Information

A. Regulatory Considerations**.** The first concern of Phase 1 trials should normally be ensuring subject safety. This should include the identification and control of drug substances and raw materials, stability

assurance, and, if necessary, non-clinical safety assessments. Quality assurance and control should be improved as products continue to be developed. The amount of information needed will vary depending on the phase of the investigation, proposed duration, dosage form, and other information available, even though sufficient information is needed in each phase of the investigation to ensure the correct identification, quality, purity, and strength of the investigational drug.

B. Drug Substance
1. Description
2. Characterization
3. Manufacturer
4. Manufacturing Method
5. Specifications for Drug Substance

C. Drug Product
1. Composition
2. Manufacture
3. Specifications of Drug Substance
4. Stability

D. Non-Clinical Information

E. Clinical Information
1. Previous Human Experience
2. Proposed Initial Studies

F. New Drug Application (NDA)

G. Biological License Application (BLA) [Mordor Intelligence. UNITED STATES PROBIOTICS MARKET SIZE & SHARE ANALYSIS - GROWTH TRENDS & FORECASTS (2023 - 2028) Available at: https://www.mordorintelligence.com/industry-reports/united-states-probiotics-market-industry#:~:text=The%20United%20States%20probiotics%20market,consciousness%20among%20them%20has%20increased].

Challenges faced in the US due to the use of Probiotics:

1. Regulation: Inconsistencies in product quality, efficacy, and safety can result from a lack of regulation.
2. Health Claims: While complying with therules, probiotic producers may have difficulties in making accurate and supported claims about the health benefits of their products.
3. Research and Evidence: Probiotic companies may have challenges in making accurate and substantiated claims regarding the health benefits of their products while adhering to these guidelines.
4. Consumer Awareness, and Education: Many people may be confused about what probiotics are, how they function, and which brands to buy. It might be difficult to educate the public about probiotics, their potential advantages, and the need of purchasing reliable goods.

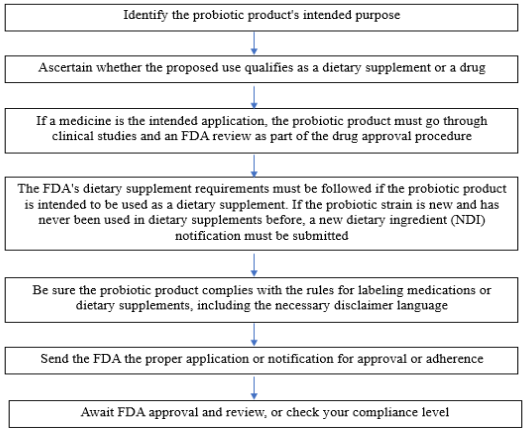
Approval procedure of Probiotics in the US:

Documents required to be submitted for approval:

I. Drug approval pathway:

(i) Investigational New Drug (IND) application: Probiotic items intended for use as medications must be submitted using this form. Before clinical trials may start, they must be submitted to the FDA [US FDA (2016) Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information. Available at: https://www.fda.gov/files/vaccines,%20blood%20%26%20biologics/published/Early-Clinical-Trials-With-Live-Biotherapeutic-Products--Chemistry--Manufacturing--and-Control-Information--Guidance-for-Industry.pdf].

(ii) New Drug Application (NDA): This form is necessary for probiotic products intended for use as medications that have undergone clinical testing and are prepared for FDA review and approval [Regulatory Focus (2017) The US environment of Probiotics in Food. Available at: https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/10/the-us-regulatory-environment-for-probiotics-in-food].



II. Dietary supplement pathway:

(i) New Dietary Ingredient (NDI) notification: This form is necessary for probiotic products meant to be used as dietary supplements and containing a novel probiotic strain that has never been used in dietary supplements before.

(ii) Generally Recognized as Safe (GRAS) notification: For probiotic strains that have been deemed GRAS by medical professionals, this form is an alternative to the NDI notification.

(iii) Structure/Function Claims Notification: If the probiotic product makes any claims about how it affects the structure or operation of the body, such as supporting immune function, then this form is necessary [US FDA (2022) Investigational New Drug Application. Available at: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application].

Fee for Probiotic products approval based on their intended use:

A. Drugs. Depending on the type of application and the company's size, different costs may be required in the US for the approval of probiotics as pharmaceuticals. The US Food and Drug Administration (FDA) determines the costs, which are subject to modification. A new drug application (NDA) costs $3,117,218 as per PDUFA FY 2023.

It is crucial to remember that not all probiotics might require medication approval. The intended purpose and the product's claims may affect the regulatory process for probiotics. For instance, certain probiotics might be sold as nutritional supplements, which are subject to different FDA regulations than pharmaceuticals [US FDA (2022) Environmental Assessment of Human Drug and Biologics Applications. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/environmental-assessment-human-drug-and-biologics-applications].

B. Dietary Supplements. The type of submission and the size of the company can affect the costs associated with probiotics' approval as dietary supplements in the US.

Dietary supplements do not need FDA premarket approval as pharmaceuticals do. However, businesses that sell dietary supplements must register their facility with the FDA and adhere to specific production and labeling regulations [US FDA (2022) Development & Approval Process/ Drugs. Available at: https://www.fda.gov/drugs/development-approval-process-drugs].

It is crucial to remember that the FDA does not approve dietary supplements before they are marketed, and it also does not assess their effectiveness and safety in the same manner that it does for medications. Thus, the manufacturer must guarantee the efficacy and integrity of their line of dietary supplements [US FDA (2022) Environmental Assessment of Human Drug and Biologics Applications. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/environmental-assessment-human-drug-and-biologics-applications].

Here are some examples of probiotic products approved as dietary supplements in the US:

Culturelle Probiotics: A nutritional supplement called Culturelle Probiotics is produced by i-Health, Inc. It includes Lactobacillus rhamnosus GG, a helpful bacterium that supports immunological and digestive health.

Renew Life Ultimate Flora Probiotics: A health supplement made by Renew Life Formulas; Inc. is called Renew Life Ultimate Flora Probiotics. It has a combination of healthy bacteria, such as Lactobacillus acidophilus, Bifidobacterium bifidum, and Lactobacillus rhamnosus, that support immunological and digestive health.

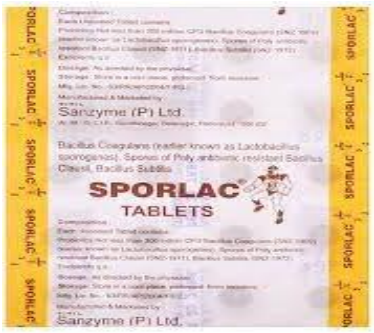
Florajen Probiotics: American Lifeline, Inc. creates the dietary supplement Florajen Probiotics. It includes the helpful bacteria Lactobacillus acidophilus and Bifidobacterium lactis, which support immune and digestive health.

Bifidobacterium bifidum, and Streptococcus thermophilus, support digestive health and help to restore the natural balance of the gut flora.

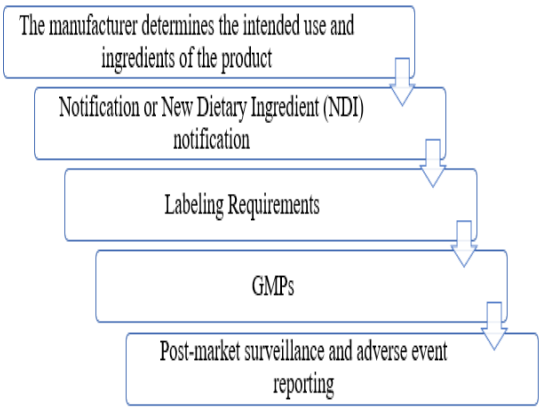
Here are some examples of probiotic products that are approved as Drugs in the US:

VSL#3: A probiotic medication called VSL#3 is produced by Alfasigma USA, Inc. and sold in India by Glenmark Pharmaceuticals Ltd. It contains a mixture of healthy bacteria, such as Lactobacillus acidophilus,

Sporlac: The probiotic medication Sporlac is created by the pharmaceutical business Sanofi India Ltd. It contains Lactobacillus sporogenes, a helpful bacterium that supports digestive health by restoring the natural balance of the gut flora.

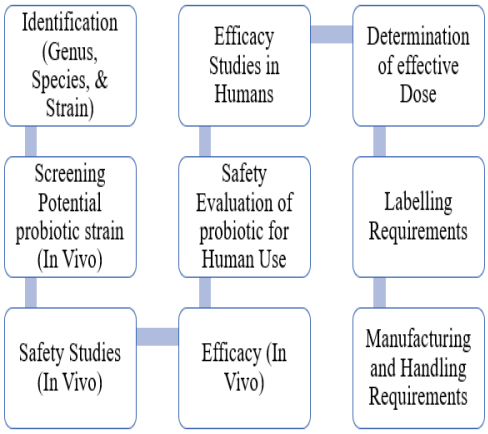


Here is a flowchart outlining the general process for approval of probiotics as dietary supplements in the US:



India:

ICMR – DBT Guidelines for Evaluation of Probiotics:



ICMR- DBT Evaluation of probiotics for human use:

a) Safety: Probiotic strains need to be described at a minimum using the following assays due to the significance of

ensuring safety, especially among bacteria groups that are widely known as safe:

•Identifying patterns of antibiotic resistance. Verify that any probiotic strain does not pose a serious threat of spreading antibiotic resistance.

•Evaluation of adverse side effects.

b) **Efficacy:**The main result of probiotic efficacy studies should be demonstrated with comparable advantages in human trials, such as statistically and clinically significant improvement in condition, symptoms, signs, wellbeing, or quality of life, decreased risk of disease, or longer time to next occurrence or faster recovery from illness. Each parameter should have a demonstrable correlation to the probiotics under test. Probiotics that are consumed through food may not be examined in Phase 3 studies (effectiveness) unless the product makes a specific health claim for which it is necessary to gather the necessary data to support conducting Phase 3 research.

c) **Labeling Requirements:** The following details need to be included on the label in addition to what is required generally by food laws:

• Genus, species, and strain names are designated using the accepted worldwide system.

•At the level at which efficacy is asserted and at the end of the shelf-life, the minimum viable numbers of each probiotic strain should be mentioned.

•The health claim or claims should be supported by evidence.

•The recommended serving size to administer the probiotic with the lowest effective dosage to the health claim. The health claim or claims should be supported by evidence.

•The recommended serving size to administer the probiotic with the lowest effective dosage to the health claim.

•Mention appropriate storage conditions [ICMR-DBT (2011) Guidelines for Evaluation of Probiotics in Food. Available at: https://dbtindia.gov.in/sites/default/files/PROBIOTICS-GUIDELINES-PDF_0.pdf].

Special FSSAI Rules for Food Items with Added Probiotic Component:

1. The culture of living microorganisms, which may be a single strain or a mix of bacteria, must be the primary component of the probiotic diet.
2. Only the approved strains, or those bacteria occasionally approved by the authorities, may be included in probiotic products (as defined in Schedule VII).
3. It must provide the consumer with certain health benefits.
4. By FSSAI requirements, it might have more prebiotics.
5. The product's labeling display panel needs to include a picture of the bacteria.
6. These must be non-GMO microorganisms.
7. The suggested serving amount per day must have a viable count of the added microorganisms of at least 108 CFU.
8. Probiotic food products are not allowed to make any claims or mentions (in the labeling or even in the advertisement) that they can prevent, cure, or treat human diseases.
9. The food authorities will only permit a corporation to include a specific statement regarding a health claim if it is backed by credible scientific data.
10. The following information must be present on the probiotic product's packaging:

a) The term "PROBIOTIC FOOD" needs to be made very explicit on the label.

b) In the list of ingredients, provide the genus and species, strain designation, and culture collection number as per MTCC (if applicable).

c) Serving size (recommended), time spent using, storage requirements, and "best by" date following container opening.

d) By the conclusion of the probiotic strain's shelf life, the viable count should be stated.

e) The advice notice "NOT FOR MEDICINAL USE" must be written clearly.

f) Any additional cautions or warnings that should be observed while ingesting, as well as any relevant information on side effects, restrictions, and product-drug interactions.

11. In probiotic formulations, only the ingredients listed in Schedule VA through Schedule VF may be utilized (FSSAI Regulations 2016) [Amrita Narula (2021) Probiotics: Origin, Products, and Regulations in India. Microbial Products for Health, Environment, and Agriculture 59-101].

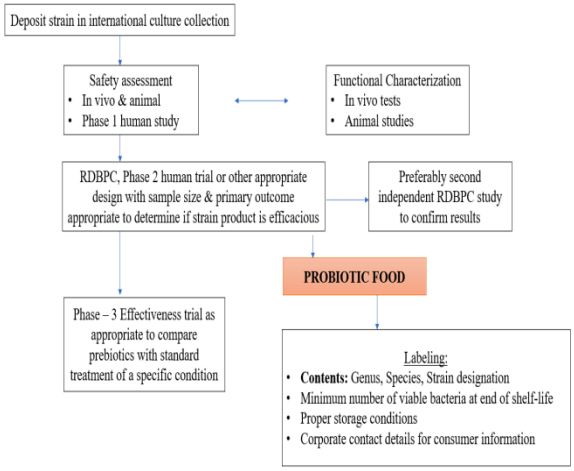
Challenges in India:

1. Quality Control: Because of differences in manufacturing techniques and regulatory monitoring, ensuring consistent quality and safety across various items can be difficult.
2. Lack of Regulatory Framework: In the lack of a defined regulatory framework, variable product quality, deceptive claims, and inadequate consumer protection might occur.
3. Limited Awareness and Accessibility:While probiotics have gained popularity in metropolitan areas,

knowledge and accessibility in rural areas may be restricted. A lack of understanding of probiotics, their potential advantages, and where to locate trustworthy goods may limit their broad usage and effect.

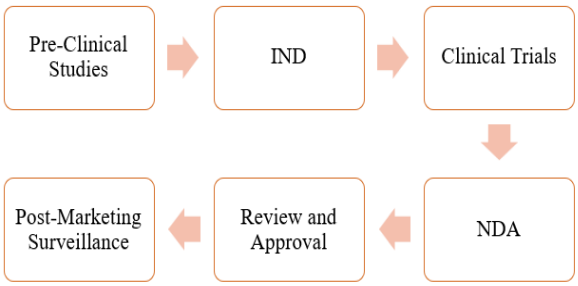
3. Cultural Factors: Incorporating commercial probiotic products into traditional diets and consumer preferences may be difficult owing to cultural preferences and preconceptions.

Evaluation of Probiotics in India:

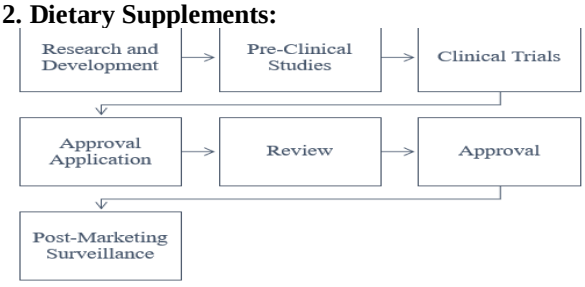


Flowchart for approval of Probiotics in India:

1. Drugs:



2. Dietary Supplements:



Documents required to be submitted for approval:

The Food Safety and Standards Authority of India (FSSAI) regulates the procedure for probiotics approval in India. The following forms and documents are necessary for probiotics to be approved in India:

•**Form FSSAI-02:** This is the form used to apply for the approval of new products, and it must be presented with the accompanying supporting documentation:

1. Information about the probiotics employed in a product's formulation, including their types and dosages.
2.Information about the production process, including the techniques utilized for fermentation and probiotic stabilization.
3. Data about the probiotic product's stability.
4. Studies on the probiotic strain(s) used in the product's safety and toxicology.
5. Information on the label, such as an ingredient list, nutritional data, and any health claims.
6. Import license (if applicable)

• **Form FSSAI-03:** Probiotics must be imported into India using this form, which must be completed with the appropriate documentation:

1. A probiotic product's certificate of analysis, issued by an accredited lab in the country of origin.
2.Import license (if applicable)

• Other documents that may be required for approval of probiotics in India include:

1.Evidence of the manufacturer's or importer's FSSAI registration or license.
2. Accreditation for the manufacturing facility's GMPs (Good Manufacturing Practices).
3. A list of the countries where the probiotic product has already received approval or is now available.
4. Any additional safety or effectiveness information that the FSSAI requests [ISAPP (2022) Probiotics. Available at: https://isappscience.org/for-consumers/faqs-probiotics/].

Fee:

According to the Food Safety and Standards Act of 2006, the cost of FORM FSSAI 02, the application form for a central license or state license, is determined by the type of authorization being applied for and the revenue of the food business.

For Central License: •For food businesses with an annual turnover of up to Rs. 30 crores: Rs. 7500/-

•For food businesses with an annual turnover of more than Rs. 30 crores: Rs. 7500/- plus Rs. 100 for every additional crore of turnover [FSSAI (2011) Food Safety and Standards (Licensing and Registration of Food Businesses) Regulations 2011. Available at: https://www.fssai.gov.in/upload/uploadfiles/files/Licensing_Regulations.pdf].

For State License:

•For food businesses with an annual turnover of up to Rs. 30 crores: Rs. 2000/-

•For food businesses with an annual turnover of more than Rs. 30 crores: Rs. 5000/- [FSSAI (2011) Food Safety and Standards (Licensing and Registration of Food Businesses) Regulations 2011. Available at: https://www.fssai.gov.in/upload/uploadfiles/files/Licensing_Regulations.pdf].

Here are some examples of probiotic products approved as drugs in India:

1.Econorm: Probiotic medication Econorm is created by Dr. Reddy's Laboratories Ltd. Saccharomyces boulardii, a non-pathogenic yeast that supports the balance of the gut flora, is present in it.

2. **Darolac:** The probiotic medication Darolac is made by Aristo Pharmaceuticals Pvt. Ltd. It contains streptococcus thermophilus, Bifidobacterium bifidum, lactobacillus acidophilus, and lactobacillus rhamnosus, all of which are helpful bacteria that support the balance of the intestinal flora.

Here are some examples of probiotic products approved as dietary supplements in India:

1. **NutriPlus Probiotics:** A nutritional supplement called NutriPlus Probiotics is created by Nutrilite, an Amway India Enterprises Pvt. Ltd. brand. A combination of the good bacteria Lactobacillus acidophilus, Bifidobacterium lactis, Lactobacillus plantarum, and Lactobacillus rhamnosus, which support the balance of the intestinal flora, is present in it.

2. Bio-Kult: A probiotic dietary supplement called Bio-Kult is created by Probiotics International Ltd. It is present in a blend of 14 healthy bacterial strains, including Lactobacillus acidophilus, Bifidobacterium bifidum, and Streptococcus thermophilus.

Table 3: Comparison of Regulatory Requirements, and Evaluation of Probiotics in the United States, and India.

Sr. No.	Parameter	United States	India
1.	Regulatory Category of Probiotics	Drugs/biologics/dietary supplements or food ingredients/live biotherapeutic product	Drugs/Food/Dietary Supplement/Biologics/Live Biotherapeutic Product
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. Drugs/biologics/live biotherapeutic agents need approval from Central Drug Standard Control Organization (CDSCO) 2. Dietary supplements and food ingredients are approved by the Food Safety and Standards Authority of India (FSSAI).
3.	Premarket Approval	Required for drugs, biologics, and live biotherapeutic agents.	Required for drugs, biologics, and live biotherapeutic agents.
		Nutritional supplements and food items are excluded.	Nutritional supplements and food items are excluded.
4.	Recommended regulatory guidelines	Depending on their intended usage, nutritional supplements, and medications have varying guidelines. The level of manufacturing controls and their controls are a serious concern for LBP.	Depending on the category of the product and their usage probiotics have various guidelines framed by the Indian Council of Medical Research- Department of Biotechnology (ICMR-DBT)
5.	Therapeutic Claims	Allowed but only to be used for food supplements; not to be used for drug substances	Allowed but only to be used for food supplements; not to be used for drug substances
6.	Assessment of safety parameters	Drugs, biologics, and LBP safety is the responsibility of the USFDA. The DSHEA oversees ensuring food safety.	Drugs, biologics, and LBP safety is the responsibility of the CDSCO. The FSSAI oversees ensuring food safety.
7.	Requirements for approval	Drug/Biologics: • Clinical data • Data to support the study of products in humans, CMC, stability, Pharmacology/toxicology Dietary Supplements, and food ingredients: • Health Claims • Structure/function Claims	Drugs/Biologics: • Clinical Data • Pharmacology, Toxicology, stability, CMC Nutritional Supplements: • Health Claims • Structure/Function Claims
8.	Available Probiotic Products	Culturelle, Align, Florastor, Goodbelly, Kefiir, Activia	Yakult, Bifilac, Vizylac, Probiotic Yogurt, Kefir
9.	Forms	**Form 3500A** - New Dietary Ingredient Notification **Form FDA 356h** – Marketing approval of new drug, biologic, antibiotic.	**Form FSSAI-02** - Approval of new products **Form FSSAI-03** – Form for import of Probiotics to India
10.	Fee	**NDA-** $3,117,218 **Dietary Supplements** - $600 for both domestic and international facilities.	**Central License**– Rs. 7500 **State License** – Rs. 2000 – Rs 5000.

CONCLUSIONS

Probiotics are products containing live microorganisms and are marketed with the promise that, when taken, they would improve or restore the health of the gut microbiota. The regulation and evaluation of probiotics in India and the US are different in several ways, The Food Safety and Standards Authority of India (FSSAI), which oversees establishing standards for food and food products, oversees regulating probiotics in India. Probiotics are functional food components, and the FSSAI has established rules for their usage in food products. According to the FSSAI's regulations, probiotics must be beneficial to health, safe, and effective.

On the other hand, in the US, the regulation of probiotics falls under the jurisdiction of the Food and Drug Administration (FDA). The FDA classifies probiotics as dietary supplements, which means that they are regulated under the Dietary Supplement Health and Education Act of 1994 (DSHEA). According to the DSHEA, dietary supplements are considered safe until proven otherwise, and manufacturers are responsible for ensuring the safety and labeling of their products.

In terms of evaluation, in India, probiotics are evaluated based on the safety and efficacy of the strain used and its potential health benefits. The evaluation process in India involves testing the probiotic strain in vitro and in

vivo before it is approved for use in food products. In the US, probiotics are evaluated based on the safety and efficacy of the product. The evaluation process in the US involves testing the finished product for purity, potency, and effectiveness and ensuring that the product is properly labelled.

Overall, while both India and the US have regulations and evaluation processes for probiotics, the specific guidelines and procedures differ between the two countries.

Conflict of interest. None.

REFERENCES

Amrita Narula (2021) Probiotics: Origin, Products, and Regulations in India. Microbial Products for Health, Environment, and Agriculture (pp.59-101).

CDSCO (2017) orAMRI Available at: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MTQ2MQ==.

Cleveland Clinic (2023) Probiotics. Available at: https://my.clevelandclinic.org/health/articles/14598-probiotics.

FSSAI (2011) Food Safety and Standards (Licensing and Registration of Food Businesses) Regulations 2011. Available at: https://www.fssai.gov.in/upload/uploadfiles/files/Licensing_Regulations.pdf.

ICMR-DBT (2011) Guidelines for Evaluation of Probiotics in Food. Available at: https://dbtindia.gov.in/sites/default/files/PROBIOTICS-GUIDELINES-PDF_0.pdf.

Impactful Insights. India Probiotics Market: Industry Trends, Share, Size, Growth, Opportunity and Forecast 2023-2028. Available at: https://www.imarcgroup.com/india-probiotics-market#:~:text=Market%20Overview%3A,20.50%25%20during%202022%2D2027.

ISAPP (2022) Probiotics. Available at: https://isappscience.org/for-consumers/faqs-probiotics/ (accessed 2022).

Mayo Clinic (2022) Prebiotics and Probiotics. Available at: https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/expert-answers/probiotics/faq-20058065.

Mordor Intelligence. UNITED STATES PROBIOTICS MARKET SIZE & SHARE ANALYSIS - GROWTH TRENDS & FORECASTS (2023 - 2028) Available at: https://www.mordorintelligence.com/industry-reports/united-states-probiotics-market-industry#:~:text=The%20United%20States%20probiotics%20market,consciousness%20among%20them%20has%20increased.

NIH (2019) Probiotics: You need to Know. Available at: https://www.nccih.nih.gov/health/probiotics-what-you-need-to-know.

Regulatory Focus (2017) The US environment of Probiotics in Food. Available at: https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/10/the-us-regulatory-environment-for-probiotics-in-food.

Suhani Sharma (2013) Probiotics in India: Current Status and Future Prospects. Drug Therapy/ Medical Updates.

US FDA (2022) Development & Approval Process/ Drugs. Available at: https://www.fda.gov/drugs/development-approval-process-drugs.

US FDA (2016) Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information. Available at: https://www.fda.gov/files/vaccines,%20blood%20%26%20biologics/published/Early-Clinical-Trials-With-Live-Biotherapeutic-Products--Chemistry--Manufacturing--and-Control-Information--Guidance-for-Industry.pdf.

US FDA (2022) Environmental Assessment of Human Drug and Biologics Applications. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/environmental-assessment-human-drug-and-biologics-applications.

US FDA (2022) FDA 101: Dietary Supplements. Available at: https://www.fda.gov/consumers/consumer-updates/fda-101-dietary-supplements.

US FDA (2022) Investigational New Drug Application. Available at: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application.

US FDA (2022) New Drug Application (NDA). Available at: https://www.fda.gov/drugs/types-applications/new-drug-application-nda.

Walker R (2006) Probiotic Microbes: The Scientific Basis. American Society of Microbiology.

WHO FAO (2006) Probiotics in Food. Available at: https://www.fao.org/3/a0512e/a0512e.pdf.

Wikipedia (2023) Probiotic. Available at: https://en.wikipedia.org/wiki/Probiotic.

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