Need and Recommendations for Universal Guidelines on Regulatory Status and Quality Control/Safety of Probiotic Products

Malika Arora¹*, Manish Arora², Parveen Bansal³ and Ashish Baldi⁴

¹Multi Disciplinary Research Unit, Guru Gobind Singh Medical College and Hospital, Faridkot, Punjab, India; ²Department of Epidemiology, Civil Surgeon office, Civil Hospital, Moga, Punjab, India; ³University Center of Excellence in Research, Baba Farid University of Health Sciences, Faridkot, Punjab, India; ⁴Department of Pharmacy, MRS Punjab technical University, Bathinda, Punjab, India

Abstract: Background: In today’s era, various health boosting products viz. probiotics, functional foods, dietary supplements and nutraceuticals are gaining great commercial interest. Although probiotics have traditional history of their use, their regulatory approval regimes across the globe are complicated and incoherent.

Objective: The present article has been compiled to give an overview of the existing approval guidelines for the probiotic products across the globe along with their associated ambiguities. Furthermore, suggestive consolidations for harmonized approval process to be implemented in future are proposed on the basis of their intended use.

Methods: The study was carried out by using secondary sources through literature survey from journals, market reports, proceedings, books and web pages of relevant regulatory authorities and a critical comparative study was conducted with respect to approval process of probiotics.

Results: As per the comparative account of the current regulatory guidelines, it has been evidenced that different countries have adopted diverse approval process for probiotics and; lack of uniformity is of great concern. But due to rapid emergence of probiotics as drugs, a harmonized approval process similar to other drugs covering all aspects of Investigational New Drug Application (INDA) and New Drug Application (NDA) has been proposed in which organisms falling under Generally Recognized As Safe (GRAS) category are exempted from INDA submission whereas non GRAS, GRAE or new organisms are not exempted. After submission of NDA and getting approval from Food and Drug Administration (FDA), product should be manufactured and marketed.

Conclusion: Regulatory bodies across the globe must ensure that probiotics based products should be regulated by lawful approval process in such a manner which will lead to maximal health benefits and minimal health risk for consumers.

Keywords: Probiotics, IND, INDA, GRAS, approval guidelines, regulatory bodies, consumers.

1. INTRODUCTION

Holistic management of health through judicious use of medicines, adoption of exercise based life styles, yoga and diet management with novel foods has become an essential part of our life. Steady increase in life expectancy and desire for improved quality of life in recent past has driven the modern era to search for natural, safe and economical medical therapies [1] for preventive measures. This has resulted in increased interest of consumers towards food products like probiotics, functional foods, dietary supplements, nutraceuticals etc. Due to the increased demand and inclination for these products, probiotic therapy is specially gaining momentum in the field of health care.

Probiotic therapy is ultimately based on the biological relationship between multi-cellular organisms and the microbial world existing within their body [2]. According to traditional history, earlier micro-organisms were used only in the dairy or
fermented products but these days probiotic microbes are also being marketed as pharmaceutical preparations and hence are likely to be consumed as “self-medication” [3].

The market place for probiotics on the basis of their intended use is presently categorized as probiotic based food products/pharmaceuticals and is known for their health claims/nutritive claims [4], as well as therapeutic claims [5]. Probiotics used as food products (functional food, medical food, dietary supplement and natural health products) are accompanied by general health claims like balancing the intestinal flora; reduced harmful bacteria; maintenance of the intestine in good health and promote the maintenance of good GIT condition etc. whereas probiotics used as pharmaceutical drug products help in the prevention, treatment and mitigation of a disease [6].

Out of these marketed products, a very few of them have been evaluated in controlled clinical studies and majority of products exist with unsubstantiated claims of efficacy. The constantly increasing demand and usage of these products amongst consumers of diverse age groups have necessitated the need to clarify the regulatory issues, which, at present, are unclear and subject to gross misinterpretation [7]. Although, safety concerns are supposed to be considered for any product suggested for health promotion or disease prevention [8-10], yet as per the current scenario, regulatory bodies across the globe consider probiotics under several categories (e.g. biologics, drugs, foods, nutritional supplements etc.). Therefore, probiotics are currently not regulated by universal guidelines rather regulated by different guidelines depending on their regulatory category [11]. Intended use of probiotics, whether as a drug or a dietary supplement, actually defines the regulatory requirements to force upon regulation of approval process for the probiotic product. Premarketing approval is an area of great concern as it involves a number of factors that are supposed to be addressed without any delay. Specifically quality, safety and efficacy of these probiotic products are of immense importance to both industry as well as consumers that eventually manufacture and use these products [6] respectively. Therefore, it is of utmost importance that efficacy and safety issues must be considered more seriously in comparison to current regulatory affairs that are highly confusing and ambiguous in relation to premarket-

ING approval and the quality of these products. It becomes pertinent for regulatory guidelines to include the approval related aspects and vigilant control of industry officials for best quality control and protection to consumers. This manuscript is compiled to analyze major features, common points and ambiguities of the currently used system for the approval of probiotic products in various countries like the USA, Europe, China and Japan in existing guidelines and to recommend suggestive consolidations for a new approval process for global acceptance.

2. MATERIALS AND METHODS

Comprehensive and relevant literature related to probiotics, their categorization and regulatory guidelines in different countries were surveyed. Existing guidelines for probiotics across the globe in countries like the USA, China, India, Japan, Europe, Canada, Korea, Malaysia and Brazil were viewed from Food and Agriculture Organization/World Health organization (FAO/WHO) guidelines, Foods for Specified Health Uses (FOSHU) guidelines (Japan), European Food & Feed Cultures Association (EFFCA) guidelines (Europe), Saudi Food and Drug Authority (SFDA) guidelines (China), Dietary Supplement Health and Education Act (DSHEA) and United States Food and Drug Administration (USFDA) guidelines (USA), Natural Health Products (NHP) guidelines (Canada), Indian Council of Medical Research/Department of Biotechnology (ICMR/DBT) and International Life Sciences Institute (ILSI) guidelines (India), National Health Surveillance Agency (ANVISA) guidelines (Brazil), Food Standards Australia New Zealand (FSANZ) guidelines (New Zealand and Australia), Ministero Della Salute guidelines (Italy), and Government Bureau of Food and Drugs (Philippines). Guidelines have been reviewed using secondary sources like electronic databases (Google Scholar, Scopus, PubMed and open online resources) as well as from journals, market reports, proceedings, books and web pages of relevant regulatory authorities.

After compiling literature from various sources, all the parameters for approval of probiotic products were reviewed. It was observed that various countries had covered approval parameters on the basis of the intended use of probiotics but in most
of the countries, approval process was not taken into consideration. Later, all the reviewed parameters were critically analyzed for their merits and demerits. Henceforth on the basis of limitations, suggestive consolidations were made.

3. PROBIOTICS AND OVERALL SCENARIO OF ITS APPROVAL PROCESS

Probiotics is a broad term used for friendly bacteria that can be defined as “live microorganisms, which when administered in adequate amount confer health benefits on the host” [12]. Probiotic based products are aimed at delivering live bacterial cells to the gut ecosystem of humans and other animals. Although researchers from diverse areas of scientific disciplines have continuously focused on clinical research to prove beneficial health effects of probiotics, yet various regulatory agencies across the globe consider probiotics under several categories like biologics, drugs, medical foods, dietary supplements in the USA [13], functional foods in Japan [14], Europe [15], China [16], nutritional supplements etc. Hence probiotics are regulated by different guidelines depending on their regulatory category. It has been observed that most of the countries have established the guidelines for probiotic under category of food rather than drugs due to their established use as food products. Furthermore, it has been observed that most of the countries have framed a convenient set of guidelines exactly fitting into their requirement or in accordance to the products manufactured in that country particularly.

Although guidelines are implicated by FAO/WHO [11], ICMR-DBT [17] and ILSI (India) [18], WGO guidelines [19], Philippines [20], and Italy [21] but these guidelines had not stated the need of approval before the marketing of probiotic product. However, FOSHU in Japan [22] and SFDA in China [15] have given the approval process for probiotics used as functional foods. As per existing guidelines, pharmaceutical products are produced under strict control whereas; approaches for pharmaceuticals and other health products differ significantly [23]. With respect to probiotics, not even a single country has covered all the aspects related to the approval and safety assessment studies of probiotic based foods and pharmaceuticals separately. The variation in guidelines on different parameters in the approval regimen of probiotics in these countries is as shown in Table 1.

4. COUNTRY WISE STATUS OF PROBIOTIC REGULATORY APPROVAL PROCESS ACROSS THE GLOBE

The concept of functional food was initially addressed and promoted by Japan by showing a close relationship between nutrition and modulation of physiological systems in 1984 [24, 25]. In the later years, in 1991, the Ministry of Health, Japan had introduced a set of rules, which were necessary to undertake the approval for the specific health-related food; later, the category was named as FOSHU (Food for Specified Health Uses) [26-28]. As a matter of fact, Japan has inculcated the interest in experts of other countries like Europe and the United States for use of functional foods and hence became the reason to create awareness for the need of such products. Nowadays, probiotic market value is achieving its highest pace in every country and hence in the near future, it can be believed that many ongoing studies on more rational approaches to strain selection and incorporation of the microbes will lead to improved probiotic efficacy of these value-added functional foods.

4.1. Status of Probiotic Approval in Japan

Japanese Ministry of Health, Labour, and Welfare (MHLW) has established a regulatory system for foods that claim health benefits and market their food products for promotion of physiological function. The major regulatory authority, MHLW, regulates health information concerning specific foods under ‘Foods for Specified Health Use’ (FOSHU) scheme. It basically approves statements contained on a label regarding the effects of foods on the human body. In Japan, Nutrition Improvement Law has various categories and FOSHU was enacted under this law in the recent years. Basically these categories include:

1. Milk powder for pregnant and lactating women.
2. Formulated milk powder for infants.
3. Foods designed for elderly individuals with difficulty in mastication or swallowing.
4. Medical foods for the ill.
5. FOSHU.
Table 1. Approval parameters taken into consideration in various countries.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameters Under Consideration</th>
<th>Japan</th>
<th>Europe</th>
<th>USA</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Functional foods</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Dietary supplements</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Drugs</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Medical Food</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Live Biotherapeutic Agents</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Biologics</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>2.</td>
<td>Regulatory authority</td>
<td>MHLW/ FOSHU</td>
<td>EFSA</td>
<td>FDA/ DSHEA</td>
<td>MOH/ SFDA</td>
</tr>
<tr>
<td>3.</td>
<td>Approval flowchart</td>
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<td>For QPS</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>4.</td>
<td>Approval documents to be consid ered</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4a.</td>
<td>GRAS status</td>
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<td>X</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>4b.</td>
<td>QPS status</td>
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<td>✓</td>
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</tr>
<tr>
<td></td>
<td>Details filled in application form</td>
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<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td></td>
<td>Name of applicant (representative) and the address</td>
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<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td></td>
<td>Name and address of head office and factory</td>
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<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td></td>
<td>Product name</td>
<td>✓</td>
<td>✓</td>
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<td></td>
<td>Shelf life</td>
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<td></td>
<td>Product formula</td>
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<td>X</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Testing Institute Toxicology safety, functionality evaluation, active ingredient analysis, product stability, sanitary inspection reports</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
</tr>
</tbody>
</table>

As the therapeutic effect intended by probiotic food articles is beyond the limit of ordinary food articles, it is strongly felt that the use of these products must be strictly regulated by establishing all the necessary guidelines.

As per Japanese guidelines, FOSHU consists of foods with functional ingredients that affect the structure/function of the body. These foods can also be used to maintain or regulate specific health conditions, such as gastro-intestinal conditions, blood pressure and blood cholesterol level [22]. Hence in the Japan, probiotic foods are also considered and approved under the category of the functional foods. As per the current status, FOSHU has been divided into four groups specifically depending upon the level of claim and scientifically supported evidence for the same. Depending on the strength of the supporting data [26], different levels of claims ranging from A to C (as mentioned in official FOSHU guidelines) are allowed. Japanese government has designated several categories for claiming health claims especially in the area of gastrointestinal health, cholesterol moderation, hypertension moderation, lipid metabolism moderation, sugar absorption moderation, mineral absorption, bone health and tooth health. For the approval process, following are the general steps involved:

1. Review of application in a hearing by MHLW experts.
2. Expert opinion about the application; whether to proceed further with the application or not.

3. If yes, MHLW passes the same application and the product is sampled into three groups:
   a. Council of Pharmaceutical Affairs for evaluation of efficacy of the product.
   b. Food Safety Commission for evaluation of safety of the product.
   c. National Institute of Health and Nutrition for the development of analytical method for testing the active ingredient of that product [29, 30].

4. All the concerned authorities send their reports back to the MHLW.

5. A committee of experienced specialists in medical, nutritional, food hygiene, and pharmaceutical fields is constituted by MHLW, whose members are generally chosen from the Japanese academic community.

6. The application is assigned to the appropriate committee for review and comment depending on the health benefit being claimed for the given product.

7. Afterward it is decided by the committee whether to ask for more data or to forward the application to MHLW for granting of approval [22-29].

The current regulatory framework of various categories of probiotics of Japan has been shown in Fig. (1).

4.1.1. Concerns Related to the Current Approval Process of Japan

The Japanese regulation system defines health foods as foods with specific health functions suitable for consumption by specific groups of people and has the effect of regulating human body functions without treating diseases. In context to these specialized foods, existing regulatory system has following ambiguities:

1. Approval process has been designed only keeping in view functional foods and live bacteria are considered to be the part of that food. Hence no differentiation amongst functional foods, probiotic products and probiotic based therapeutic formulations has been made separately.

2. Japan allows the manufacturers to conduct identity tests of microbes at their own level and hence may encourage a bias by the manufacturer leading to disputed quality/credibility of these products.

3. There is no authority in Japan to regulate food and drugs separately as no emphasis has been laid for clinical trials or other related regulatory issues.

4.2. Status of Probiotic Approval in European Union

As per existing guidelines in European countries, traditional strains are categorized as food ingredients, processing aids and additives. Probiotic cultures containing foods are most often considered as food supplements or dietetics as well as pharmaceuticals also. Within the European Union, various directives and regulations have an objective to harmonize and scrutinize regulatory practices [31, 32]. For the food and food-associated domains, following scientific committees are involved [33]:

1. Scientific Committee on Food (SCF),
2. Scientific Committee on Animal Nutrition (SCAN) and
3. Scientific Committee on Plants (SCP).

In addition to these, the European Food Safety Authority (EFSA) has been established for governing food and feed in the member states at the community level [34, 35]. As per current guidelines, each new microbial strain (a strain not in earlier use) should be introduced only after going through an official procedure with thorough safety checks.

In the EU legislative framework, nowadays, probiotic products intended for animal feed additives are closely regulated in contrast to other
products. As per European guidelines, SCAN has acted as an expert body both in evaluating the feed additives and in formulating the guidelines. These guidelines have been structured keeping in view the safety of microorganisms with respect to the target animal, operator/user and consumer as well [36].

As per the EFSA, the use of Qualified presumption of Safety (QPS) for the evaluation of micro-organisms intended for fermentation and or as feed additives is being explored on case-to-case basis. As per these guidelines, unnecessary extensive evaluations should be avoided for all those microorganisms for which evidences on their safety already exist. Otherwise, application of QPS should be consistent for all the new and effective microorganisms. In case new microorganism qualifies QPS, the same should be immediately considered for QPS. The QPS should only be taken as valid for bacteria that enter the food chain and are free of any acquired resistance to antibiotics of importance in clinical /veterinary medicine. The presence of antibiotic resistance determinants would not exclude their safe use for production purposes provided that only the fermentation products are retained in the final product [37].

Fig. (1). Flowchart representing approval process for FOSHU in Japan.
Within the EU, QPS is a similar system as Generally Recognized as Safe (GRAS) applicable to microorganisms and their products in the USA. Such a system has led to qualify only those microorganisms that will not have properties with adverse effects on human health or the environment [38]. The current regulatory framework of various categories of probiotics of Europe has been shown in Fig. (2).

The QPS approval flow chart for microorganisms being used in various food products in Europe involves following steps:

1. Appropriate biochemical and molecular biological identification for strain level testing and biochemical characteristics of the component strain necessary for submission of experimental data under a variety of relevant environmental conditions.

2. A microbe can only be awarded with QPS status if environmental concerns and pathogenicity profiles are definable and controllable; otherwise, it is announced as not suitable for QPS.

4.2.1. Problems Related to the Current Approval Process of European Union

At present general public in European Union (EU) has a limited degree of trust in industries and scientific communities involved in the food sector that has resulted in a negative perception about probiotic products. The current regulatory system for approval of such products in EU has following limitations:

- The concept of quality presumption test has been emphasized in the approval process but distinction between fermented foods (dealing especially with LAB), probiotic based other products and GMOs derived from plant and animal origin has not been clarified.
- Approval process for probiotic based food products and probiotic based pharmaceuticals has not been distinctly compiled.
- Although list of microbes having history of safe use or those qualifying...
QPS are considered yet these QPS qualified microbe may be safe in one particular food and it may not be safe for some other modified intended use. Hence approval should be modified accordingly.

- Due to consideration of probiotic products under functional foods no emphasis has been made on clinical trials related to associated health claims in the current regulatory approval process.

4.3. Status of Probiotic Approval in China

State Food and Drugs Administration (SFDA) have been authorized to direct and conduct all affairs relating to functional foods since 2003 and have promulgated the functional foods [26] in China. As per these guidelines functional foods constitute diverse variety of foods that have specific health functions; are suitable for consumption by specific persons; has the effect of regulating human body and probiotics. These functional foods may also include various safe microorganisms. Hence, for each functional food, many tests including toxicity tests, functional tests (except for nutritional supplements), stability tests, hygiene tests, identification tests for functional ingredients etc. should be done before filing application. All the tests should be done by following the standard procedures by specialized agencies or laboratories qualified by the Ministry of Health (MOH) and SFDA [16]. The approval flow chart for functional foods in China, involves following steps:

1. Submission of application and samples to Institute of Nutrition and Food Safety (INFS) for carrying out safety, tox-
cology, function, active ingredient, hygiene and stability studies. Finally, INFS releases report to the applicant.

2. Submission of application to SFDA.

3. If accepted, SFDA send samples to designated testing for confirmation and collection of reports from designated agencies.

4. Formation of expert committee for technical and administrative examination.

5. If accepted, SFDA issues improved health food certificate.

The current regulatory framework of various categories of probiotics of China has been shown in Fig. (3).

4.3.1. Concerns Related to Current Approval Process of China

Functional foods are considered to hold a significant position and gain much popularity for public health and economic benefits for last few years. Despite a long history of the usage of functional foods, their regulatory approval issues are still debatable for consumers and manufacturers. Although Chinese authorities have covered the majority of the essential aspects of their current regulatory framework yet considerable limitations in the Chinese approval of regulations for functional foods including probiotics are as follows:

- Compilation of approval process has been done with respect to functional foods and live bacteria are considered to be the part of that food only.

- Approval process includes functional foods and no differentiation amongst functional foods and drugs has been mentioned.

- Identification of the probiotic strains has not been emphasized in the current regulatory guidelines and could be of major risk due to the fact that probiotic action is strain specific. List of microbes, which are to be included in novel foods or functional foods has been given rather than the list of microbes having safe history.

- Moreover, one kind of microbe may be safe in one particular food and it may not be safe for another modified intended use.

- Functional claim testing does not seem to be appropriate and hence needs to be modified for future use.

- Clinical trials are not considered in these approval guidelines and are merely based on the health claim, animal tests alone.

4.4. Status of Probiotic Approval at USA

In USA, FDA is the primary agencies for regulation of various probiotics products on the basis of its intended use i.e. foods, drugs (including biologics), dietary supplements, medical devices, and cosmetics. As per FDA guidelines, till date there is no central pathway to deal with all the probiotic products. FDA does not even have a regulatory definition of probiotics rather these probiotics are regulated on a case-to-case basis as per their use either in food or drugs or biologics [38]. Probiotics virtually fall in each product category and hence all the various categories are regulated by a center at the FDA [39]. Probiotic products for human use in USA are regulated by following:

1. The Center for Food Safety and Applied Nutrition (CFSAN).

2. The Center for Drug Evaluation and Research (CDER).

3. The Center for Biologics Evaluation and Research (CBER).

In the United States, food and substances used in food are regulated according to the Food Drug and Cosmetic Act (1958), in which the status of Generally Recognized as Safe (GRAS) holds a significant importance. GRAS status is a notification, which denotes the history of safe use or some other evidences of safety or if a product is used under the conditions recommended or suggested in the labeling of the dietary supplements. Determination of GRAS status has prime importance as it may vary from product to product. A microorganism labeled as GRAS for one type of food may not always be a GRAS for other food products.

According to FDA, a probiotic may be considered as a drug only if it is intended to diagnose,
cure, mitigate, treat or used for prevention of disease (FD&C Act). Only then these products will be approved as drug products (21 U.S.C. 321. Sect 2012004). The issue of category assignment is of significant importance especially in case of probiotic products. If a probiotic product is classified as a drug, it always triggers the extensive Investigational New Drug application (IND) process, which typically includes Phase I, II, and III clinical trials. All drugs must be approved prior to marketing by the FDA. Otherwise if a probiotic product is intended to be used as a dietary supplement, it is regulated under different guidelines, which will be regulated by DSHEA [13]. Foods and dietary supple-ments, however, do not require agency premarket approval.

Probiotics may also be considered as “biological product” or live microorganisms. As per FDA; biological products are defined as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergic product or analogous product, applicable to the prevention, treatment or cure of a diseased conditions of human beings [40]. This critical distinction between drug, dietary supplement or biological product must define the regulatory pathway to be followed for approval of probiotics as new drug, food ingredient/supplement or biological product.

Only US federal regulations has focused on exploring and documenting the possible health-related benefits of probiotics by conducting human clinical studies. USFDA guidelines for probiotics have stated following points about approval:

a. If a product is considered as dietary supplement, there is no need of approval from FDA; rather only notification to FDA is sufficient.

b. At present, for approval process of ‘new drug’, either chemical or biological, is similar and Investigational New Drug Application (INDA) must be submitted and authorized by FDA before its administration into humans. But if probiotic products are considered as live microorganisms, it must demonstrate safety, purity and potency.

c. Most of the probiotics are defined as “Generally Recognized as Safe” (GRAS) for food. GRAS microbes should be excluded from conventional approval pathway followed by drug/biologics and new strain having novel health benefit and generally acting as GRAS.

d. For marketing of a biologics based drug, Biological License Application (BLA) is mandatory. For marketing a new drug, New Drug Application (NDA) approval is required but currently, there are no probiotics approved as “drugs” in the United States. A probiotic sponsor is required to file an IND application with the FDA before the initiation of clinical trials for a “drug” indication.

The current regulatory framework of various categories of probiotics of USA has been shown in Fig. (4).

4.4.1. Problems of the Current Approval Process of USA

As per current status, approval process in the USA for dietary supplements, new drug ingredient, foods with health claims, drugs and biologics differs as per their intended use and as per their involvement in curing of diseases. Existing difference in approval process had led to following problems:

- The current regulatory framework followed in USA does not address the role of foods in treating, mitigating, or curing disease. Probiotic foods and dietary supplements which are committed to cure various diseases should automatically be placed in the drug category.
- A major concern relating to probiotic regulation is the filing of IND as probiotic formulations should conform to the rigorous and costly IND process.
- Another serious issue of concern is the use of dietary supplements, foods; food-derived products regulated as dietary ingredients as part of a clinical trial, which is unclear.
• With respect to IND, there are no categorical determinations in regard to the approval process. It is quite likely that for the same product, INDs may be required for some studies and not for the others. In some of the cases, FDA may require an IND for studies relating to probiotics even in cases where an IND may not be required or appropriate (such as studies with probiotics that have a history of safe use in the target population). Whenever a GRAS microbe is used in some alternative way, it must be approved after filling IND but should not increase the risk to subjects in comparison to risks to consumers. Hence it is totally ambiguous whether an IND is required or not [41].

• Probiotics fall into multiple product categories, and hence probiotics approval process has spread unevenly across multiple centers at the FDA. A single authoritative agency is not there, which may address all the issues related to probiotics. Ultimately these ambiguities may lead to intercenter inconsistencies in interpretation and application of regulations and the content of potentially relevant guidance documents about probiotics.
Apart from it, in context to premarketing approval of probiotic products presented by USFDA, even today following points are still supposed to create so much of confusions as per existing approval scenario:

a. GRAS category is excluded from the conventional approval pathway, but novel strains; which are generally effective and acting as GRAS should not be excluded from the approval pathway due to lack of documented history of safe use.

b. Use of INDA, NDA and BLA are not clearly mentioned in context to probiotic based food and pharmaceutical products and hence some ambiguity exists on the part of researchers and Institutional Review Boards (IRBs) with respect to whether clinical investigations of probiotics must be conducted or not.

5. FUTURE RECOMMENDATIONS

So keeping in view the urgent need of the approval process as well as current ambiguities, following suggestive consolidations are supposed to be included in guidance document for the approval process of the probiotics in a uniform manner at global level:

- Guidance document associated with approval process of probiotics should specify the kind of assays to be done for initial identification with respect to microbial load and strain specificity.

- Regulatory bodies associated with the approval of probiotic foods and probiotic pharmaceutical products should clearly set differences between the supportive documentations required for the approval of foods as well as drugs. Improper use of the term ‘probiotics’ under different categories must be rectified with appropriate categorization of probiotics, and hence characterization protocols should be accurately developed for probiotics in foods, dietary supplements as well as in drugs.

- On the basis of rectified categorization, approval process must include well established proposals with flexible characterization standards enough to encompass new technologies and must be specific enough to allow for proper/precise identification of strains.

- The guidance document for the approval of the probiotic based products should be commenced lawfully to assure whether an IND application is required before a clinical study or not. Investigators, researchers and institutional review boards should consider the regulatory categorization of the probiotics prior to the approval process on the substance under investigation.

- All products must be issued with a certificate of analysis about the organisms present along with its quantity by a reputable company for filing IND/NDA for each lot produced.

- An independent reference culture must be deposited by the company and maintained by the certifying authority for assuring consistency of the microorganism added to probiotic product.

Therefore harmonized guidelines for approval of probiotics should be designed and implemented in a unified manner at a global platform. In accordance to the above recommendations stated, ambiguities and to bring harmonization of standards, a modified appropriate definition, categorization of probiotics, appropriate identification up to genus/species/strain level of probiotic microbes are significantly important aspects. Henceforth all the above-mentioned parameters should be taken into consideration before granting approval process to probiotic based products. Besides all these factors, clear cut demarcation of Investigational New Drug Approval (INDA) and New Drug Approval (NDA) (for GRAS probiotic, live microbes other than GRAS, Generally Recognized as Effective (GRAE) and if new microbe with probiotic potential) should be clarified for approval process related to probiotic based food products and probiotic based pharmaceuticals. Hence, real care has been taken into consideration while designing the
approval process for probiotics. The steps proposed for probiotic approval are as follows:

5.1. Step 1: Identification of Probiotic Strains

In context to the appropriate approval process, first and foremost point taken into consideration is based upon the identification of the probiotic organism. Identification of the strain will decide whether it should be taken into consideration or not for probiotic-based product manufacturing. Henceforth correct identification via a polyphasic approach (i.e. phenotypic and genotypic collectively) is essential to guarantee their accurate identity, safety and efficacy of proclaimed health benefits.

5.2. Step 2: Evaluating GRAS/QPS Status

After a microbe qualifies the identification test, it undergoes a test for GRAS or GRAE status. After qualifying the GRAS status, it can be directly used for its category of intended use. In case of failure in qualifying the GRAS status, QPS status will be checked. The QPS qualified products will also be able to enter the next phase of the approval process. Hence all the GRAS and QPS microbes will directly be checked for their intended use. However, GRAE qualified microbes and new microbial entities will be approved differently. European Union has approved a list of microbes on the basis of QPS and microbes are enlisted in Table 2.

5.3. Step 3: Evaluation of Category of Intended Use

In proposed recommended approval process for marketing of probiotic-based products, probiotics are categorized into two broad categories known as nutribiotics (probiotics serving as food products providing nutritive claims only) and pharmabiotics (probiotics based pharmaceutical formulations providing general or specialized health claims) [4]. Pham biotic microorganisms are further classified into the following categories:

- **Beneficial and safe**
  This category particularly includes all those microbes, which do not qualify limits of probiotic potential but are used as a starter culture (possessing a role in fermenting food) and hence considered to be safe for internal use. Hence these types of microbes can be used for the treatment of oral cavity associated diseases because of their inability to survive in stomach owing to their low sensitivity for acid produced in stomach or bile production.

- **Clinically proven potential probiotic strains**: This particular category of the probiotic will include microbes already documented for their beneficial health effects as evidenced by studies in humans. These clinically proven microbes can be utilized by any target site like mouth, skin, vaginal with their delivery in any form of administration/use as dairy, powder, food, cream or other forms. This category further includes bifurcations, which are as follows.
  a) **Clinically proven potential probiotic strains with general health benefits**: This category includes microbes possessing general probiotic potential and can be exploited for a broad range of consumers.
  b) **Clinically proven potential probiotic strains with specific health benefits**: This category includes microbes possessing additional probiotic potential, not conveyed by all other probiotic strains and conferring a specific health claim when delivered.
  c) **Clinically proven potential probiotic strains for narrow use only**: This category includes microorganisms with additional probiotic potential but conferring health benefits for narrow use or for a narrow range of consumers. Considerable confusions in the approval process exist amongst various countries due to its intended category of use. Hence before undergoing
Table 2. European Union has approved a list of microbes on the basis of QPS and microbes.

<table>
<thead>
<tr>
<th>Regulatory Agencies</th>
<th>Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Japan</strong></td>
<td>Approval process has been designed only keeping in view functional foods and live bacteria are considered to be the part of that food. Hence no differentiation amongst functional foods, probiotic products and probiotic based therapeutic formulations has been made separately. Japan allows the manufacturers to conduct identity tests of microbes at their own level and hence may encourage a bias by the manufacturer leading to dispute quality/credibility of these products. There is no authority in Japan to regulate food and drugs separately as no emphasis has been laid for clinical trials or other related regulatory issues.</td>
</tr>
<tr>
<td><strong>European Union</strong></td>
<td>The concept of quality presumption test has been emphasized in the approval process but distinction between fermented foods (dealing especially with LAB), probiotic based other products and GMOs derived from plant and animal origin has not been clarified. The approval process for probiotic-based food products and probiotic-based pharmaceuticals has not been distinctly compiled. Although the list of microbes having history of safe use or those qualifying QPS is considered yet these QPS qualified microbes may be safe in one particular food and it may not be safe for some other modified intended usage. Hence approval should be modified accordingly. Due to consideration of probiotic products under functional foods, no emphasis has been made on clinical trials related to associated health claims in the current regulatory approval process.</td>
</tr>
<tr>
<td><strong>China</strong></td>
<td>Compilation of the approval process has been done w.r.t. functional foods and live bacteria are considered to be the part of that food only. Approval process includes functional foods and no differentiation amongst functional foods and drugs has been mentioned. Identification of the probiotic strains has not been emphasized in the current regulatory guidelines and could be of major risk due to the fact that probiotic action is strain specific. List of microbes, which are to be included in novel foods or functional foods has been given rather than the list of microbes having a safe history. Moreover, one kind of microbe may be safe in one particular food and it may not be safe for another modified intended use. Functional claim testing does not seem to be appropriate and hence needs to be modified for future use. Clinical trials are not considered in these approval guidelines and are merely based on the health claim, animal tests alone.</td>
</tr>
<tr>
<td><strong>USA</strong></td>
<td>The current regulatory framework followed in the USA does not address the role of foods in treating, mitigating, or curing disease. Probiotic foods and dietary supplements which are committed to cure various diseases should automatically be placed in the drug category. A major concern relating to probiotic regulation is the filing of IND as probiotic formulations should conform to the rigorous and costly IND process. Another serious issue of concern is the use of dietary supplements, foods; food-derived products regulated as dietary ingredients as part of a clinical trial, which is unclear. With respect to IND, there are no categorical determinations in regard to the approval process. It is quite likely that for the same product, INDs may be required for some studies and not for the others. In some cases, FDA may require an IND for studies relating to probiotics even in cases where an IND may not be required or appropriate (such as studies with probiotics that have a history of safe use in the target population). Whenever a GRAS microbe is used in some alternative way, it must be approved after filling IND but should not increase the risk to subjects in comparison to risks to consumers. Hence it is totally ambiguous whether an IND is required or not [41]. Probiotics fall into multiple product categories, and hence, probiotics approval process has spread unevenly across multiple centers at the FDA. A single authoritative agency is not there, which may address all the issues related to probiotics. Ultimately these ambiguities may lead to intercenter inconsistencies in interpretation and application of regulations and the content of potentially relevant guidance documents about probiotics. Apart from it, in context to premarketing approval of probiotic products presented by USFDA, even today; following points are still supposed to create so much of confusion as per the existing approval scenario: GRAS category is excluded from the conventional approval pathway, but novel strains; which are generally effective and acting as GRAS should not be excluded from the approval pathway due to lack of documented history of safe use. Use of IND, NDA and BLA is not clearly mentioned in context to probiotic based food and pharmaceutical products and hence some ambiguity exists on the part of researchers and Institutional Review Boards (IRBs) with respect to whether clinical investigations of probiotics must be conducted or not.</td>
</tr>
</tbody>
</table>
Table 3. Documents to be submitted while IND or NDA submission.

<table>
<thead>
<tr>
<th>Documents Required for IND Submission</th>
<th>Documents Required for NDA Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Application for (permission for manufacture/import/clinical trial – purpose should be clearly mentioned),</td>
<td>➢ Title page,</td>
</tr>
<tr>
<td>➢ Name of the applicant,</td>
<td>➢ Table of contents,</td>
</tr>
<tr>
<td>➢ Name of the probiotic including genus, species and strain designation,</td>
<td>➢ Study objective(s) (primary as well as secondary) and other logical relation to the study design,</td>
</tr>
<tr>
<td>➢ Prescribed application form complete in all respect duly signed and stamped by an authorized person of the firm,</td>
<td>➢ Study design and population involved,</td>
</tr>
<tr>
<td>➢ Proof of fee submission as demanded by the regulatory authority (for phase II/III),</td>
<td>➢ Subject eligibility – Inclusion criteria and Exclusion criteria,</td>
</tr>
<tr>
<td>➢ Copy of valid manufacturing license as per GMP, probiotic source along with the documents showing the passage history and origin,</td>
<td>➢ Study assessments and treatment,</td>
</tr>
<tr>
<td>➢ Information regarding the active ingredients in the formulation,</td>
<td>➢ Adverse events,</td>
</tr>
<tr>
<td>➢ Specified data on formulation,</td>
<td>➢ Ethical considerations,</td>
</tr>
<tr>
<td>➢ Animal pharmacology studies data,</td>
<td>➢ Study monitoring and supervision, investigational product management, data analysis and undertaking by the investigator,</td>
</tr>
<tr>
<td>➢ Animal toxicology data,</td>
<td>➢ Details/elements representing the investigator’s undertaking, and as per study subject’s informed consent document(s),</td>
</tr>
<tr>
<td>➢ Reports of toxicity studies along with clinical trial applications of different phases for INDs,</td>
<td>➢ Data related to informed consent documents (patient information sheet),</td>
</tr>
<tr>
<td>➢ Regulatory status in other countries, countries where the drug is marketed or approved or withdrawn due to some reasons.</td>
<td>➢ Informed consent form etc.) Mentioning, “In case of study related injury or death M/s. &lt;&lt; NAME OF THE COMPANY &gt;&gt; will provide complete medical care along with compensation for the injury or death”.</td>
</tr>
</tbody>
</table>

the approval process, the category of their intended use must be decided and should be approved accordingly by the concerned authority. This practice may overcome category-based ambiguities in approval process.

5.4. Step 4a: Approval for the Manufacturing of “Nutribiotics”

Only probiotic based food products having nutritive claims will be pursued for approval under their existing national or regional food authorities.

On qualifying all the related parameters and satisfying all the documentation as required by the concerned regulatory authority these products will get an approval for manufacturing of probiotic-based food stuffs.

5.5. Step 4b: Approval for the Manufacturing of “Pharmabiotics”

Probiotic based pharmaceuticals with specified health claims need IND and NDA submission and FDA review before undergoing the manufacturing. The conditions of IND and NDA submission are exclusively dependent on their GRAS/QPS status. After assessing GRAS/QPS status, the microbes qualifying GRAS/QPS status need not to submit IND rather they only need to get NDA approval before undergoing manufacturing and marketing approval, whereas, microbes without GRAS/QPS status are further categorized in two categories i.e. either GRAE but not GRAS or a new microbial entity having probiotic potential. Whenever a GRAS microbe is used in some alternative way, it must be approved after filling application by submitting all the supporting documents related to safety of the consumers. Hence, while undergoing IND or NDA approval of the above categorized entities, following documents should be enclosed as shown in Table 3.

On the basis of all the documents, FDA should review the file and will either grant approval or ask for supplementary information or may reject the file. Once FDA grants approval for the marketing, these products may enter the market for consumers use. The flow chart based upon the above said consolidations has been compiled and has been shown in Fig. (5).

As per earlier available data, it has been observed that probiotics fall into multiple product categories, and hence the approval process for probiotics has spread unevenly across multiple centers at the FDA. A single authoritative agency to address all the issues related to probiotics does not exist. Besides this, there were no categorical
bifurcations for IND requirements. Sometimes for the same product, FDA may require an IND but not for others of the same category. The use of IND and NDA is quite vague and unclear till date. Ultimately these ambiguities may lead to inter-center inconsistencies in the application of regulations as well as interpretation about safety and efficacy of these products. Henceforth major concerned issues related to efficacy and safety can be resolved by following an appropriate approval process [42]. The proposed approval framework clarifies all the concerned ambiguities related to the category of the probiotic on their intended use as well as approval protocol to be followed for GRAS/QPS microbes, non-GRAS/GRAE and new microbial entities. If this proposed protocol is lawfully implemented on all the probiotic based food products and formulations, it will definitely en-

Fig. (5). Proposed flowchart for approval of probiotic based products.
force appropriate realization and utilization of the exciting potential of probiotic based products. Apart from it, the proposed process will prevent the entry of misbranded or unlawful products to the market. Hence this approval protocol will ensure proper manufacturing process along with the increased consumer acceptance.

CONCLUSION

Probiotic based products are supposed to be effective for public health due to the increased awareness amongst consumers. These products have also established a link between public health officials, consumers and industrialist from various food industries. But as a matter of fact, probiotics falling into the category of pharmabiotics would have certain characteristics that distinguish them from nutribiotics and hence safety of these products is supposed to be the overarching concern amongst stakeholders viz. probiotic companies, manufacturers, regulatory agency professionals and consumers. Existing guidelines have made it clear that approval of probiotic products still leaves much to be desired, because of the underdeveloped legal framework for probiotic products. The proposed approval process will provide a systematic approach to deal with the safe and judicious use of probiotics. In this context, change can only occur through lawful execution of recommended approval process and through the goodwill of suppliers and manufacturers. Products, not meeting the requirements, may subject to strict action by the concerned regulatory authority. A consistent and internationally harmonized approval process is becoming a necessity to impose good regulatory decisions, and ultimately, it will lead to increased consumer acceptance, reduced entry of false and misbranded products to the market with greater safety and accuracy. These proposed guidelines should also strengthen the export and import of probiotic products overseas along with an opportunity for consumers from all countries to avail/enjoy the benefits of globally accepted products.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are the basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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