Regulatory framework and challenges for live biotherapeutic products in Taiwan

Shirley Pan, Jia-Chuan Hsu, Kuo-Teng Hung, Ching-Jung Ho*

Taiwan Food and Drug Administration, Ministry of Health and Welfare, Taipei, Taiwan

Abstract

Products containing live microorganisms may be classified as food or drugs depending on their intended use; live biotherapeutic products (LBPs) with therapeutic claims are defined as medicinal products containing live bacteria or yeasts intended to prevent or treat disease. Based on their characteristics, LBPs are classified as biological drugs and must be registered as biological drugs before they can enter the Taiwanese market. As research into the microbiota and its role in health and disease continues to advance, LBPs are expected to play an increasingly important role in medicine and biotechnology. With the growing popularity of microbial applications in recent years, there is still a lack of awareness regarding the management and regulation of such products. This article outlines the development, manufacturing, and marketing requirements of LBPs in Taiwan. After searching relevant literature, we summarized the regulations or related guidelines on LBPs from regulatory agencies such as the U.S. FDA, EMA, PMDA, and ICH. And compare the current requirements for LBPs in Taiwan. Key regulatory aspects of LBPs in Taiwan include definitions and classifications, quality and manufacturing requirements, clinical evidence, labeling and packaging information, post-marketing surveillance, etc. Regulations of LBPs in Taiwan align with international standards, but Taiwan authorities must be more inclusive in addressing new challenges facing LBPs innovation. This highlights the importance of continuous regulatory adaptation to foster innovation while ensuring safety and efficacy. Collaboration between regulatory bodies, industry stakeholders, and scientific communities will be essential to promoting innovation while maintaining robust regulatory oversight in the LBPs sector. In summary, while LBPs have significant therapeutic potential, addressing the regulatory challenges associated with their development, approval, and post-marketing surveillance is critical to ensure their safety, efficacy, and successful integration into clinical practice.

Keywords: Fecal microbiota transplantation (FMT), LBPs, Live biotherapeutic products, Live microbial products, Next-generation probiotics (NGPs)

1. Introduction

Live microbial products are often designed to modulate the host's microbiota to restore or maintain a balanced microbial ecosystem in the gastrointestinal tract or other body parts. In addition to the gastrointestinal tract, microorganisms may also affect the function of the liver, pancreas, heart, lungs, brain-gut axis, and central nervous system [1]. Depending on their intended use and claims, live microbial products can be classified as food or drugs. Health foods are intended to maintain or enhance the health status of healthy people; drugs are designed to treat or prevent disease or pathological conditions in patients [2]. The lines between food and drugs may seem blurry, but classification affects the regulatory pathways, standards, and documentation required for market approval.

A joint Expert Committee for the Food and Agriculture Organization (FAO) and World Health Organization (WHO) defined probiotics in 2001, revised by Hill *et al.* in 2014, as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [3]. The International Scientific Association of Probiotics and Prebiotics (ISAPP) issued a position statement in

Received 4 November 2024; accepted 20 February 2025.
Available online 13 June 2025

* Corresponding author at: No. 109, Ln. 130, Sec. 1, Academia Rd., Nangang Dist., Taipei 115, Taiwan.
E-mail address: daeda11@fda.gov.tw (C.-J. Ho).

https://doi.org/10.38212/2224-6614.3540

2018 outlining the minimum criteria for food probiotics [4] (Fig. 1). These criteria are intended to ensure that probiotics on the market are safe and effective [5].

According to the provisions of Article 6 of the Pharmaceutical Affairs Act [6], products claimed to be used to diagnose diseases, treat diseases, alleviate diseases, prevent diseases, or affect the structure and function of the body are classified as drugs in Taiwan. LBPs contain live microorganisms that are intentionally used for their therapeutic properties. Therefore, LBPs refer to drugs that are different from probiotics that are generally used to maintain health.

The regulatory frameworks for the classification of live microbial products as food or drugs in different regions are briefly compared and summarized in Table 1. In the European Union (EU), food is regulated by the European Food Safety Authority (EFSA), and there is an EU approved microbial safety list, QPS (Qualified Presumption of Safety). Drugs are regulated by the European Medicines Agency (EMA). In Japan, the Food Safety Council (FSC) provides scientific risk assessments related to Foods for Specific Health Uses (FOSHU), the Pharmaceutical and Medical Device Agency (PMDA) conducts scientific review of pharmaceutical products, and the Ministry of Health, Labor and Welfare (MHLW) grants final marketing authorization based on their recommendations. In the United States (U.S.), food and drugs are regulated by the Food and Drug Administration (FDA). Even within the same regulatory body, the regulations are still different. Probiotic strains used in foods or dietary supplements must be Generally Recognized as Safe (GRAS) or meet equivalent safety standards, while probiotic strains used as drugs must undergo preclinical and clinical safety and efficacy evaluations. And this is also the case in Taiwan.

2. Main categories of LBPs in Taiwan

The three main categories of LBPs in Taiwan are described below.

2.1. Probiotics in over-the-counter drugs

In Taiwan, drugs are categorized into two main types based on how they are accessed by consumers: prescription and over-the-counter (OTC) drugs. The review of OTC drugs is currently governed by 18 specific guidelines, known as the OTC monograph category [7]. One of these categories is gastrointestinal preparations. The active ingredients in this category include live bacteria, such as Bacillus, Bifidobacterium, Clostridium, and Lactobacillus. For

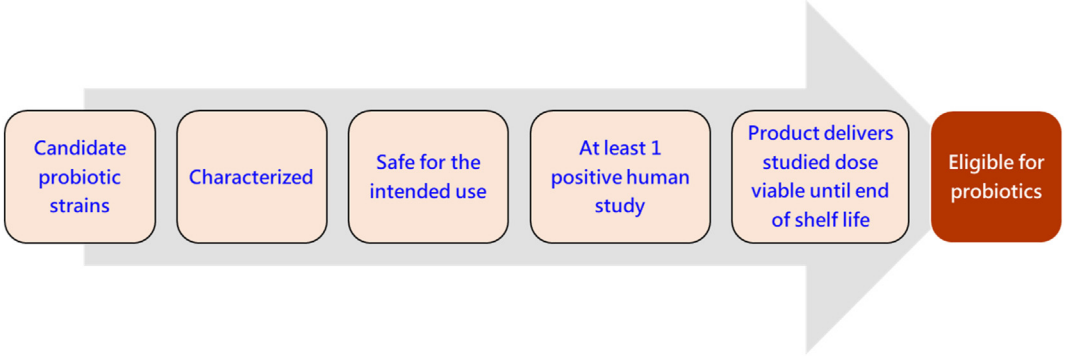

Fig. 1. Criteria to qualify microorganisms as probiotics in foods and dietary supplements.

Table 1. A brief comparison of the regulatory frameworks for live microbial products classified as food or drugs.

	Health Foods or Dietary Supplements	Biological Drugs
EU	- EFSA - Health claims/QPS list	- EMA - Quality as required in Ph. Eur. - Clinical trial for safety and efficacy
Japan	- MHLW/FSC - FOSHU	- MHLW/PMDA - Biotherapeutic drugs
U.S.	- FDA/Center for Food Safety and Applied Nutrition - GRAS notification for safety	- FDA/Center for Biologics Evaluation and Research - For prevention or treatment of disease
Taiwan	- TFDA/Division of Food Safety - Probiotics with general health effect	- TFDA/Division of Medicinal Products - LBPs as defined in TWP

these preparations, the number of bacteria contained in the daily dose of the finished product must not be less than 1×10^6 (1,000,000 CFU). The declared indications for these products include relief of mild diarrhea, relief of abdominal pain or constipation, improvement of intestinal functions (adjustment of bowel movements), and softening stools.

2.2. Therapeutics for specific conditions

LBPs are used to treat specific medical conditions such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and *Clostridium difficile* infection (CDI). The most well-known example is fecal microbiota transplantation (FMT). The Ministry of Health and Welfare adopted the 2018 consensus of the Microbiota Consortium in Taiwan [8]. In September of that year, FMT was included in the regulation of special medical techniques authorized by Article 62 of the Medical Affairs Act, and it was conditionally approved as one of the routine medical treatments [9]. The conditional approvals include qualified centers and FMT team members, transplant indications are limited to recurrent or refractory CDI, donors, and recipients must sign informed consent, and all cases need to be registered in the National Registry of the National Institutes of Health [10]. This incorporation of FMT into routine medical care falls under the scope of medical technology. FMT falls within the scope of human trials for other indications beyond recurrent CDI, such as cancer immunotherapy or rheumatic immune diseases. If FMT products are intended to be mass-produced and commercialized, they will be included in the scope of new drug development.

2.3. Innovative therapeutics

Emerging applications of LBPs include areas like cancer therapy, metabolic disorders, and enhancing the effectiveness of vaccines. Next-generation probiotics (NGPs) are considered a striking development over traditional probiotics with a history of safe usage in humans. Potential NGPs such as *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, *Bacteroides fragilis*, *Bifidobacterium spp.*, *Prevotella corpri*, *Christensenella minuta*, *Parabacerides goldsteinii*, were under intensive development [11]. The study and analysis of NGPs have become a new theme in research and development. Taiwan has a growing body of research on LBPs, focusing on a variety of therapeutic areas, including gastrointestinal disorders [12], allergic diseases [13], metabolic disorders [14,15], neuropsychological disorders [16–18], and certain cancers [19]. Research on improving or treating NGPs for different diseases will be classified as new drug development. These products are subject to varying degrees of regulation depending on their intended use, claims, and the jurisdiction in which they are marketed [20].

3. Regulatory requirements for biologics

3.1. LBPs classified as biologics

In Taiwan, biological drugs comprise serum, antitoxins, vaccines, toxoids, and bacterial fluids produced based on microbiology and immunology [21]. LBPs are typically classified as biological drugs or biopharmaceuticals products, subject to regulatory requirements similar to those for other biologics. To obtain marketing authorization for biological drugs, comprehensive technical documentation must be submitted to the Taiwan Food and Drug Administration (TFDA).

3.2. Pharmaceutical lifecycle management [22] and regulatory compliance [23]

The process from research and development to drug marketing can be divided into different stages. TFDA will apply review, audit, inspection, and other means combined with various standards (GXPs) to form a complete drug life cycle management. For example, Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) inspections must be conducted at non-clinical studies and clinical trials stage to ensure studies quality; Good Manufacturing Practice (GMP) must be complied with during the stage of pharmaceutical manufacturing; and Good Pharmacovigilance Practice (GPvP) must be continuously followed during the stage of post-marketing to ensure drug quality and safety monitoring, to fully achieve the management goals of the drug life cycle (Fig. 2).

3.3. Key components of biopharmaceutical application

Necessary documentation and data must be submitted to regulatory authorities for product approval. These documents cover aspects such as quality (chemistry, manufacturing, and controls - CMC), preclinical safety data, and clinical efficacy [24].

Biological quality components typically include drug substance and product description, manufacturing process, characterization and specifications, quality control, stability data, and GMP compliance to ensure consistent and reproducible manufacturing processes.

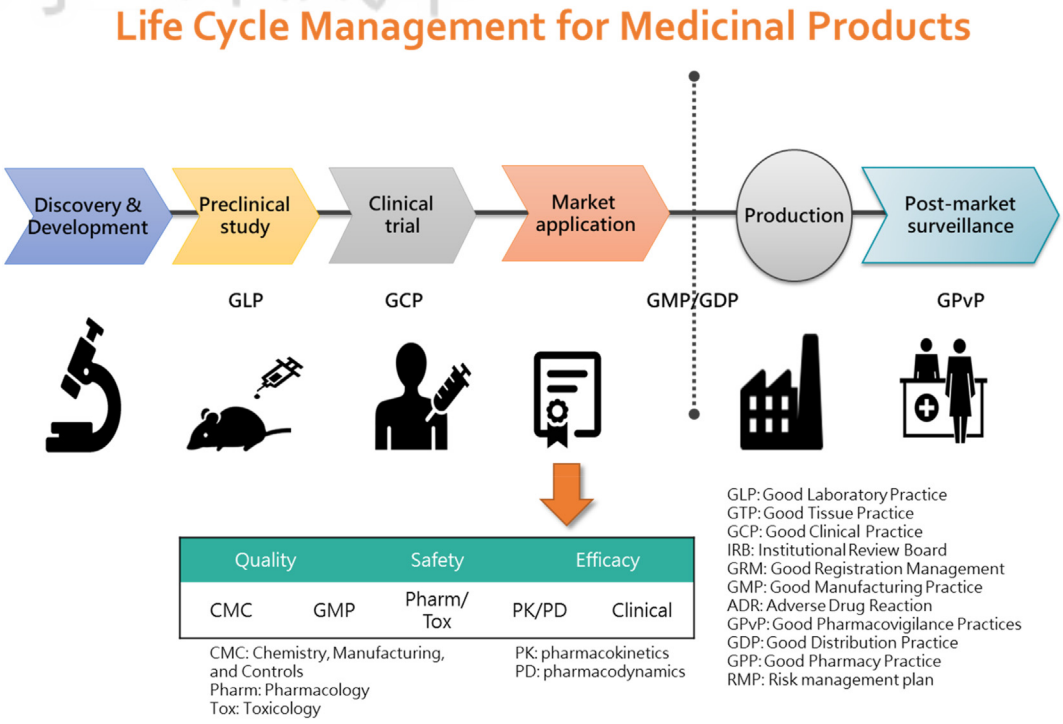

Fig. 2. Life Cycle management framework for medicinal products.

Preclinical safety data include pharmacokinetic (PK), pharmacodynamic (PD), toxicology, and safety pharmacology studies. These components are generally used to evaluate potential adverse effects and ensure the products' overall safety for human use.

Clinical trial data are the key basis for proving the safety and effectiveness of drugs. A good trial protocol must be designed to protect the subjects' health and specifically answer the research questions. The protocol components consist of objectives, endpoints, number of subjects, level and exposure, type and duration of active and passive monitoring, as well as study conduct, integrity of data collection, and subsequent analysis. Clinical efficacy studies are conducted to demonstrate that the product is effective for its intended therapeutic use. Usually, at least two pivotal trials are required as confirmatory trials for new drug registration to support the drug's indications, dosage, route of use, and safety.

3.4. International guidelines

Taiwan is a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). Membership includes a commitment to follow consensus-based guidance for pharmaceuticals, including biologics. The guidance on biologics provided by ICH covers four key areas: quality, efficacy, safety, and multidisciplinary [25]. These guidelines provide the industry with a reference for developing products, and manufacturers can submit the required data and justification to demonstrate positive benefit-risk results to obtain marketing authorization while complying with regional regulatory requirements.

The use of the Common Technical Document (CTD) format facilitates the submission and review process by providing a standardized format for regulatory submissions. This harmonization helps streamline the development and approval across different regions, making it easier for manufacturers to process a global development and approval of biologics. The brief technical document required for review and registration of bio-pharmaceutical products and LBPs are shown in Table 2.

4. Regulatory challenges for LBPs

LBPs present unique challenges due to their living nature and therapeutic potential.

4.1. LBPs' living nature

LBPs present unique scientific challenges related to their complex mechanisms of action, microbial composition variability, and host-microbiome interactions. The consistency and quality control of

Table 2. Brief technical document required for review and registration of bio-pharmaceutical products and LBPs.

	Bio-pharmaceutical Products (Common items)	LBPs (Special considerations)
CMC	Drug Substance - Appearance and Description - Manufacture - Characterization/Identity - Specification/Potency - Purity and Impurities - Stability	- Characterization includes determination of the phenotype and genotype of the strain. - Assessing the microorganisms for antibiotics resistance or the presence of transferable drug resistance genes to prevent the spread of resistant strains. - Virulence factors must be investigated.
	Drug Product - Description and Composition - Pharmaceutical Development - Manufacture - Control of Excipient - Control of Drug Product - Specification/Potency - Purity and Impurities - Stability	- Bioactivity - For oral products, survivability of the microorganism in the human gut is demonstrated by *in vitro* gastric acid and bile resistance tests. - Purity, Test for microbial contamination should be assessed. - For microbial consortia, the stability of each constituent strains should be evaluated.
Non-clinical Safety	Various Toxicologicl Studies	- Challenges such as animal to human translation and/or to the suitability of certain preclinical animal models.
	Pharmacological Studies Pharmacodynamics (PD)	- Challenges such as strain specificity and complex interactions.
	Pharmacokinetics (PK) - Absorption - Distribution - Metabolism - Excretion	- LBP is not expected to enter the systemic circulation, so traditional absorption, distribution, and metabolism studies are not applicable. However, specific studies to demonstrate colonization patterns, viability, shedding, and clearance from the host in the gastrointestinal tract are necessary.
Efficacy	Clinical Efficacy Studies - Medical literatures - Clinical trials	- Challenges due to variability in microbial strains, interactions with host physiology, and limited understanding of mechanisms of action.

the production process are very important to ensure quality [26]. Since LBPs contain living organisms, their manufacturing process is more complex and difficult to standardize. The live nature of LBPs raises safety concerns regarding potential pathogenicity, the transmission of infectious agents, and unintended effects on host-microbiota [27].

4.2. LBPs' therapeutic potential [28]

The efficacy of LBPs poses challenges due to variability in microbial strains, interactions with host physiology, and limited understanding of mechanisms of action. Designing clinical trials for LBPs can be challenging due to patient heterogeneity, variability in microbial response, and the lack of standardized endpoints.

4.3. Specific guideline

Given the unique nature of LBPs, clear regulatory pathways and guidelines are crucial for manufacturers to navigate the approval process efficiently. Regulatory authorities may require innovative approaches to assess the safety and efficacy of LBPs in clinical settings.

4.4. Post-marketing surveillance

Post-approval monitoring of LBPs is critical for detecting and addressing adverse events. Additionally, more effort is required to assess long-term safety and efficacy, and to ensure continued compliance with regulatory requirements.

5. Global harmonization of LBPs regulation

In the face of the challenges described in the previous section, it is necessary to develop specific modules that address unique considerations for LBPs, such as viability testing, strain characterization and antibiotic resistance. The following are the developments and considerations of the ICH key regulatory agencies in evaluating LBPs.

5.1. LBPs regulation in the U.S.

In the U.S., LBPs are regulated primarily by FDA. The FDA introduced the LBPs category in a 2012 guidance, defining LBPs as biological products containing live microorganisms (e.g., bacteria) intended to prevent, treat, or cure human diseases. This guidance outlined the necessary CMC information required to ensure the safety and quality of

LBPs during early clinical trials. It was revised in 2016 to include considerations when using commercially available conventional foods and dietary supplements as test products in clinical trials [29]. Carlson *et al.* published a paper on U.S. regulatory considerations for live biotherapeutics, pointing out additional factors for CMC evaluation, such as strain characteristics, product release criteria, and other issues with genetically modified LBPs [30]. Dr. Carlson also published an article on regulatory considerations for fecal microbial transplant products, highlighting that the manufacturing process may affect the viability of individual microbiome species, which may affect the product's overall effectiveness and safety [31].

The evolving regulatory considerations reflects the complexity and novelty of LBPs, which require careful oversight due to their living nature and potential impact on human health. The FDA emphasizes the need for robust research to address gaps in understanding the mechanisms of LBPs and their long-term safety.

5.2. LBPs regulation in the EU

The EMA plays a crucial role in the oversight of LBPs within the EU, and the quality of medicine is regulated by the European Pharmacopoeia (Ph. Eur.) established by the European Directorate for the Quality of Medicines and Healthcare (EDQM). While the EMA is responsible for evaluating these products, national regulatory authorities grant marketing authorizations to each EU member state. Two major safety concerns associated with using LBPs are infectious complications and the potential transfer of antibiotic-resistance genes or putative virulence/toxin genes to other microorganisms within the human microbiome. This could exacerbate the global challenge of antibiotic resistance or cause otherwise benign microorganisms to exhibit harmful characteristics [32].

In response to these challenges, Ph. Eur. took an important step forward in 2019 by officially recognizing LBPs as a medicinal product for human use. This recognition was accompanied by the adoption of monograph 3053, which sets out the quality and safety requirements for LBPs during production and in the finished product. The monograph addresses the preceding safety concerns by establishing rigorous standards for strain characterization, production controls, and testing. Alongside monograph 3053, the Ph. Eur. also introduced two general chapters 2.6.36 and 2.6.38. These texts provide detailed methodologies for microbial contamination enumeration and specific microbial testing methods. The official adoption of LBPs in the Ph. Eur. marks a pivotal development in the field, reflecting the growing importance and recognition of these products in modern medicine [33].

5.3. LBPs regulation in Japan

Japan has made significant progress in the development and evaluation of biopharmaceuticals, including biosimilars [34]. The Japanese Pharmacopoeia (JP) includes general chapters that provide principles for ensuring the quality of biotechnological products or biopharmaceuticals. However, there is no specific regulatory definition of LBPs in Japan as a distinction from other live microbial products. It can be stated in an indirect way that when live microbial products is used for treatment, it is classified as a medicine and regulated under the Pharmaceuticals and Medical Devices Act (PMD Act). This classification distinguishes LBPs from probiotics marketed as foods or supplements, which are regulated under a separate framework.

The PMDA aligns its evaluation framework with the guidelines of ICH. Points to consider for gut bacteria products are released based on PMDA's 2022 Microbiome Research Report. In the report, PMDA emphasized the need for clinical evidence against strains, including evidence of therapeutic efficacy, safety and viability in humans [35].

As of now, JP does not explicitly include a dedicated general chapter or monograph for LBPs. However, components relevant to LBPs, such as microbiological quality, are addressed indirectly through general standards applicable to pharmaceuticals.

5.4. LBPs regulation in Taiwan

In Taiwan, LBPs are regulated by TFDA under the Ministry of Health and Welfare. While TFDA has its own regulatory framework, it is generally aligned with international standards, including those set by EMA and FDA, thereby promoting global regulatory harmonization.

The General Chapter 5229, titled Living Biological Therapeutic Products, was introduced in Supplement 3 of the Eighth Edition of the Taiwan Pharmacopoeia (TWP) in 2019 [36]. This chapter defines LBPs as live microbial medicines containing bacteria or yeasts for human use, including single or multiple strains from the same or different microbial species. It outlines requirements for the development, quality control, and manufacture of such products. The standards emphasize the importance of detailed microbial analysis at the

Table 3. Key aspects of LBPs regulation in Taiwan.

Aspects	Characteristics
Definition and Classification	LBPs are classified under biological products and defined as products containing live microorganisms, such as bacteria or yeast, intended to have a therapeutic effect on the human body.
Quality and Manufacturing Standards	A detailed technical dossier covering all aspects of the product, including its development, manufacturing process, and quality control measures required. Manufacturing facilities are subject to inspection by regulatory authorities to ensure compliance with GMP.
Clinical Trials and Evidence	Requirements for conducting well-designed clinical trials to demonstrate the safety and efficacy of LBPs in specific patient populations.
Labeling and Packaging	Labels and packaging must contain information, including product ingredients, dosage, storage conditions, and administration instructions.
Regulatory Review and Approval Process	The process for registering and reviewing LBPs is structured with clear timelines and controls. The approval of applications is based on rigorous scientific evidence, including the product's quality, safety, and effectiveness.
Post-Marketing Surveillance	Mechanisms for monitoring safety and effectiveness after marketing approval, including pharmacovigilance activities to detect and respond to adverse events.

strain level, such as strain phenotype and genotype determination, antibiotic resistance testing, safety evaluation, and survival ability in the human intestine. Two additional general chapters, such as 5231 and 5233 have also been added, specifically addressing testing for microbial contamination of LBPs, including microbial contamination enumeration methods and testing for specific microorganisms. Details information that must appear on labels, such as strain identity, potency, and storage conditions.

Taiwan's regulatory approach for LBPs aligns with international standards, such as ICH guidelines and codified in the Pharmacopoeia. The inclusion of LBPs in the TWP represents a forward-thinking approach to regulating microbiome-based therapies.

As part of the approval process, sponsors may be required to submit a risk management plan (RMP) detailing how they intend to monitor and manage risks associated with LBPs. This ensures that potential safety issues, such as adverse side effects and gene transfer risks, are carefully considered and mitigated. Post-marketing surveillance data and safety assessments performed by TFDA are also similar to those performed by other international bodies.

6. Conclusion and perspective

6.1. Key aspects of LBPs regulation

Taiwan's regulation of LBPs covers several key aspects, including clear definitions and classifications, products must be manufactured in compliance with PIC/S GMP, comprehensive biopharmaceutical technical dossier, well-designed clinical studies, adequate labeling and packaging information, and continuous pharmacovigilance. The competent authorities have established clearly structured timetables and control measures for the registration and review process of LBPs. Applications are approved based on rigorous scientific evidence, including product quality, safety, and effectiveness (Table 3).

6.2. Future perspective

LBPs, including probiotics and live microbial therapies, hold significant potential for improving gastrointestinal health, immune function, and overall health. With ongoing advancements in biotechnology and healthcare infrastructure, the future perspective of LBPs in Taiwan appears promising. The regulation of LBPs is expected to evolve with the advancement of biotechnology and regulatory standards. Regulatory agencies worldwide, including Taiwan, will develop more comprehensive guidelines specifically for LBPs to ensure safety, efficacy, and quality control.

The red yeast rice incident involving Japanese Kobayashi Pharmaceutical in 2024 has attracted public attention and caused people to lose confidence in products containing live microorganisms or fermented ingredients, including LBPs. The concerns will gradually ease with advances in biotechnology and a better understanding of the human microbiome. Regulators are increasingly focusing on quality issues such as strain characterization and identification, genetic stability, and the product's mechanism of action. Post-marketing surveillance and pharmacovigilance are also being strengthened to monitor the safety and efficacy of LBPs in real-world clinical settings. More precise regulatory management will help restore and maintain public confidence in LBPs and support their integration into mainstream healthcare.

Collaboration between regulatory bodies, industry stakeholders, and scientific communities will be essential to promoting innovation while maintaining robust regulatory oversight in the LBP sector.

In summary, although LBPs present significant therapeutic potential, it is essential to tackle the regulatory hurdles involved in their development, approval, and ongoing monitoring after they hit the market. Ensuring the safety and efficacy of LBPs requires robust regulatory frameworks encompassing rigorous quality controls, comprehensive clinical trials, and ongoing monitoring after the products enter the market. By effectively managing these challenges, LBPs can be successfully integrated into clinical practice, providing new avenues for treating and preventing diseases.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

The author thanks the speech invitation at the 7th Annual Conference of the Taiwan Microbiota Consortium, which facilitated the collection of literature and materials to write this article.

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