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Guidelines

Expert Recommendations on Supervision System for Microbiota Transplantation Technology: Dual-Track Regulatory Governance Framework

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Abstract

Microbiota transplantation represents a pivotal individualized therapeutic strategy for drug-resistant infections, inflammatory bowel diseases, and refractory chronic disorders. Nevertheless, the global uniformity of pharmaceutical-oriented supervision has long restricted the clinical translation and innovative development of microbiota transplantation technologies. China has established an innovative dual-track regulatory governance system for emerging biomedical technologies, which differentiates standardized mass-produced microbial preparations from highly individualized microbiota intervention techniques. This article elaborates the top-level institutional design of the dual-track framework, clarifies the regulatory boundary between routine clinical microbiota transplantation and innovative engineered microbial technologies, and interprets the exemption rules and hierarchical risk management mechanism for conventional fecal microbiota transplantation. Furthermore, it summarizes the differentiated supervision pathways, priority review strategies for unmet clinical needs, and existing implementation challenges.

Key words: Microbial therapy; dual-track regulation; intestinal microbiota transplantation; live biotherapeutic products.

1. Introduction

Microbial medicine has entered an explosive development phase since 2010. Technological breakthroughs in human microbiota, bacteriophages, genetically engineered probiotics, synthetic consortia, and oncolytic microorganisms have continuously rewritten the diagnostic and therapeutic paradigms for infections, tumors, inflammatory bowel diseases, metabolic disorders, and rare diseases. The digestive disease sector has matured first, while drug-resistant bacterial infections and oncology pipelines have entered a period of rapid clinical expansion. For a long time, the global regulatory framework has generally lagged behind the pace of technological iteration. Represented by the U.S. FDA and the European EMA, all live microbial intervention approaches are uniformly classified as live biotherapeutic products or advanced therapy medicinal products. This classification enforces the application of standardized pharmaceutical, manufacturing, and quality control requirements, large-scale confirmatory clinical trials, and stable mass production commercialization systems. The FDA has incorporated all new microbiome therapeutic technologies, including bacteriophages, engineered bacteria, and synthetic consortia, into the biologics registration pathway. It mandates the establishment of rigorous seed banks, stable large-scale production lines, and large-sample phase Ⅲ confirmatory clinical trials, which are highly compatible with standardized mass-produced products. EMA has added a small number of flexible clauses for advanced therapy medicinal products, but the core review logic remains anchored to drug consistency and batch-to-batch stability, making it difficult to align with the inherent characteristics of highly individualized technologies such as microbiota transplantation and customized bacteriophages (1). Many regional authorities have released stool bank and FMT guidance documents. The European stool-bank consensus sets unified standards for donor screening, sample processing, and quality control under medical-institution-based preparation modes; the United States FDA has issued multiple FMT guidance drafts, implementing risk-based monitoring for stool-bank products. Compared with these overseas single-track pharmaceutical-oriented regulatory modes, China’s dual-track framework provides a new governance option for highly individualized microbiota interventions, while simultaneously bringing new practical challenges such as boundary identification between technical categories and cross-hospital quality consistency control.

Intestinal microbiota transplantation (IMT), as the most mature microbial intervention method (2,3), has varying regulatory standards across countries worldwide. In contrast, examining China's pharmaceutical and medical device regulatory reforms over the past more than a decade, the drug and medical device evaluation and approval system has been continuously optimized. It has established and improved systems for registration, inspection, and adverse reaction monitoring of biopharmaceuticals and medical devices in alignment with international standards. Standardized mass-produced microbial pharmaceuticals, such as single-strain probiotic preparations, can smoothly follow the pharmaceutical registration pathway. However, a large number of difficult-to-standardize and highly personalized cutting-edge microbial technologies have long been trapped in a regulatory gray area. New microbial therapeutic technologies, including engineered bacteriophages, custom-synthesized microbial consortia, and gene-modified functional bacteria, do not fully align with the traditional definition of drugs and are not within the scope of conventional medical devices. Healthcare institutions, research and development enterprises, and scientific research institutes all lack clear compliant pathways. Many clinical needs can only rely on exploratory research, with ethical considerations, charging standards, and risk management lacking national-level unified regulatory support. Although IMT has been clinically applied for more than a decade with clear therapeutic efficacy, there is no unified top-level administrative regulation nationwide. The implementation standards of local Health and Wellness Commissions vary, leading to inconsistencies in charging codes, medical insurance coverage, and donor screening criteria, which has hindered the large-scale development of the industry.

Against this industry background, on September 12, 2025, the 68th session of the State Council Standing Committee deliberated and adopted the Regulations on Clinical Research and Clinical Translation and Application of New Biomedical Technologies (Order No. 818). The regulations were promulgated on September 28, 2025, and will be fully implemented on May 1, 2026. Microbial therapy as a new technology is listed alongside gene, cell, tissue and organ, and brain-

computer interface as five major regulatory categories. It precisely delineates three sub-technologies: oncolytic microorganisms, bacteriophages, and microbiota transplantation. Concurrently, it explicitly states that conventional IMT is exempt from Regulation 818 oversight and is incorporated into routine clinical treatment technology management, thereby forming highly characteristic tiered and categorized implementation details.

The institutional core of the Regulations is not to relax safety controls, but to abandon the global single pharmaceutical regulatory model. It is designed to address five unique industrial characteristics of microbial therapeutic strains: diversity, individual adaptability, donor heterogeneity, multiple administration routes, and mechanism of action dependent on host microbiota. The regulation establishes rules for broad filing, strict translation, and priority channels. During the clinical research phase, an institutional self-determination plus national online filing system is implemented to lower early exploration barriers, encouraging tertiary hospitals to collaborate with scientific research institutions in conducting small-sample mechanism validation and dose exploration. A dual-track regulatory system provides two compliant pathways: ① Microbial preparations that are mature, stable, and scalable continue to follow the National Medical Products Administration pharmaceutical registration route; ② Novel microbial technologies with strong personalization, no existing drugs of the same mechanism, and targeting rare diseases proceed through the biomedicine new technology conversion approval route. These two pathways complement each other in a staggered manner, do not conflict, and comprehensively cover the entire lifecycle of microbial innovation.

2. Top-level Architecture and Institutional Positioning of a Dual-track Regulatory Framework for Microbial Therapy

For microbial therapeutics, the dual-track classification system is guided by three core evaluation dimensions: capacity for standardized mass manufacturing, the degree of personalization, and the availability of alternative marketed products. Microbial preparations featuring fixed compositions, stable production workflows, scalable mass-production capacity, and applicability to large homogeneous patient cohorts-such as standardized lyophilized powders of single-strain medicinal probiotics - fall under the pharmaceutical supervision of the National Medical Products Administration and are required to complete registration clinical trials as live biotherapeutic products. By contrast, highly customized microbial intervention technologies that demand patient-tailored formulations, cannot adopt unified mass-production quality control standards, and lack marketed therapeutics or validated clinical pipelines with identical mechanisms of action are governed by the regulatory regime for emerging biomedical technologies. This top-tier institutional design effectively resolves structural flaws inherent to the traditional single-track pharmaceutical supervision model. Standardized mass-produced agents rely on the pharmaceutical regulatory system to guarantee consistent nationwide quality, batch-to-batch uniformity, and sustainable large-scale supply. Highly personalized innovative technologies, however, are managed under the emerging technology framework to accommodate small-cohort precision medicine, flexibly iterative treatment protocols, and one-on-one clinician-patient matching models.

Ethical review and informed consent procedures constitute cornerstones for compliant deployment of personalized microbiota transplantation under the dual-track regime. Regulators must build a tiered, holistic, and stringent review and patient disclosure framework that aligns with dual-track logic, while reconciling patient rights, donor privacy, and standardized translational research practices. Unlike standardized microbial pharmaceuticals, individualized IMT exhibits distinct traits, including pronounced inter-individual variation and poorly characterized long-term biological outcomes. Accordingly, informed consent protocols must go beyond routine medical disclosure. Patients must be fully notified of unresolved risks stemming from persistent gut microbial colonization, adaptive strain mutations, and horizontal gene transfer among commensal bacteria. Clinicians are also obligated to elaborate on potential adverse outcomes, including permanent disruption of intestinal microecological balance, dissemination of antibiotic resistance genes, and unforeseen metabolic perturbations. This thorough disclosure ensures patients possess comprehensive information to exercise autonomous medical decision-making and eliminates involuntary treatment scenarios. Notably, even for routine clinical IMT that obtains exemption from Regulation No. 818, hospital-level ethical governance shall still be strictly enforced.

Standardized informed consent, donor data anonymization, and full-life-cycle sample traceability are mandatory according to medical-institution clinical technical management specifications, which cannot be omitted because of regulatory exemption.

Simultaneously, rigorous ethical safeguards for stool donors and a robust confidentiality system for fecal biological samples must be fully enforced. Full anonymization of donor personal data is mandated across all workflows, alongside standardized protocols for specimen collection, storage, and end-to-end traceability. Regulators shall also delineate clear ownership boundaries for biological materials, draw a firm distinction between clinical therapeutic use and research/commercial translational applications, and clarify intellectual property ownership of discoveries derived from donor samples. Ethical review panels shall prioritize auditing risk-benefit evaluations, the completeness of informed consent documentation, and specimen traceability workflows. All personalized microbiota transplantation projects demand full lifecycle traceability, structured long-term patient follow-up, and dynamic surveillance of delayed safety risks. These measures address existing ethical governance gaps in individualized microbial therapy and achieve integrated governance of clinical efficacy, safety control, and stakeholder rights protection.

3. Precise Definition and Exemption Rules for Microbial Therapy Technologies

Providing rigorous definitions for three categories of microbial new technologies included in Regulation 818, while establishing differentiated exemption clauses, serves as the core operational basis for the implementation of the entire regulatory system. New technologies for oncolytic microbial therapy and phage therapy are subject to regulation under Regulation 818. For the third category of microbiota transplantation technologies, which involve the transplantation of uncultured composite functional microbiota, isolated single strains, or artificially proportioned mixed microbiota (which may be genetically modified or unmodified) administered via oral, endoscopic, vaginal, enema, or other routes to reshape the human microbiome, pure healthy donor fecal original microbiota and basic IMT without deep processing are explicitly exempt from the Regulations and are not included in the scope of new technology regulation. For boundary clarification: “basic unprocessed IMT” for exemption refers to fecal material derived directly from healthy donors, processed and prepared inside medical institutions for single-patient clinical use. Stool-bank-manufactured frozen microbiota suspensions, microbial capsules, and washed microbiota preparations shall be judged case-by-case: simple physical separation, concentration, cryoprotectant addition and freezing inside hospitals for single-patient use still fall into the exempted scope; while products for cross-hospital large-scale distribution, commercial batch production or artificial multi-component recombination shall be categorized as new biomedical technologies subject to Regulation No.818 supervision. At present, this boundary judgment follows logical deduction based on regulatory text; further official regulatory interpretation documents are expected for clearer implementation guidance.

IMT exemptions represent a distinctive institutional design in China's regulatory framework, backed by substantial practical experience and legal rationale. There are three primary reasons for this: ① IMT has been clinically applied in China for over a decade, accumulating clinical data from tens of thousands of cases involving recurrent Clostridium difficile infection, inflammatory bowel disease, graft-versus-host disease, etc. Their safety and efficacy have been long-term real-world validated (4-7). It should be emphasized that real-world long-term follow-up cohort data in China remain limited at present. The incidence of horizontal gene transfer, the long-term metabolic disturbance risk for recipients, and potential microbiota-related impacts on recipients’ offspring have not been fully clarified. Real-world monitoring for exempted routine IMT still needs to be strengthened to fill these evidence gaps. ② China's National Health Commission has long included basic fecal microbiota transplantation in the 'National Technical Specifications for Medical Service Items', which is a mature and routine clinical treatment technology. Currently, 18 provinces and municipalities across the country have implemented charging codes for medical institutions, and they possess a complete system for in-hospital quality control, donor screening, and operational standards. ③ The core variables of basic IMT are only healthy donor fecal microbiota, without high-risk operations such as gene editing or artificial engineering modification. The risk level is significantly lower than that of engineered bacteria, customized bacteriophages, and gene-modified synthetic microbiota, and thus does not require strict approval processes for cutting-edge high-risk new technologies. Exemption does not equate to

abandonment of regulation. Basic IMT remains subject to constraints from the Clinical Technical Management Measures for Medical Institutions and core medical quality and safety systems. Regular intra-hospital quality control inspections are conducted, establishing a gradient risk management model characterized by lenient intra-hospital management for mature routine techniques and strict new technology approval for high-risk innovative microbiological techniques. In contrast, genetically modified microbiota transplantation, artificial multi-strain microbiota formulations, and vaginal customized microbiota transplantation do not fall within the scope of original fecal microbiota. They must complete the entire process of filing and transformation approval in accordance with Regulation 818, and strictly implement risk classification control.

4. An urgent need for a dedicated priority review and approval channel for microbial technology

The Regulations establish a breakthrough priority review pathway, assigning top priority to two categories of microbiological therapeutics: ① those used for treating life-threatening diseases for which there are no effective clinical treatments currently available; ② Technical solutions urgently needed for public health emergency prevention and control, such as rapid review directly applicable to scenarios involving multidrug-resistant bacterial outbreaks, severe infections, and secondary microbial dysbiosis from major infectious diseases. Multidrug-resistant bacteria have no new antibiotics available, and customized bacteriophage therapy is recognized as a core life-saving intervention. Priority pathways directly open the gate for accelerated translation of bacteriophage pipelines targeting drug-resistant bacterial infections. Similarly, IMT is also an important means for the prevention and control of drug-resistant bacterial infections, particularly those related to hematopoietic stem cell transplantation (8-10).

5. Existing Implementation Challenges and Optimization Pathways of the Regulatory System

After the current regulatory system is implemented, it will establish specialized microbial technology guidelines and quality control standards for the field of microbiota transplantation technology. Regulation 818, together with top-level defining guidelines, establishes a macro framework. However, detailed technical guidelines for strain identification, toxicological evaluation, in-house preparation quality control, clinical endpoint design, long-term colonization monitoring, and risk assessment of antibiotic resistance genes for the three categories of new microbiota technologies have not been fully issued. Therefore, there is an urgent need to propose a comprehensive set of guiding principles for microbiota transplantation technology. Microbial live interventions differ from small-molecule chemical drugs, as they pose long-term unknown risks such as prolonged in vivo colonization lasting 5-10 years or even a lifetime, horizontal gene transfer among the microbiota, and impacts on the host's offspring microbiome. The Regulations require renewal reviews based on long-term real-world data. However, China's unified microbial new technology follow-up database and long-term adverse reaction tracking platform are still in the initial construction phase. The accumulation of large-sample long-term safety data takes an extremely long time. Therefore, establishing a benefit-risk assessment model for small-sample real-world scenarios presents a challenge in review technology. The following recommendations are proposed: optimize and improve the implementation path in the medium-to-long term, iteratively release comprehensive operation guidelines for microbial sub-technical areas in phases, construct a graded quality control standard library, implement specialized review for core technologies of synthetic microbiota transplantation, establish separate first-level highest risk management regulations for gene-modified high-risk microorganisms, set up a national standard reference strain library for microorganisms and unified donor health screening criteria, standardize evaluation benchmarks across all third-party assessment institutions nationwide to eliminate discrepancies in evaluation scales; simultaneously cultivate at least three national-level third-party technical verification and ethical assessment institutions with specialized microbial qualifications, expand professional review talent reserves, and establish a targeted training system for microbial regulation within the healthcare and wellness sector.

6. Summary

Under the new dual-track governance pattern, microbiota transplantation technology can be managed and developed efficiently and effectively. In the future, efforts will be made to build a national

unified big data platform for long-term real-world monitoring of microbial therapy and to innovate small-sample risk assessment models. This is also an expert-proposed developmental suggestion instead of existing regulatory mandate: establish a national-level follow-up database and require real-time upload of data for each microbiota transplantation patient. Record stratified follow-up microbiota sequencing results, treatment outcomes, and safety adverse events. Additionally, it is necessary to cultivate an innovative ecosystem for the microbiome therapy industry across the entire chain. Concurrently, support the industrial chains of microbiome detection and sequencing, as well as strain cultivation equipment, to reduce laboratory hardware procurement costs and build an independently controllable full-chain supporting capability. In the future, as the list is dynamically updated, supporting details are continuously improved, microbiota transplantation technology will emerge as a track for differentiated competitive advantages in biopharmaceuticals, offering millions of patients with refractory diseases to conventional drugs new therapeutic options for life.

Declarations

1. ***Consent to publication***
   We declare that all authors agreed to publish the manuscript in this journal based on the signed Copyright Transfer Agreement and followed publication ethics.
2. ***Ethical approval and consent of participants***
   Not applicable.
3. ***Disclosure of conflict of interests***
   We declare that no conflict of interest exists in this work.
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5. ***Availability of data and material***
   We declare that the data supporting the results reported in the article are available in the published article and from the corresponding author upon reasonable request.
6. ***Authors' Contributions***
   All authors reviewed and approved the final version of the manuscript.
7. **Acknowledgement**
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8. ***Authors' biography***
   None.

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