npj | biofilms and microbiomes

Review

Published in partnership with Nanyang Technological University

https://doi.org/10.1038/s41522-025-00683-0

The regulatory framework for microbiome-based therapies: insights into European regulatory developments

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The emergence of a broad spectrum of microbiome-based therapies has triggered changes in European regulatory frameworks. The first part of the review describes these innovative therapies. The second part provides an overview of the current framework and key changes introduced by the Regulation on substances of human origin (SoHO) for the development of microbiome-based therapies, highlighting the need of microbiome regulatory science to unlock the full potential of microbiome-based therapies.

Recent scientific advances have revealed the central role of the human microbiome (a complex community of microorganisms living in and on the human body) in maintaining human health, influencing disease development and progression, and even offering new therapeutic avenues[1]. These discoveries have brought the microbiome into the spotlight as a fertile ground for biotechnology and pharmaceutical innovation. Microbiome-based products represent a wide range of products, from food to medicinal products, including food supplements, foods for special medical purposes, cosmetics or medical devices. The different regulatory statuses of these microbiome-based products are governed by different legislative texts (Table 1). These regulatory frameworks are crucial for developers, prescribers and consumers, as the regulatory status of a product specifies the restrictions, standards and requirements to reach the market. A single substance (including micro-organisms) can be developed and marketed under different regulatory statuses, depending on the envisaged type of finished product, the target effect or targeted population. Microbiome-based products are no exception to that rule.

The *intended use* of a finished product, regardless of the substance it contains, is a key determinant of the product's regulatory status. The FDA defines the concept of "*intended use*" as "*the objective intent of the persons legally responsible for the labelling of an article […]. The intent may be shown by such persons' expressions, the design or composition of the article, or by the circumstances surrounding the distribution of the article […]. This objective intent may, for example, be shown by labelling claims, advertising matter, or oral or written statements by such persons or their representatives*"[2].

Products intended for the prevention or treatment of disease are to be registered as medicinal/drug products (see definition for Medicinal Products in Table 1). The FDA specifies that a product's intended use(s) is of high importance, because it can affect how the product will be regulated: it can make the product a drug, or not, regardless of its ingredients and whether or not it is considered a drug[3].

A drug candidate's quality, safety and efficacy within the intended population is assessed by drug competent authorities. In the European Union (EU) there is complementarity between two European bodies: (1) The European Directorate for the Quality of Medicines (EDQM), elaborating binding standards for controlling the quality of pharmaceutical ingredients and drugs and (2) The European Medicines Agency (EMA), supplemented by national drug authorities, who are competent in terms of risk/benefit assessment. In the US, the respective equivalents are the US Pharmacopeia (USP) and the US Food and Drug Administration (FDA).

This review will focus on the development of microbiome-based therapies (MbT), including microbiota transplantations (MT) and microbiome-based medicinal products (MMPs). Indeed, these therapies are now increasingly being investigated or recognized as prophylactic and therapeutic approaches for diseases where traditional drugs fail or have severe side effects. The recent marketing approval of the first MMPs underscores this potential and marks a transformative shift in how we approach treatment and prevention. In November 2022, Rebyota™ (a liquid mix of trillions of live microbes sourced from the stool of qualified human donors) became the first MMP approved by the FDA for the prevention of recurrent *Clostridioides difficile* infections (rCDI)[4]. This first approval was followed by the approval of oral capsules intended to be used for rCDI: VOWST®[5]. Other MMPs are currently under clinical evaluation (a non-exhaustive list is provided in Table 2). To date, only MMPs intended to be used for rCDI have received marketing authorisation.

As MbTs gain traction, the regulatory landscape is evolving to address the unique challenges and opportunities they present. Current regulatory frameworks are not fully adapted to the assessment of safety, efficacy, and quality of these new types of therapies as it is the case for all innovative products. This discrepancy has catalysed the emergence of 'regulatory science', a field dedicated to developing new tools, standards and methodologies for the evaluation and approval of innovative regulated products[6,7].

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Table 1 | List of the different regulatory status applying to microbiome-based products with their respective definitions and legislative acts

Type of products	*Definition*	*Legislative Act*
Medicinal product	'Medicinal product' refers to (a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.	EU Directive 2004/27/EC amending Directive 2001/83/EC *Texts currently in revision*
Medical device	'Medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: — diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, — diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability, — investigation, replacement or modification of the anatomy or of a physiological or pathological process or state, — providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.	EU Regulation 2017/745
Food (or foodstuff)	'Food' (or 'foodstuff') means any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans.	Regulation EC 178/2002 (General food law regulation)
Food supplements	'Food supplements' means foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities.	EU Directive 2002/46/EC
Food for special medical purposes (FSMP)	'Food for special medical purposes' means food specially processed or formulated and intended for the dietary management of patients, including infants, to be used under medical supervision; it is intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolise or excrete ordinary food or certain nutrients contained therein, or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved by modification of the normal diet alone.	Regulation (EU) 609/2013
Cosmetic product	'Cosmetic product' means any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours.	EU regulation 1223/2009/EC

Microbiome-based products represent a large range of products from food products to medicinal products including food supplements, foods for special medical purposes, cosmetics and medical devices. Table 1 provides the definitions of these different products, with the corresponding EU legislative texts (Directives or Regulations).

According to the EMA definition, regulatory science refers to the range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout the lifecycle of a medicine. It encompasses basic and applied biomedical and social sciences and contributes to the development of regulatory standards and tools[8]. Regulatory bodies, such as the FDA and the EMA, are actively working to refine and adapt guidelines that address innovations, while promoting a balance between ensuring patient safety and fostering scientific progress and innovation.

In the first part of this review, we will be presenting an overview of the large spectrum of MbTs currently under development or recently placed on the market. We will then summarise the current changes in the European regulatory landscape, in response to these new therapies, and discuss future regulatory challenges that still need to be addressed to facilitate the development and approval of future MbTs. By examining these aspects, we aim to provide a comprehensive understanding of the opportunities and hurdles in this rapidly evolving field.

The spectrum of microbiome-based therapies

Microbiome-based therapies represent a large and diverse range of innovations that can be viewed as a continuum from MT, rationally-designed microbial ecosystems (co-culture of various strain for their synergistic activities), all the way to live biotherapeutic products (LBPs – Single strains or mixtures of multiple strains grown separately and are then blended in the appropriate amounts), non-living biotherapeutic products or phage therapies (Fig. 1). It is important to insist that considerable overlap can exist between area of the MbT continuum and therefore each product on the continuum should be assessed based on its specific characteristics and intended use.

Depending on the type of therapies, the donor/origin of the microbiome sample, used to produce the therapeutic end product, can have a greater or lesser importance in the risk-benefit balance. For therapies such as MT, the donor/origin of the microbiome sample will have a major importance in the determination of the benefit/risk ratio, as these therapies are only partly characterized and controlled. Indeed, there is currently, no analytical method able to fully characterize these complex microbiome samples. However, for therapies with a higher degree of characterization and control (e.g., a single bacterial strain), the impact of donor/origin of the microbiome sample on the benefit/risk ratio will decrease. When specific microorganisms are isolated from humans or from other microbiome samples, such as food or environmental samples, the impact of the donor/origin of the microorganism(s) might become less important in terms of risk, because of the required level of characterization and the reduced complexity of the product. The microorganisms' origin, however, must always be documented, as clarified in the FDA guidance[9,10].

Microbiota transplantation

Microbiota transplantation can pragmatically be defined as "*the transfer of biologic material containing a minimally manipulated community of microorganisms from a human donor to a human recipient (including autologous use), with the intent to beneficially affect the microbiota of the recipient*"[11]. However, there is no consensus on a scientific or legal definition

https://doi.org/10.1038/s41522-025-00683-0

Table 2 | Examples of microbiome-based therapies (non-genetically modified) at clinical stage (current or more recent phase)

	Delivery	*Product*	*Indication*	*Primary outcome*	*Current phase*	*Study status*	*Clinical trial ID*	*Reference Pubmed ID (when available)*
Products derived from donor feces	Oral capsule	Seres Therapeutics, SER-109 (VOWST®)	Reduction of Recurrence of *Clostridioides difficile* Infection (CDI)	Superiority of SER-109 as compared with placebo in reducing the risk of CDI recurrence up to 8 weeks after dosing.	III	Completed studies	NCT03183128	*Feuerstadt et al.N Engl J Med. 2022* PMID: 35045228
	Liquid suspension (enema, colonoscopy or upper GI administration)	Biomebank, Biomictra	Recurrent *Clostridioides difficile* infection (CDI)		*Not available*			
	Enema	Rebiotix, RBX2660 (Rebyota®)	Preventing recurrent episodes of *Clostridioides difficile* Infection (CDI)	Absence of CDI diarrhea for 8 weeks after study treatment.	III	Completed studies	NCT03244644	*Khanna et al. Drugs. 2022* PMID: 36287379
	Oral capsule	Finch, CP-101	Prevention of Recurrent *Clostridioides difficile* Infection (CDI)	CDI recurrence through 8 weeks.	III	Terminated study	NCT05153499	
	Enema	MaatPharma, MaaT013	Steroid Refractory Graft Versus Host Disease (GvHD)	Overall response rate of gastrointestinal-acuteGvHD at Day 28.	III	On-going study	NCT04769895	
	Oral capsule	MaatPharma, MaaT033	Hematological malignant patients under intensive chemotherapy	Evaluation of safety and tolerability of MaaT033 in patients with hematologic malignancies up to 10 weeks.	Ib	Completed study	NCT04150393	
	Oral capsule	MaatPharma, MaaT033	Prevention of allogeneic Hematopoietic Cell Transplantation (HCT) complications	Comparison of the efficacy of Maat033 with its placebo on overall survival at 12 months after alloHCT.	IIb	On-going study	NCT05762211	
Products derived from donor cervico-vaginal secretions	Vaginal administration	Freya Biosciences, FB101	Vaginal dysbiosis	Changes in relative abundance of vaginal lactobacilli species.	I	Completed	NCT05850078	
Rationally-designed bacterial consortium	Oral treatment	MRM Health, MH002	Ulcerative colitis	Safety and tolerability of MH002 in subjects with mild to moderate ulcerative colitis.	IIa	Completed study	EudraCT Number: 2020-004355-33	
Multiple strains LBP	Oral capsule	Biomica, BMC 128 in combination with nivolumab (immunotherapy)	Non-small Cell Lung Cancer, Melanoma or Renal Cell Carcinoma	Safety and tolerability assessments (through study completion, an average of 1 year)	I	On-going study	NCT05354102	
	Oral capsule	Vedenta, VE-303	Prevention of Recurrent *Clostridioides difficile* Infection	Percentage of participants with toxin-positive, laboratory-confirmed, or clinically diagnosed and treated CDI recurrence before or at Week 8 (i.e., 8 weeks after the first dose of study treatment).	II	Completed studies	NCT03788434	*Louie et al. JAMA. 2023* PMID: 37060545

Table 2 (continued) | Examples of microbiome-based therapies (non-genetically modified) at clinical stage (current or more recent phase)

Delivery	Product	Indication	Primary outcome	Current phase	Study status	Clinical trial ID	Reference Pubmed ID (when available)
Oral capsule	Vedenta, VE-303	Prevention of Recurrent *Clostridioides difficile* Infection	Proportion of participants with laboratory-confirmed CDI recurrence before or at Week 8.	III	On-going study	NCT06237452	
Oral capsule	Vedenta, VE-202	Mild-to-Moderate Ulcerative Colitis	Proportion of participants with endoscopic response on flexible sigmoidoscopy after 8 weeks of treatment with VE202 or placebo.	II	On-going study	NCT05370885	
Oral administration	Vedenta, VE-416	Food allergy	Number of participants with treatment-related adverse events (Phase I) The geometric mean of the maximum tolerated dose of peanut protein at DBPCFC (Double-blind, placebo-controlled food challenge - Phase II)	I/II	On-going study	NCT03936998	
Oral administration	Vedenta, VE-800 in combination with nivolumab (immunotherapy)	Advanced or Metastatic Cancer	Safety and tolerability of VE800 in combination with nivolumab: Number of Participants with Adverse Events from the first dose to the last dose (up to 56.7 weeks), plus 100 days of post-treatment follow-up.	I/II	Completed study	NCT04208958	
Oral administration	Seres Therapeutics, Ser-401 in combination with nivolumab (immunotherapy)	Cancer	Percentage of patients with adverse events up to 2 years	Ib	Completed study	NCT03817125	*Glitza et al. Cancer Discov. 2024* PMID: 38588588
Oral administration	Seres Therapeutics, Ser-155	Reduction of the risk of infection and Graft vs. Host Disease (GvHD) in Adults Undergoing Hematopoietic Stem Cell Transplantation (HSCT)	Safety and tolerability of SER-155, including incidence and severity of adverse events, serious adverse events, or adverse events of special interest (Day 100)	Ib	On-going study	NCT04995653	
Oral capsule	NuBiyota, MET-2	Recurrent *Clostridioides difficile* Infection (CDI)	Clinical resolution of diarrhea with no CDI relapse at 30 days following the last dose of MET-2.	I	Completed	NCT02865616	*Kao et al. Lancet Gastroenterol Hepatol. 2021* PMID: 33631102
Oral capsule	NuBiyota, MET-4 in combination with immunotherapy	Cancer	Cumulative relative abundance of immunotherapy-responsiveness associated species at day 12 of MET-4	III	On-going study	NCT03686202	

Table 2 (continued) | Examples of microbiome-based therapies (non-genetically modified) at clinical stage (current or more recent phase)

	Delivery	*Product*	*Indication*	*Primary outcome*	*Current phase*	*Study status*	*Clinical trial ID*	*Reference Pubmed ID (when available)*
	Mucoadhesive vaginal pills	LC106 and LC115 (*Lactobacillus crispatus*)	Prevention of recurrent bacterial vaginosis	Detection of any one strain from the LBP at 5% relative abundance or greater, or any combination of strains at 10% relative abundance or greater using shotgun metagenomic sequencing over 5 weeks.	I	On-going study	NCT06135974	
	Vaginal capsule	Freya Biosciences, FB301	Women infertility	Safety, tolerability of single and multiple dosing; change in vaginal microbiome.	I	On-going Study	EudraCT Number: 2024-517539-38	
Single strain LBP	Oral suspension	Infant Bacterial Therapeutics (IBT) IBP-9414 (*Limosilactobacillus reuteri*)	Prevention of Necrotizing Enterocolitis	Confirmed necrotizing enterocolitis (NEC) and time to sustained feeding tolerance from the first dose until the infant reaches 34 weeks + 6 days post-menstrual age.	III	On-going study	NCT03978000	
	Oral capsule	OxThera, Oxabact® OC5 (*Oxalobacter formigenes*)	Primary Hyperoxaluria	Change from baseline in plasma oxalate concentration after 52 weeks of treatment.	III	Completed study, Primary endpoint was nearly achieved ($p = 0.06$)[a]	NCT03116685	
	Oral capsule	4D Pharma, Blautix (*Blautia hydrogenotrophica*)	Irritable bowel syndrome (IBS)	Percentage of participants with overall response (from baseline up to week 8).	II	Completed study, Significant increase in overall response at week 8 (24.1% in active group versus 17.5% in placebo)[b]	NCT03721107	
	Oral liquid	Destiny Pharma, NTCD-M3[c] (Non-toxigenic *C. difficile* M3 strain)	Prevention of recurrence of *C. difficile* infection	Number of participants with treatment-emergent adverse events and serious adverse events from baseline up to 7 days after the last dose of study drug (up to Week 3).	II	Completed study, Significant reduction in recurrence of *C. difficile* infection compared to placebo (5% in optimal dose regimen v 30% in placebo group)	NCT01259726	*Gerding et al. JAMA. 2015* PMID: 25942722
	Oral capsule	Biogaia Pharma, BGP345A (*Lactobacillus gasseri*)	Constipation due to opioid-based medications	Change in the average weekly number of spontaneous bowel movements (expressed in number of stools/week) over the 4 week treatment period.	II	On-going study	NCT05133076	
	Oral capsule	Biogaia Pharma, BGP-014 (*Limosilactobacillus reuteri*)	Ulcerative colitis	Safety and tolerability of BGP-014 up to 10 weeks.	I/II	On-going study	NCT05118919	
	Oral capsule	4D Pharma, MRx0518 in combination with pembrolizumab (*Enterococcus gallinarum*)	Solid tumors	Safety and tolerability of MRx0518 in combination with pembrolizumab; preliminary evidence of anti-tumor activity. Time frame: baseline to treatment discontinuation up to a maximum of 35 treatment cycles (one cycle = 21 days)	I/II	Terminated study	NCT03637803	

Table 2 (continued) | Examples of microbiome-based therapies (non-genetically modified) at clinical stage (current or more recent phase)

Delivery	Product	Indication	Primary outcome	Current phase	Study status	Clinical trial ID	Reference Pubmed ID (when available)
Oral capsule	Ysopia, Xla1 (*Christensenella minuta*)	Obesity	To assess the safety and tolerability of Xla1 in healthy adult volunteers [part 1], and, subsequently, in overweight and class I obese adults [part 2].	I	Completed study, Significant reduction of LDL-cholesterol at week 16 [d]	NCT04663139	
Oral capsule	Genome & Company, GEN-001 in combination with avelumab (*Lactococcus lactis*)	Solid tumors	Incidence of adverse events (1 year), laboratory abnormalities (1 year) and dose-limiting toxicity (28 days). Objective response (OR) of GEN-001 in patients with advanced or metastatic solid tumors, when administered as combined with avelumab (2 years)	I	Completed study	NCT04601402	
Oral capsule	Adiso Therapeutics, ADS024® (*LPA3 agonist-producing Bacillus velezensis*)	Prevention of recurrence of *C. difficile* infection	Safety and tolerability of ART24 based on the percentage of subjects experiencing treatment-emergent adverse events. Safety and tolerability of ART24 based on the number of subjects observed with a change from baseline in clinical laboratory tests, vital signs, physical examination.	I	Completed study	NCT04891965	
Oral capsule	Exeliom Biosciences, EXL01 (*Faecalibacterium* prausnitzii)	Maintenance of steroid-induced clinical response/ remission in participants with mild to moderate Crohn's disease	Systemic and intestinal safety and tolerability of orally administered EXL01 up to 43 weeks.	I	On-going study	NCT05542355 EudraCT Number: 2021-003432-81	
Oral administration	Scioto Biosciences, SB-121, (*Limosilactobacillus reuteri* with Sephadex® and Maltose)	Autistic disorder	Adverse event of special interest and adverse events leading to discontinuation.	I	Completed study	NCT04944901	*Schmitt et al. Sci Rep. 2023* PMID: 36997569
Oral administration (sachet)	Osel, CBM588, in combination with nivolumab and ipilimumab (*Clostridium butyricum*)	Metastatic renal cell carcinoma	Change in Bifidobacterium composition of stool (from baseline up to week 12).	I	Completed study	NCT03829111	*Dizman et al. Nat Med. 2022* PMID: 35228755
Vaginal administration	Osel, Lactin-V (*Lactobacillus crispatus* CTV-05)	Pregnant women at high-risk of preterm birth	The number of participants that demonstrate a change in vaginal colonisation during and following LACTIN-V use (2-4 years).	I	Completed study	NCT03992534	*Bayar et al. Benef Microbes. 2023* PMID: 36815494
Oral capsule	MoonBiotech, MNC-168 (*Enterococcus strain MNC-168*)	Advanced Malignant Solid Tumors	Safety evaluated by The National Cancer Institute Common Terminology Criteria for Adverse Events.	I	Ongoing study	NCT05383703	

Table 2 (continued) | Examples of microbiome-based therapies (non-genetically modified) at clinical stage (current or more recent phase)

	Delivery	Product	Indication	Primary outcome	Current phase	Study status	Clinical trial ID	Reference Pubmed ID (when available)
	Oral capsule	Microba, MAP315	Ulcerative colitis	Safety, tolerability and pharmacokinetics of MAP 315 in 32 healthy adults.	I	Completed study	ACTRN12623000291684	
Non-living biotherapeutic products	Intradermal injection	Immodulon, IMM101 (heat killed *Mycobacterium obuense*) in combination with checkpoint inhibitor therapy	Advanced Melanoma	Incidence, frequency and severity of treatment emergent adverse events throughout the study.	II	Completed study	NCT03711188	
Phage therapy-based medicinal products	Oral liquid	Intralytic Inc, EcoActive	Level of intestinal Adherent Invasive *Escherichia coli* (AIEC) in patients with inactive Crohn's disease (CD)	Incidence of adverse events, severity of adverse events, effect on Harvey Bradshaw Index, effect on inflammation as indicated by C-reactive protein and fecal calprotectin (up to 6 months)	I/IIa	Ongoing study	NCT03808103	

Non-exhaustive list of microbiome-based medicinal products currently (Dec 2024) in clinical evaluation, or that completed their clinical evaluation and have already been approved. The type of products, their name, indication and mode of delivery are presented. The table also provides information about the phase of evaluation for the product, the most recent outcomes obtained, the clinical trial identifier and the reference if the results are published.
LBP Live Biotherapeutic Products, *IBS* Irritable Bowel Syndrome, *CDI Clostridium Difficile* Infection, *GvHD* Graft vs. Host Disease, *HSCT* Hematopoietic Stem Cell Transplantation, *LDL* Low Density Lipoproteins.
[a]Results released on OxThera's website (https://oxthera.com/clinical/, February 2022). [b]4D Pharma 2021 Annual Report. [c]Formerly known as VP20621. [d]Results released at Obesity Week 2021. [e]Formerly known as ART24.

of MT at the European Union (EU) level. The preparations (e.g. from faecal material) used during MT procedures, may be associated with a higher risk of pathogen transmission and with the risk of transferring a microbiome inducing potential long-term negative health outcomes for the recipient[12–14]. Even if most of the currently performed MTs are faecal or intestinal MTs, data showing the potential benefit of vaginal and skin MTs are arising in the literature[15,16].

Donor-derived microbiome-based medicinal products

Since (again) no official definition exist, these products could be referred to as "faecal microbiota-based medicinal products" or, more precisely, "*human intestinal microbiome whole-ecosystem-based medicinal products*" as proposed by a consortium of European based companies[17]. These products consist of whole or highly complex ecosystems, for which the starting materials are human microbiome samples and which differ from MT preparations as they are "*manipulated*" or "*industrially manufactured*"[9,17]. However, there remains a pressing need to clarify and harmonize the terminology for these products to ensure consistency and reduce confusion between the regulators, academia and industry[18].

To our best knowledge, whole ecosystems-based products currently only exist for intestinal microbiota-based products and vaginal microbiota-based products are currently in development and early clinical phase (Table 2). In the near future, the concept could potentially be extended to other microbiomes, such as the skin or lung microbiomes.

Donor-independent microbiome-based medicinal products

When increasing the level of manipulation and going towards the selection of specific strains and/or microbial functions, developers may move away from the "whole-ecosystem-based medicinal products" to enter another area of the MbT continuum, referred to within the Pharmabiotic Research Institute as "rationally designed ecosystem-based medicinal products".

"Rationally designed ecosystem-based medicinal products" are obtained by selecting microbial strains with the purpose to produce a desired ecosystem within the product. The objective is to shape a "controlled ecosystem" able to synthesize metabolites of interest and/or to re-establish targeted microbial functions, identified as desirable within the host. These products can contain dozens or, potentially in the future, even hundreds of different microbial strains, produced during a unique co-fermentation process (Table 2). In contrast to the "whole-ecosystem-based medicinal products", these "rationally designed ecosystem-based medicinal products" are produced from clonal cell banks and not directly from a human donor microbiome sample.

With increased manipulation levels of the microbiome sample, including the isolation of specific strain(s) and their preservative banking, the impact of the donor/origin of the microbiome sample on the benefit-risk ratio assessment is nearly completely eliminated. Nonetheless, the impact of the processes applied must still be considered, because, due to the complexity of the product, risks may arise from the lack of control of these early manipulations or from the (co-)fermentation steps as well as culture stabilization procedure. In conclusion, the production process, as a whole, needs to be validated (process qualification).

As the product is designed based on targeted functional characteristics of the ecosystem, characterization of the composing microbial strains must be thorough, including potency tests as well as critical quality attributes related to safety and efficacy. Appropriate levels of quality control and batch-to-batch consistency are crucial in order to obtain marketing authorization. Nevertheless, batch-to-batch consistency may remain a challenge due to the complexity of (co-)fermenting multiple strains and the different impacts that the downstream processing may have on the different microbial components of the product.

Another area of the MbT continuum consists of products produced from clonal cell banks via the fermentation of a single microorganism. These products are referred to as Live Biotherapeutic Products (LBPs). The origin of the isolated micro-organism can be broad, including, for example, the human, food, environmental or animal microbiomes. These products can

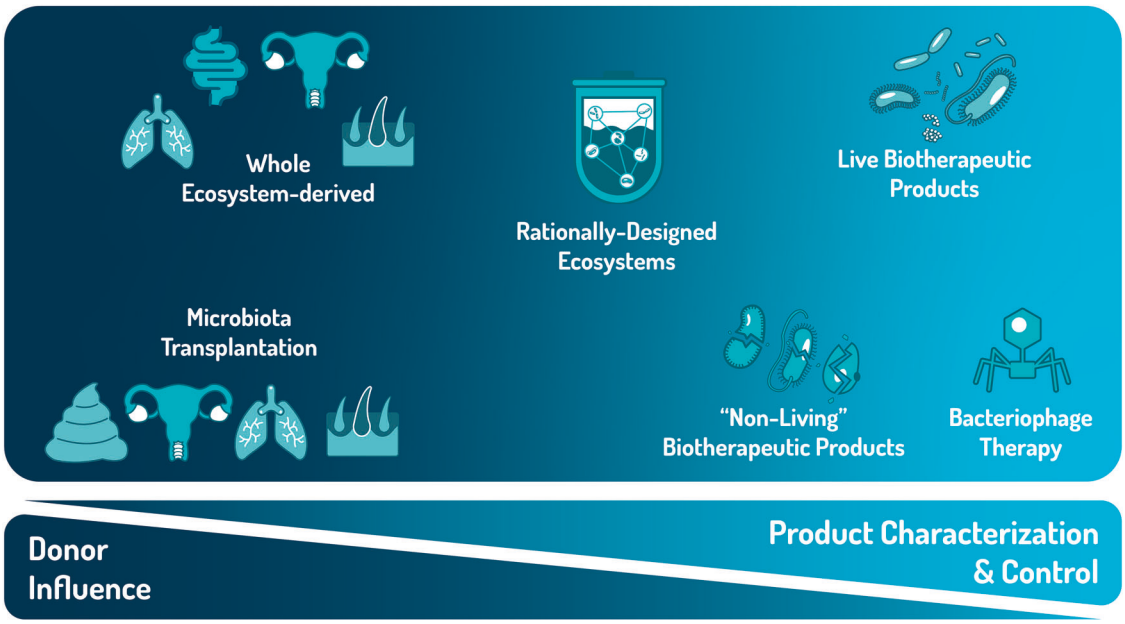

Fig. 1 | Microbiome-based therapies spectrum. Microbiome-based therapies represent a large and diverse range of innovations and can be viewed as a continuum, ranging from microbiota transplantation (on the left), whole ecosystem-based medicinal products, rationally-designed microbial ecosystems (co-culture of various strains for their synergistic activities) all the way to live biotherapeutic products (LBPs – Single strains or mixtures of multiple strains), non-living biotherapeutic products or phage therapies (on the right). For the therapies on the left of the spectrum such as microbiota transplantation and whole ecosystem-based medicinal products, the donor/origin of the microbiome sample has a major importance in the determination of the benefit/risk ratio as these therapies are only partly characterized and controlled. However, when moving to the right of the spectrum, the impact of donor/origin of the microbiome sample on the benefit/risk ratio decreases while the degree of characterization and control of the products themselves increases.

contain only one strain or a mixture of strains. In the latter case, it is important to note that, in the case of LBPs, the different strains are grown separately and then blended in the right amounts. These strains can be from the same origin or from different origins/ donors. The different strains are highly characterized through genotypic and phenotypic characterization and manufacturing process, dealing with the production from the drug substance (DS) all the way to the final drug product (DP), is subjected to very high levels of control. In this context, the donor/origin of the strain has a low impact on the benefit/risk ratio. However, information relating to strain isolation, banking and manufacturing become major parameters impacting this benefit-risk assessment.

From a regulatory perspective, LBPs are the only MMPs with a legal definition, both in Europe and the USA. In the USA, LBPs are defined by the guidance for industry on "Early clinical trials with live biotherapeutic products: chemistry, manufacturing and control information" as "*a biological product that: 1) contains live organisms, such as bacteria; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine*"[10]. In Europe, LBPs are defined by the European Pharmacopoeia general monograph 3053 as "*medicinal products containing live microorganisms (bacterial or yeasts) for human use*"[19]. This monograph mainly addresses quality requirements for LBPs administrated orally or vaginally. However, it is important to note that new products with other delivery routes are under development, such as products with topical administration or for systemic injection[20]. These products will create new regulatory challenges regarding their manufacturing process controls and quality assessment, but also for safety and efficacy demonstration. A roadmap for safety assessment of LBPs has already been proposed, highlighting the importance of science-driven benefit/risk analysis to demonstrate a positive benefit/risk ratio within a specific intended use and target population[9].

In addition to the products containing live microorganisms, medicinal products containing microorganisms which are intentionally rendered 'non-living', are also emerging in the spectrum of MbT[21]. Within the Pharmabiotic Research Institute, we referred to these products as "Non-living biotherapeutic products". These products are associated with regulatory challenges linked to the characterization of the product, the enumeration of the "non-living cells" in the final drug product, as well as the safety assessment related to the presence or not of remaining living cells. This means that the inactivation step should be an integrated part of the production process. Relevant key parameters and controls have to be defined and confirmation of the "non-living" state of the cells should be provided. Importantly, the "non-living" state of these microorganisms does not guarantee the safety of these products. In addition, Qualified Presumption of Safety (QPS) or Generally Recognized As Safe (GRAS) status of the progenitor microorganisms is not sufficient to demonstrate the safety of the non-living biotherapeutic end product, as GRAS or QPS designations are established for food products, in the context of the general population, an intended use which is very different from a medicinal product intended for a diseased or vulnerable population.

Phage therapy-based medicinal products (PTMPs) represent a rather particular type of medicinal product, based on bacteriophages, targeting and infecting specific bacterial micro-organisms. High specificity can be obtained through appropriate phage selection from environmental or human samples. PTMPs can be a way to safely modulate microbiomes[22]. Thanks to their specificity, PTMPs can be associated with a high level of safety. Therefore, it is essential that the ecological and functional role of the bacterial target that PTMPs will eliminate from the microbiome is well known. PTMPs are also developed to fight the increasing problem of antibiotic resistance[23,24]. Due to the specific isolation and characterization process, the influence of donor/origin is less significant in the risk analysis of PTMPs, while the long-term implications of microbiome modulation by phage therapy may require a more in-depth and long-term safety assessment. Other challenges in developing PTMPs may reside in the more "personalized" approach of this type of therapy, requiring a regulatory difficult case-by-case approach[25].

The diversity of MbT is striking, with a wide range of innovations emerging rapidly (Table 2). As is often the case, innovation tends to precede regulation, which leads to significant regulatory challenges when

considering breakthrough innovations such as microbiome science-based products. Once more products and innovations are in late-stage development and are becoming available, hence when regulators have been confronted with a diversity of products, this process finally results in the needed regulatory adaptation. These changes are currently reshaping the EU regulatory landscape and are discussed in the following section.

The regulatory landscape for microbiome-based therapies

Regulatory framework for microbiota transplantations

Current regulatory framework. In the USA, the result of a stool preparation procedure, suitable for faecal microbial transplantation (FMT), is designed as "*FMT product*". Being considered a biological product (drug product), all FMT products require an investigational new drug (IND) application and are consequently subject to FDA approval for clinical use in humans. There is an exception for the FMT used to treat *Clostridioides difficile* (*C. difficile*) infection not responsive to standard therapies, when the FMT product is not obtained from a stool bank and when the other conditions described in the FDA guidance (such as appropriate consent from the patient; screening and testing of the stool donor and stool sample) are met[26].

In Europe, the regulatory framework is substantially different. Currently, there is a clear lack of harmonization regarding the regulatory status of preparations administered during MTs. EU Member States have taken different positions as the regulatory status of any preparation is in the remit of the National Competent authorities. A recent report published by the Heads of Medicines Agencies shows that FMT can be regulated a) as a medicinal product or equivalent; b) as a therapeutic intervention; c) as a tissue and cell preparation or d) on a case-by-case basis[27]. The lack of regulatory harmonization is reinforced by the lack of clarity on the "FMT" terminology[18]. Many stakeholders use the term "FMT" (the procedure) to refer to "stool-derived preparations" (the preparation administered during the procedure), or, in analogy, use the term "VMT" to refer to "vaginal microbiota-derived preparations"[27]. There is a good chance that this lack of harmonization regarding the regulatory status of FMT will be solved by the new EU '*Regulation on standards of quality and safety for substances of human origin (SoHO) intended for human application*', as discussed in the next section.

Future regulatory framework. On 17 July 2024, the new EU SoHO regulation was published in the Official Journal of the EU (Regulation (EU) 2024/1938)[28]. The new Regulation came into force on 7 August 2024 and will apply from 7 August 2027, after a transition period of 3 years. This new Regulation will repeal the existing EU legislation on blood, tissues and cells (Directive 2002/98/EC on safety and quality of human blood and blood components and Directive 2004/23/EC on safety and quality of human tissues and cells)[29,30] and aims to improve harmonisation, ensuring a uniform level of protection for SoHO donors and SoHO recipients across the EU, while at the same time facilitating the cross-border exchange of- and access to- SoHO therapies. Indeed, the Regulation is expected to reduce the disparities in the implementation of the rules by different Members States for all types of SoHOs. In the microbiome field, this regulation will introduce a major change, as human microbiomes will fall under the scope of this new SoHO Regulation, whereas they are not expressly specified in tissues and cells legislation. Indeed, 'SoHO' is defined in the regulation as "*any substance collected from the human body, whether it contains cells or not and whether those cells are living or not, including SoHO preparations resulting from the processing of such substance*" and 'SoHO preparation' as "*a type of SoHO that: (a) has been subjected to processing and, where relevant, one or more other SoHO activities; (b) has a specific clinical indication; and (c) is intended for human application to a SoHO recipient or is intended for distribution*". Based on these definitions, it is clear that all microbiome samples collected from the human body will fall under the scope of this text.

This new SoHO regulation shall apply to: a) SoHO intended for human application (both in the context of clinical research and clinical practice) and SoHO used to manufacture products regulated by other European Union legislation (such as medicinal products or medical devices) and intended for human application; (b) SoHO donors, SoHO recipients and offspring from medically assisted reproduction; (c) SoHO activities that have a direct impact on the quality, safety or effectiveness of SoHO. The Regulation considers the following SoHO activities (Fig. 2): (i) SoHO donor registration; (ii) SoHO donor history review and medical examination; (iii) testing of SoHO donors; (iv) collection; (v) processing; (vi) quality control; (vii) storage; (viii) release; (ix) distribution; (x) import; (xi) export; (xii) human application and (xiii) clinical outcome registration.

In the context of the microbiome research, numerous actors are thus concerned by this new regulation, as they will need to be registered as "SoHO

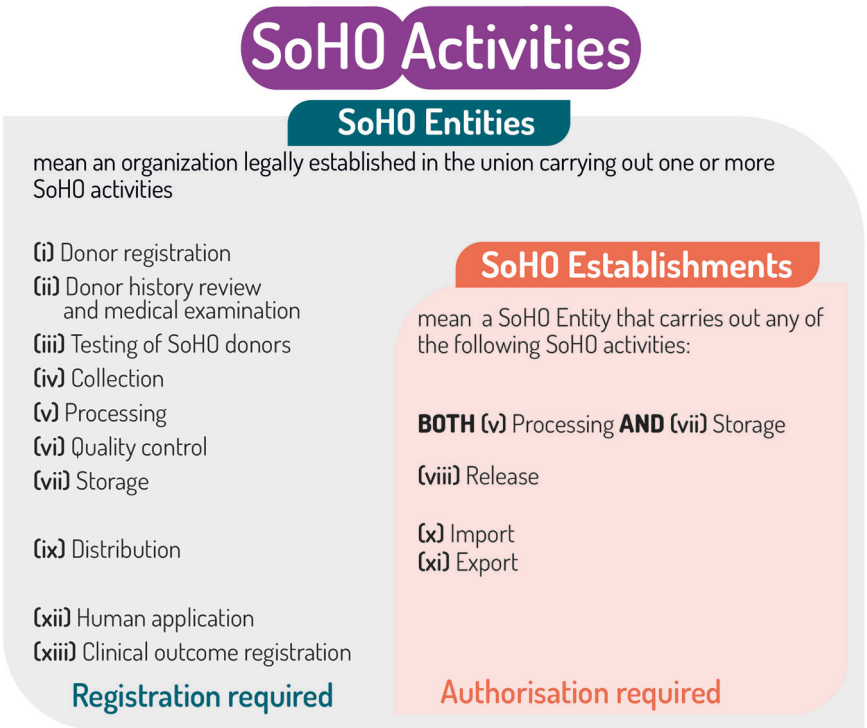

Fig. 2 | SoHO activities, SoHO entities and SoHO establishments as defined by the new EU SoHO Regulation (Regulation (EU) 2024/1938). The SoHO Regulation will apply to SoHO activities that have a direct impact on the quality, safety or effectiveness of SoHO. These SoHO activities are mentioned in Fig. 2. The SoHO Regulation defines a SoHO entity as an organization legally established in the European Union and carrying out one or more SoHO activities. These SoHO entities must be registered. However, some specific SoHO activities have to be carried out by a SoHO establishment, which will be authorised by the competent authority. Only registered SoHOs entities and authorised SoHO establishments will be permitted to carry out SoHO activities and release SoHO preparations.

entities". A SoHO entity means "*an organization legally established in the European Union, carrying out one or more SoHO activities*". In addition, some specific SoHO activities must be carried out by a SoHO establishment that has been authorized to do so by the Competent Authority (Fig. 2). One of the key implications of this new Regulation is that only registered SoHO entities and authorised SoHO establishments will be permitted to perform SoHO activities and to release SoHO preparations. However, for SoHO used exclusively in the context of in vitro or animal research, the only requirement set out in this Regulation is to comply with the standards concerning voluntary and unpaid donation, in order to ensure a consistently high level of protection for SoHO donors.

Another major implication of the new SoHO regulation is the requirement for formal approval by a SoHO competent authority of a SoHO preparation. For instance, authorisation will be required for a SoHO preparation intended to be used for MT. This authorisation will involve a review of all SoHO activities performed for that SoHO preparation and that might influence the quality, safety and effectiveness of that SoHO preparation. The assessment of a SoHO preparation will be carried out by SoHO competent authorities, based on all scientific evidence and clinical data regarding the expected benefit and risk provided by the applicant SoHO entity. If scientific evidence and clinical data is not sufficient, or if the risk is more than negligible, further clinical studies may be required. The extent of the clinical monitoring plan will depend on the level of risk.

Regulatory framework for medicinal products

In the EU, medicinal products for human use are governed by the Directive 2001/83/EC. This directive specifies that "*a biological medicinal product*" is "*a product, the active substance of which is a biological substance*". A biological substance is "*a substance that is produced by or extracted from a biological source and that needs, for its characterization and the determination of its quality, a combination of physico-chemical-biological testing, together with the production process and its control*". MMPs are biological medicinal products for which the active substances are microorganism(s) coming from microbiome samples (such as food, environmental or human microbiome samples) (Fig. 3).

Generally speaking, for all medicinal products using starting materials from human origin, there is an additional layer of legislation to consider. For example, this is notably the case for advanced-therapy medicinal products (ATMP) produced from human cells and tissues where regulatory interplay between the ATMP legislation and the tissues and cells legislation is clearly defined in Regulation 1394/2007 on ATMP. The new SoHO regulation will by 2027 harmonize practices in Europe by including human microbiomes in the broader concept of "substances of human origin" in its extended scope, and clearly envisages that SoHO (including the human microbiomes) can be collected for the purpose of manufacturing medical devices (regulated by Regulation (EU) 2017/745), medicinal products (regulated by Directive 2001/83/EC), advanced therapy medicinal products (regulated by Regulation (EC) No 1394/2007) or investigational medicinal products (regulated by Regulation (EU) No 536/2014). However, the interplay with the other regulatory frameworks is intentionally not specified in the SoHO regulation and will be laid out in the other regulatory frameworks. In this context, it is important to note that a revision of the EU general pharmaceutical legislation is also ongoing[31]. The proposal published by the European Commission (EC), after going through parliamentary process and final approval

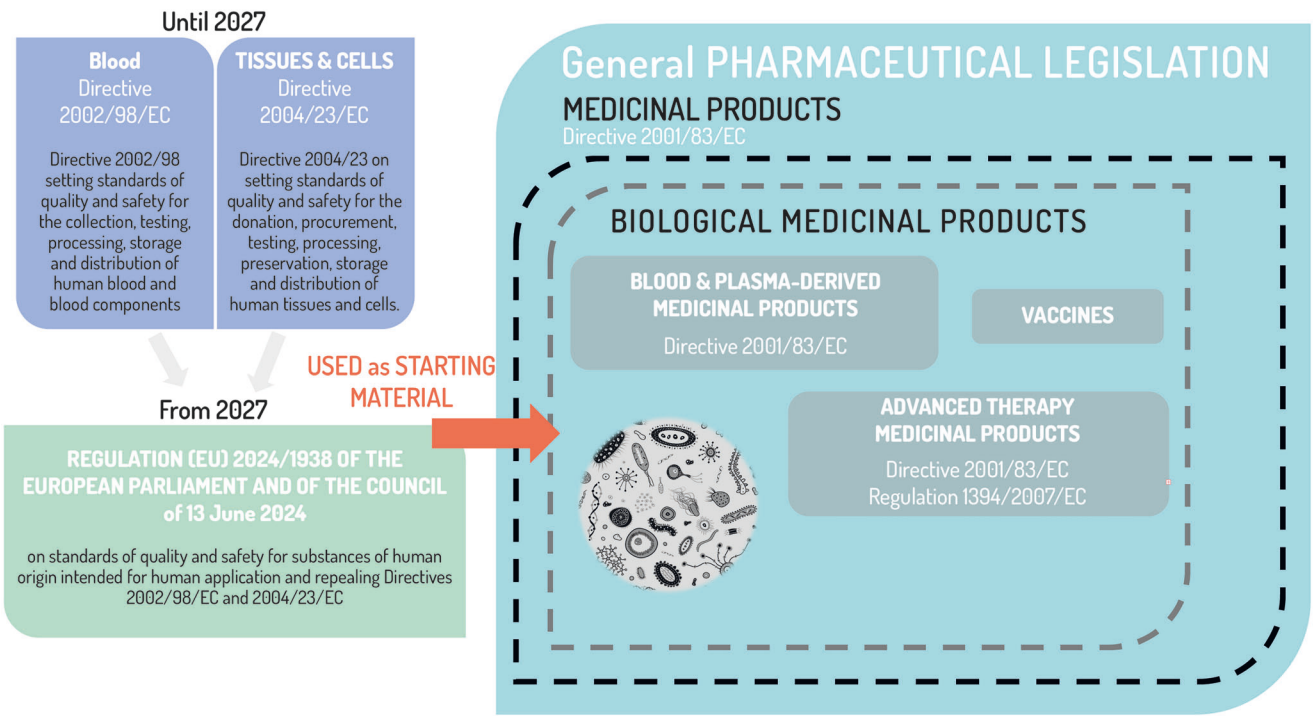

Fig. 3 | The current regulatory changes for microbiome-based therapies. In the European Union, medicinal products for human use are governed by the Directive 2001/83/EC. Biological medicinal products comprise several diverse product types, including blood and human plasma-derived medicinal products, immunological medicinal products (i.e. vaccines, toxins, serums and allergens) and Advanced therapy medicinal products (ATMPs). By their nature, microbiome-based medicinal products are considered as biological medicinal products but currently they do not have a "separate status" and are not referred to in any of the legislations. For some of these biological medicinal products, such as the blood and plasma-derived medicinal products, but also the ATMPs, the starting material can be tissues and cells from human origin. In this case, an additional piece of legislation is to be taken into account. For the EU, until August 2027, this additional piece of legislation consists of the blood directive (2002/98/EC) and the tissues and cells directive (2004/23/EC) (together designated as the BTC directives). In 2027, the regulation on standards of quality and safety for substances of human origin (SoHO) intended for human application (so called "SoHO Regulation") will replace the BTC directives. The SoHO Regulation includes human microbiomes within the scope of this regulation, meaning that human microbiomes used as starting material for the production of microbiome-based medicinal products will have to follow the standards and requirements set by this new SoHO Regulation, in addition to the one set by the pharmaceutical legislation.

by the European Parliament and the Council, will replace the existing EU pharmaceutical legislation (Directive 2001/83/EC). Among the main changes expected, are clarifications of some definitions, and proposals for new ones, such as "*SoHO-derived medicinal product other than ATMPs*". Thanks to this new definition proposal, the interplay between the pharmaceutical legislation and the SoHO regulation will probably be further clarified in the context of microbiome samples and MbTs.

Regarding the application of phages to humans, there are currently no phage-specific provisions in the EU legislation currently in force. So far, EMA has only stated that some principles introduced in the "Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections" can also be applied to phages[32]. The EC's proposal for a new Directive for medicinal products for human use also clearly addressed the question of "*phage-containing medicinal products*", considering it "*as a category of products which may in some instances require adapted rules to fully take account of their specific characteristics*"[31]. This is why "phage-containing medicinal products" (PTMPs) are currently the only medicinal products mentioned in Annex VII of the proposal, as an area in need for an adapted framework, covering products that will be subject to specific scientific or regulatory requirements, due to the characteristics or methods inherent to that medicinal product[31]. Other regulatory developments regarding PTMPs are also ongoing, with e.g. the publication by the European Pharmacopoeia of a draft chapter on "Phage therapy active substance and medicinal products for human and veterinary use"[33]. Finally, in December 2023, the EMA launched a process to prepare a guideline on the development and manufacture of human medicinal products specifically designed for phage therapy[34].

All these regulatory updates will need to be monitored by stakeholders wanting to develop and/or distribute microbiome-based therapies in Europe, ensuring their development plans reflect tomorrow's regulatory reality.

Conclusion

The regulatory landscape for microbiome-based therapies is currently evolving rapidly and significantly. This progress is marked by the recent approval in the US of some microbiome-based medicinal products intended to be used for rCDI. These approvals represent the formal recognition of the prophylactic and therapeutic potential of the human microbiome, through products derived from the human microbiome. In line with these developments, a new regulatory framework, the new SoHO regulation, including human microbiomes, is currently being implemented in the EU. In contrast, the regulatory framework for microbiome-based therapies in low- and middle-income countries (LMICs) is currently underdeveloped and varies significantly across regions. Many LMICs lack specific guidelines or policies addressing the development, approval, and oversight of these innovative treatments[35,36]. Microbiome stakeholders have to deal with a new, but rapidly evolving global market, and could gain great benefit in anticipating harmonization across countries/regions to avoid hampering the global development and patients access to MbT.

Despite this encouraging progress, there is still an urgent need for more robust regulatory science activities in the field. A number of challenges continue to impede the development and approval of microbiome-based therapies. These include the complexity of designing clinical studies targeting the human microbiome, dealing with numerous confounding factors that can affect the safety and efficacy of new MbT candidates. In addition, there is a lack of validated analytical methods that can accurately assess and characterize the composition and functionalities of the microbiome. This gap is not only critical to the discovery of new candidates and ensuring the safety and efficacy of these products but also represents a major limiting factor in the qualification of microbiome-based biomarkers, a tool for accelerating clinical studies and drug development[37]. The lack of validated analytical methods can also limit the development of IVD microbiome testing and, thus, the integration of microbiome data in clinical practice[38]. Another major challenge is the lack of consensus on key definitions. For example, there is currently a need to define what characterizes a "healthy" versus a "dysbiotic" microbiome[39]. The lack of a consensus definition makes it difficult to develop standardized guidelines and benchmarks for microbiome-related research and product development. The complexity of pharmacodynamic and pharmacokinetic assessments for microbiome-based therapies adds another layer of difficulty, as traditional models may not fully capture the dynamic interactions between the microbiome, host, and the therapeutic agents tested. Translating preclinical data into clinical settings also presents additional hurdles. Inter-individual variability in microbiome composition makes it difficult furthermore to predict clinical outcomes based on preclinical studies.

While the recent regulatory developments and product approvals are promising, continued efforts are needed to overcome the remaining challenges. Ongoing initiatives (such as IHMCSA, Human Microbiome Action project; or MMHP, Million Microbiome of Humans Project) are important steps towards achieving this goal, and their success will depend on continued collaboration and commitments from all stakeholders. Advancing regulatory science and fostering innovation in microbiome research are thus necessary steps to unlock the full potential of microbiome-based therapies and improve health outcomes for patients worldwide.

Data availability

No datasets were generated or analysed during the current study.

Received: 19 December 2024; Accepted: 15 March 2025;
Published online: 28 March 2025

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Author contributions

J.R., M.C.S., and C.D. drafted the first version of the manuscript. All authors revised and approved the final version of the manuscript.

Competing interests

J.R., M.C.S., and C.D. are employees of the Pharmabiotic Research Institute. B.P. is a board Member of the Pharmabiotic Research Institute. B.P. is an employee of Yakult Europe BV.

Additional information

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