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# Microbiome Medicinal Products: Concept to Commercial


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**A growing body of pre-clinical and clinical research has implicated the influence of bacteria on human health which over the last decade led to a flurry of venture capital and biopharma interest. The collection of non-human cells living within the gut, skin, and other tissues (collectively referred to as "microbiota" or the "microbiome") has a profound influence on maintaining normal physiologic function (homeostasis).**

Disruption of this balance ("dysbiosis") can influence the development and progression of pathologic disease states such as cancer and autoimmunity. As the FDA has recently approved the first two bacterial based products for the prevention of Clostridioides difficile infections (Ferring's Rebyota and Seres' Vowst), Scendea and Back Bay Life Science Advisors reviewed the current regulatory issues for biotherapeutics as well as the state of investment and development in therapeutic areas beyond gut disease.

# Introduction

**Humans and animals are exposed to many organisms in food, water, and environment and, in many cases, normal physiologic function cannot be maintained in the absence of symbiotic organisms such as bacteria. For many years it has been known that bacteria, protozoa, fungi, and archaea play an important role in digestion. Collectively, this group of microscopic organisms is known as the microbiome and there is an increasing body of evidence suggesting that the microbiome plays a far more important role in maintaining health and immune function than previously thought.**

Within the human body there are about 40 trillion microorganisms. Most of them reside in the gastrointestinal (GI) tract, which is colonized by approximately 500 to 2000 microbial species in its healthy state (Khanna & Pardi, 2016; Sender et al., 2016). Commensal microbiota are integral in maintaining bodily homeostasis, whereas dysbiosis, or a disturbed microbial milieu, is linked to multiple disease states. Although each person's microbiota profile is distinct, relative abundance and distribution along the intestine of these bacterial phylotypes is similar among healthy individuals (Carabotti et al., 2015).

Many things to which humans are exposed contain bacteria or other microorganisms including food and drink – yoghurt or probiotics being obvious examples. When considering the classification of items that can contain microorganisms, it is principally the target population that determines whether it is classified as a food or nutrient-based product (e.g., probiotic, supplement, or nutraceutical) or whether it is classed as a drug, or live biotherapeutic product (LBP).

For centuries, microbial replacement therapy or fecal microbial transplantation (FMT), which refers to the process of transferring gut microbiota from a healthy donor to a diseased recipient, has been utilized by Chinese medicine practitioners for the treatment of disorders of the GI system such as food poisoning, diarrhea, vomiting, and constipation (Zhang et al., 2021). Adoption of FMT in the US is more recent and is believed to have been first investigated in the clinic in the late 1950s for the treatment of pseudomembranous colitis (Eiseman et al., 1958). Over the past decade there has been a surge in the development of microbiome-related therapeutics by pharmaceutical and biotech companies, with early development focused on the gut microbiota and disorders of the GI tract.

# Regulatory Considerations

In the US, the FDA has provided guidance for sponsors wishing to develop LBPs (Early Clinical Trials With Live Biotherapeutic Products, 2021). If an LBP is intended to be evaluated or used for the treatment, prevention, or cure of a disease in humans *and* it contains live microorganisms *and* it is not a vaccine, it is classed as a drug and, therefore, subject to the same regulations as defined in 21 CFR Part 312 -- Investigational New Drug Application.

An LBP marketed as a food or supplement, as defined in the Food, Drug and Cosmetics Act, would not be classed as a drug *unless* it is claimed that the LBP would or is intended to treat or manage diseases or conditions in an individual human or animal. Indeed, a food product containing live organisms may continue to be marketed even where an Investigational New Drug (IND) is in place to study the effects in human disease. Per FDA-2013-D-0811 Industry Guidance for FMT, sponsors must comply with IND requirements and "ensure that the stool donor and stool are appropriately qualified by screening and testing and that centralized processing of FMT adheres to appropriate current good manufacturing practice."

Within the EU, the status of LBPs was clarified in European Pharmacopoeia (Ph. Eur.) Monograph 3053 (Live Biotherapeutic Products f... - European Pharmacopoeia 11.0). As with the FDA Guidance for Industry, an LBP is defined as a medicinal product containing live organisms and thus falls within the scope of Directive 2001/83/EC. However, the LBP definition appears to be more specific within the Ph. Eur. Monograph in that LBPs are limited to bacteria and yeasts given orally or intra-vaginally, whereas the US guidance mentions these specifications but can be more liberally interpreted – for example, can "include microorganisms such as bacteria" and the "dose form and route can vary". Whereas per EMA/204935/2022, for FMT specifically, there is no agreed EU approach to classify FMT-based products.

A number of companies and groups are developing LBPs for treatment of human diseases. One such group developing an LBP containing a single species obtained advice and recommendations from both the FDA and EMA (Paquet et al., 2021). Although it was noted by the authors that there were some differences, these were largely due to the slightly different focus between the two agencies. But overall, there was a high degree of concordance.

Both the FDA Guidance and Ph. Eur. monograph specify a number of critical quality attributes (CQAs) that should be applied to the LBP (as drug substance or drug product). As with any investigational drug, CQAs evolve during the clinical development of LBPs, but the inherent variability seen in live cultures create specific challenges. These are discussed in subsequent sections of this paper, and both agencies recommend early interaction to ensure that there is alignment on the overall development plan.

## Chemistry, Manufacturing and Controls (CMC)

The quality requirements for live biotherapeutic products (LBPs) for human use are defined in the Ph. Eur. general monograph live biotherapeutic products for human use (3053) and the US FDA Guidance for Industry for Early Clinical Trials With Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information describes the recommendations regarding IND submissions for LBPs in early phase development. Much of the guidance and real-world experience are aligned for CMC requirements. There still remain topics that often are debated during review and can be blocking steps to progression of development. Some of the more common points are discussed below.

### Starting material

The individual bacterial strain, or strains in the case of a consortium, should be considered as starting material. These should be banked and stored under current good manufacturing practices (cGMP), and history of the strain origin and development information should be available. In the case that limited information is available on the origin, this may be justified based on a thorough risk assessment and testing to provide evidence that the use of the strain will not pose a safety risk.

### Potency testing

Potency as a measure of viable cells, expressed in colony forming units (CFUs), is considered appropriate regarding the nature of these products. Additional in vitro analysis supporting the mechanism of action (MoA) of the LBP for the desired clinical outcome should be developed and included in the characterisation panel as development progresses.

### Comparability

Changes are likely to be required during the course of development. These may include changes in manufacturing scale, manufacturing process, equipment and materials, facility, analytical test methods, and container closure. In each case, a stepwise approach to comparability should be implemented, beginning first with a risk assessment to evaluate the impact to product quality attributes, efficacy, and safety.

Based on the outcome of this, any identified risks should be mitigated. This is often done by the performance of a comparability evaluation of material generated before and after the change. As an example, following a facility technology transfer of a manufacturing process, the comparability study may include the comparison of in-process data against process performance targets, release data, characterisation data, and comparison of stability profiles of pre- and post-change material.

During early development this comparison may be limited to comparison of single batches to each other and later in development comparisons consisting of at least 3 batches tested pre- and post-change may be required.

**Multiproduct facility evidence of testing**

In the case where a facility that manufactures other products is used to manufacture the LBP, sufficient information should be available to confirm adequate controls are in place for cleaning and to avoid cross contamination. As clinical and product development proceeds, additional controls may be necessary.

# Device Considerations

For co-packaged combination products (e.g., the drug product is provided with a separate enema bag or applicator), the medical device and the medicinal product are regulated individually under their respective regulations. If the LBP is delivered as part of an integral drug device combination (e.g., in a pre-filled enema bag or pre-filled applicator), the regulations that will govern the combination product are determined based on the product's principal MoA.

To reduce regulatory burden, ideally, a device with an EU CE mark and US Drug Master File (DMF)/510(k) number should be used. If a DMF is available for the device, a letter authorizing reference to this from the manufacturer should be supplied and included in the IND submission. If the device is not CE marked/DMF reference is not available, further details on the device will be required in the dossier.

For co-packaged products in the EU, evidence should be provided that relevant standards have been met, e.g., EU Declaration of Conformity or, where applicable, EU certificate, or other appropriate documentation such as summary information confirming compliance with relevant general safety performance requirements (GSPR). Whereas for integral products, with the introduction of the Medical Devices Regulation (EU Regulation 2017/745) in May 2021 replacing the previous Medical Device Directive (93/42/EEC), the requirements that combination product manufacturers must fulfill have undergone significant changes. If the administration device is marketed as a single integral product intended exclusively for use in the given combination and is not reusable, the combination product is regulated under the medicinal products framework. In this case, the relevant GSPR requirements of the Medical Device Regulation (MDR) apply to the device part. The relevant GSPRs set out in Annex I to this Regulation apply as far as the safety and performance of the device component of the single integral product. The conformity of the device (part) with relevant GSPRs (Annex I of EU Regulation 2017/745) should be included in accordance with Article 117 of the MDR, without the requirement to be regulated as a CE mark device. Manufacturers need to seek a Notified Body Opinion (NbOp) for this confirmation.

In the US, for both co-packaged and integral products, if a DMF reference is not available, the information required for the EU notified body dossier is usually sufficient.

Further, it should be noted that if a device is not single use, additional data to support the multidose functionality and cleaning should be presented. Data demonstrating the compatibility of the device with the LBP should be generated and include evidence of acceptable performance and stability following the planned clinical material preparation and administration procedure.

**Cost of goods**

To ensure the LBP can be feasibly marketed and generate the required profit margins, the cost of goods in relation to pricing and reimbursements should be considered as part of the development process. Additional information on pricing & reimbursement dynamics for currently marketed products may be found below.

# Preclinical Considerations

In respect of non-clinical development, both EU and US regulators acknowledge that a conventional drug development strategy is likely to be inappropriate when assessing risks to a patient population. There is also considerable overlap between the CQAs and assessment of non-clinical safety and there should be a joint approach in assessing the need and extent of any studies needed to support clinical studies in human subjects.

As described, a thorough assessment of the attributes of an LBP, be that a single source or a mixture, is required and the characteristics of the organism(s) should be well understood in order to determine if additional studies are required to support clinical trials.

## Efficacy

When conventional therapeutics begin clinical trials, it is required that the pharmacology and pharmacodynamic effects of the potential therapeutic have been assessed, with the data used for many purposes including demonstrating a mechanistic proof-of-concept, efficacy, development of appropriate biomarkers and supporting identification of dose schedules and/or dose level for human clinical trials. However, these studies are designed around pharmaceuticals that have a direct effect on one or more pharmacologically relevant targets, such as blocking specific receptors.
For LBPs, demonstrating efficacy or proof of concept is particularly challenging because the MoA is generally indirect and can involve several pathways or MoAs simultaneously.

These indirect effects may not be demonstrable in conventional models of human disease as the MoA is usually specific to the human microbiome, which is typically significantly different from other species, meaning results are not always translatable. Both EU and US authorities expect sponsors to try to provide data that describes the intended MoA but agree that such studies are likely to be supportive rather than definitive. These studies can include in vitro biomarker studies, such as cytokine release or changes in immune cell populations, or complex in vitro models which can be used to predict the behavior of an LBP in an artificial setting. Multiple complementary studies evaluating relatively specific aspects or components of the response to an LBP can be useful here.

## Safety

In assessing the safety of an LBP, a number of things must be considered, although several of these are related to the physical characterization of the LBP. As part of the assessment of the CQAs of an LBP, tests for virulence/pathogenicity, antibiotic resistance and transferability, stability of a transgene modification (if any), biological activity, release of endotoxins or other biologically active materials, as well as the source of the LBP and its identification at a species and strain level by genetic sequencing are typically included. All of these factors may impact the safety of an LBP and an integrated approach between the CMC and non-clinical development is essential.

In addition to the physical characterization, the other key factors which can impact the safety of an LBP are its ability to cross mucosal or endothelial barriers. The human body has developed many complex and inter-linked systems for preventing the entry of bacteria into systemic circulation or tissues. It is an essential part of the assessment to understand the LBP's ability to cross these barriers, especially in the intended target population as the mucosal barrier in a diseased individual may be significantly different from that of a healthy subject and there is a higher risk of infection in many diseases where an LBP could be used. The EMA and FDA suggest that sponsors should assess the ability of an LBP to cross epithelial or mucosal barriers, although it is not specified whether this can be modelled using an in vitro system or if an in vivo model should be used. It would normally be expected that the sponsor be able to justify the selection of an appropriate model.

The strain/species characterization, pharmacology, and potential safety risks will guide the sponsor and the agencies in determining the need or usefulness of toxicology studies. For example, an LBP (or its components) composed of commensal bacteria commonly found in the human microbiota that do not cross mucosal barriers and are confined to the GI tract may be considered low risk and thus toxicology studies are likely not warranted. Whereas an LBP which can translocate to the systemic circulation may pose a higher risk due to potential inflammatory responses and warrant additional studies, especially if the LBP is resistant to antibiotics or susceptible to transfer of genetic material from or to other bacteria.

Any proposed strategy for non-clinical safety study should be discussed with the appropriate agencies as early as possible to avoid unnecessary studies or delays in starting clinical trials. This is especially important for LBPs as there is much less of a defined regulatory pathway for the clinical development (Cordaillat-Simmons et al., 2020; Rouanet et al., 2020).

## Clinical Trial Considerations

The main objective of early clinical phases is to define the appropriate dosage range and the administration schedule to be used in confirmatory clinical trials based on the tolerability of the product. It is important to remember that the various risks associated with LBPs may not always be directly related to the dosage as they depend highly on the host-microbiota interactions, the patient's mucosal barrier integrity, and the host's immune status.

Another point regarding study design adaptation is the potential bias in safety assessment during early clinical trials with healthy volunteers. For strain(s) isolated from healthy humans, it can be expected that some healthy volunteers might carry, if not the same, at least some representative strain(s) from the same species in their native ecosystem, or carry strains that provide functional redundancy. Consequently, Phase I studies that enroll patients rather than healthy volunteers are, in our opinion, more appropriate, especially when LBPs have been developed to, e.g., correct a large dysbiosis affecting certain species in the patient population. For long-term use of LBPs, it may be beneficial to have patients consent to biobank their samples obtained from different phases, so that in the future, long-term assessments that may not have been originally anticipated can be tested.

Immunocompromised populations (e.g., young, old, pregnant, or immune deficient) are understandably of concern and, as for all special populations, it is important to lay out strategies to mitigate and manage risks, and the accompanying contingency plan, in the clinical trial design. Clinical outcomes relating to such risks, like routine body temperature recording, could allow for early detection and early intervention, including an immediate stop of the administration and/or treatment with an appropriate antimicrobial for which the LBP had been proven sensitive to during the non-clinical characterization phase of development (Rouanet et al., 2020).

## Risks & Limitations

One of the most important risks associated with the administration of living microorganisms is translocation. Bacterial translocation in the gut is defined as the passage of members of the GI microbiota across the lamina propria to the local mesenteric lymph nodes and beyond (O'Boyle et al., 1998). It has been suggested as a direct cause of infection and inflammation, which, in certain conditions, may result into sepsis and subsequent organ failure.

Gut-derived bacteria produce biogenic amines (BAs). BAs play an important role in cellular physiology and their concentration should be carefully regulated in the case of LBPs. Metabolic pathways potentially leading to BA formation should therefore be assessed, taking the patients' population characteristics into consideration. Particular attention should be given to the patients' sensitivity to BAs, including their drug use.

Human commensal bacteria are now known to be capable of metabolizing drugs and/or drug metabolites affecting the pharmacokinetics of the drug. An approach similar to a "drug-drug interaction" investigation could be used to test LBP impact on relevant drugs or known biological markers of a specific disease. In cases where such potential is expected or demonstrated, appropriate risk mitigations must be implemented.

## Clinical and Commercial Development

The evolution of the field has driven rapid expansion for microbiome-based therapeutics; the most common area of development currently is infectious diseases (ID). This includes GI-related infections such as Clostridioides difficile (C. difficile) infections (CDI), dermatologic infections like methicillin-resistant Staphylococcus aureus (MRSA), and urinary tract infections (UTIs). There have been recent successes in this space, as the end of 2022 saw the FDA approval of the first microbiome-targeting product. Ferring Pharmaceuticals' fecal microbiome product, Rebyota, a single rectal dose of donor fecal matter, was approved for prevention of recurrence of CDI in patients 18 years or older, following antibiotic treatment for recurrent CDI. In the pivotal PUNCH CD3 trial, Rebyota was successful in preventing recurrence through 8 weeks in 70.6% of patients vs. 57.5% in the placebo group. Not long after Rebyota's approval, Seres Therapeutics completed the Phase III trial of SER-109, an oral

microbiome therapeutic composed of purified Firmicutes spores for the treatment of recurrent CDI. In the pivotal Ecospor III trial, SER-109 prevented CDI recurrence through 8 weeks for 88% of participants vs. 60% in the placebo group. On the heels of this data, the FDA approved the oral product, brand named Vowst, for the prevention of CDI following antibiotic treatment of recurrent CDI (Seres, 26 April 2023). Ferring and Seres are both expected to pursue European approval, but at this time there are no approved microbiome-targeting therapies in the EU as the European Medicines Agency (EMA) is still developing a regulatory pathway for FMT products, as was discussed above.

Drug development within the microbiome space has not been without its challenges. In 2016, SER-109 failed to outperform placebo in a Phase II trial for CDI. It wasn't until Seres Therapeutics increased the dose of SER-109 by tenfold that positive results were achieved to advance the asset to Phase III. Similarly, in 2021, another Seres Therapeutics microbiome-based candidate, SER-287, a donor-derived consortia of bacteria, failed to improve outcomes over placebo in a Phase II trial for ulcerative colitis. Immediately following the release of this data, shares in Seres Therapeutics fell by ~60%, and the remainder of the study was terminated.

Suffering similar setbacks, Finch Therapeutics' CP101 asset for CDI incurred several hiccups during its Phase III trial. Issues began in 2021, soon after Phase III initiation, with FDA concerns that CP101, a donor fecal product, could infect patients with SARS-CoV-2. In 2022 Takeda withdrew its support and this ultimately resulted in the termination of the Phase III trial along with reduction of 95% of staff in early 2023. Finch Therapeutics cited a poor outlook for capital or partnerships, slow trial enrollment, and intellectual property (IP) infringement as the driving force for these decisions. These setbacks raised questions about the use of consortia of bacteria and cast doubt over the emerging field. However, there remains significant promise in the space, as manufacturers are working to overcome hurdles of properly identifying microbes to address diseases, addressing safety and regulatory concerns, and ensuring stable colonization of therapies.

**Pricing & Reimbursement**

With two microbiome therapies approved by the FDA, the industry will watch closely to gauge the success of commercial uptake. Notably, both products have been approved for a bacterial disease, a therapeutic area that has seen a number of commercial flops and faces substantial pricing pressures due to the US reimbursement environment (Bak, 2018). Nevertheless, Rebyota launched at wholesale acquisition cost (WAC) of $9K/unit (Redbook, 22 March 2023). Vowst was recently launched with a WAC price of $17.5K and a robust patient assistance program sponsored by Seres (Redbook, 5 April 2023; Seres, 27 April 2023). While these medicines are approved for prevention, not treatment of CDI, this is well above the US price of branded antibiotics (e.g., Dificid) and other preventative therapies (e.g., Merck's mAb Zinplava) which are priced in the range of $2-5K per course of therapy. While pricing of therapeutics is a multifaceted process that considers size of the patient population, unmet needs, cost of alternative therapies, and potential cost savings of complications/comorbidities, the cost of manufacturing these products may be a key driver of the significantly higher price relative to existing branded agents. While still early days, payers have begun to determine their coverage policy of Rebyota, mainly requiring prior authorization confirming that patients have experienced at least one recurrent CDI episode, have completed their course of antibiotics, and recently tested positive for C. difficile (Aetna, 0844; Blue Cross Blue Shield, J3590).

# Evolution of Therapeutic Areas of Development

## INTEREST IN NEUROLOGY

As the area of using LBPs to treat gut associated diseases has seen its successes and challenges, researchers and biopharma have cast their eye toward other therapeutics areas where microbes may influence human health. The gut microbiome has been found to have a direct impact on metabolic health, including the proper function of the pancreas, liver, and even the cardiovascular system. Several metabolic processes such as insulin secretion by the pancreas and lipogenesis by the liver are influenced by the gut microbiota, where dysbiosis can similarly contribute to pathogenesis of these processes (Fan & Pedersen, 2021; Olofsson & Backhead, 2022). Whereas for dermatology, the microbiome of both the gut and the skin influences immune regulation as well as diseases of the skin, suggesting both serve as potential targets for treatment (Yu et al., 2020; Ellis et al., 2019).

Notably, recent research has demonstrated a pivotal role for the gut microbiome in influencing bidirectional communication with multiple organs through a variety of pathophysiological mechanisms (Schroeder & Backhed, 2016). The gut-brain-axis (GBA) links the central and the enteric nervous system (CNS and ENS, respectively). This connection facilitates bidirectional

communication between the brain and peripheral intestinal functions. The role of the GBA is to monitor and integrate gut functions as well as to link emotional and cognitive centers of the brain with peripheral intestinal functions and mechanisms such as immune activation, intestinal permeability, enteric reflex, and entero-endocrine signaling (Rhee et al., 2009; Carabotti et al., 2015; Morais et al., 2021).

Both clinical and experimental evidence suggest that enteric microbiota has an important impact on GBA, interacting not only locally with intestinal cells and the ENS, but also directly with the CNS through neuroendocrine and metabolic pathways. Studies on germ-free (GF) animals have shown that bacterial colonization of the gut is central to the development and maturation of both the ENS and CNS (Uzbay, 2019). The absence of microbial colonization is associated with an altered expression and turnover of neurotransmitters in both nervous systems as well as alterations of gut sensory-motor functions. All these anomalies are restored after animal colonization in a bacterial species-specific manner.

Interestingly, in the last 10 years, several studies reported that probiotics have an influence in the CNS by showing efficacy in improving psychiatric disorder behaviors. Alterations in gut microbiota composition have been associated with the pathogenesis of various neurological disorders, including Parkinson's disease (PD), autism spectrum disorder (ASD), and psychiatric disorders such as depression (Carabotti et al., 2015).

When considering the evolution of microbiome-based research and development, the growth in clinical development focus has mirrored the growing data implicating the gut microbiome in disease far afield from the GI tract. In a comparison of the field assessing microbiome-based programs in 2019 vs. 2023, ID and oncology continue to be areas with high levels of development, both of which saw a 38% increase in the number of programs (Figure 1).

Whereas development of microbiome programs for GI-related diseases only increased by 13% over the four years, which may be due to the number of programs already in development and challenges encountered by prior assets, the area with the largest percent increase (41%) in total number of programs within this time was neurology, followed closely by metabolic diseases (39%) (Figure 1).

Figure 1.

**Distribution of Microbiome Programs Over Time**

*2019 versus 2023*

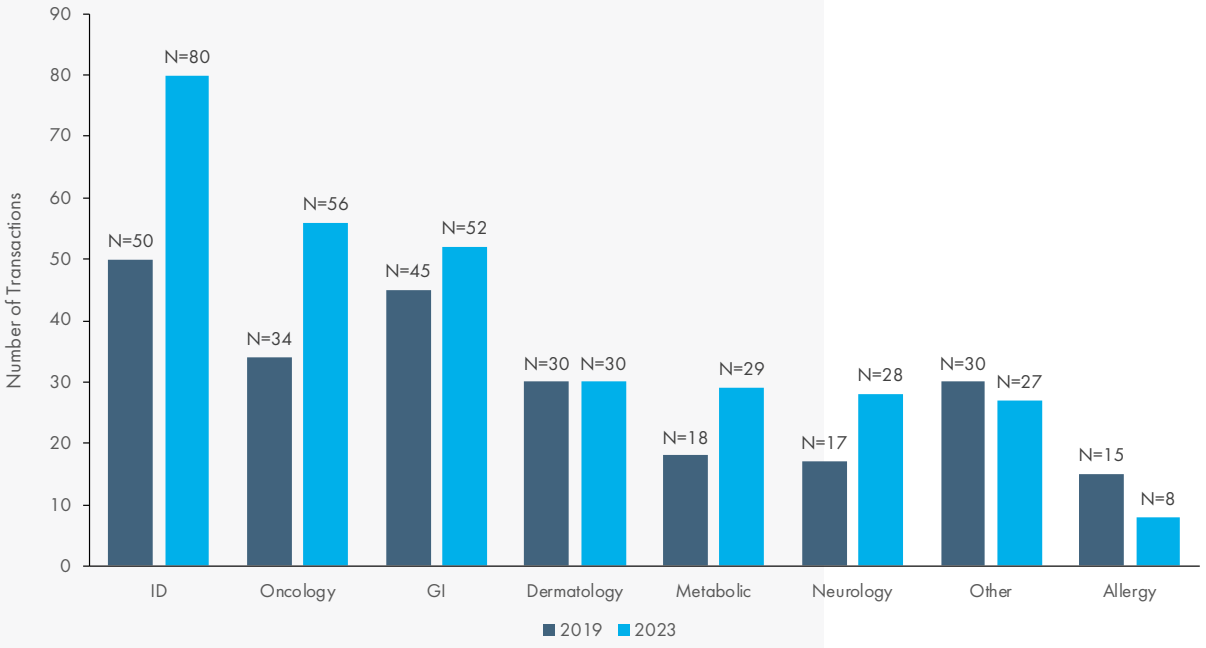



*Figure generated by BBLSA, 2023*

Furthermore, as compared to the pre-pandemic time frame, there are proportionally fewer companies with lead programs in GI and ID. Instead, oncology, neurology, and dermatology companies now command a greater proportion of the total investment landscape post-pandemic compared to pre-pandemic, with neurology growing significantly from 5% of companies to 14% (Figure 2).

Figure 2.

**Shift in Target Indications for Microbiome Programs Over Time**

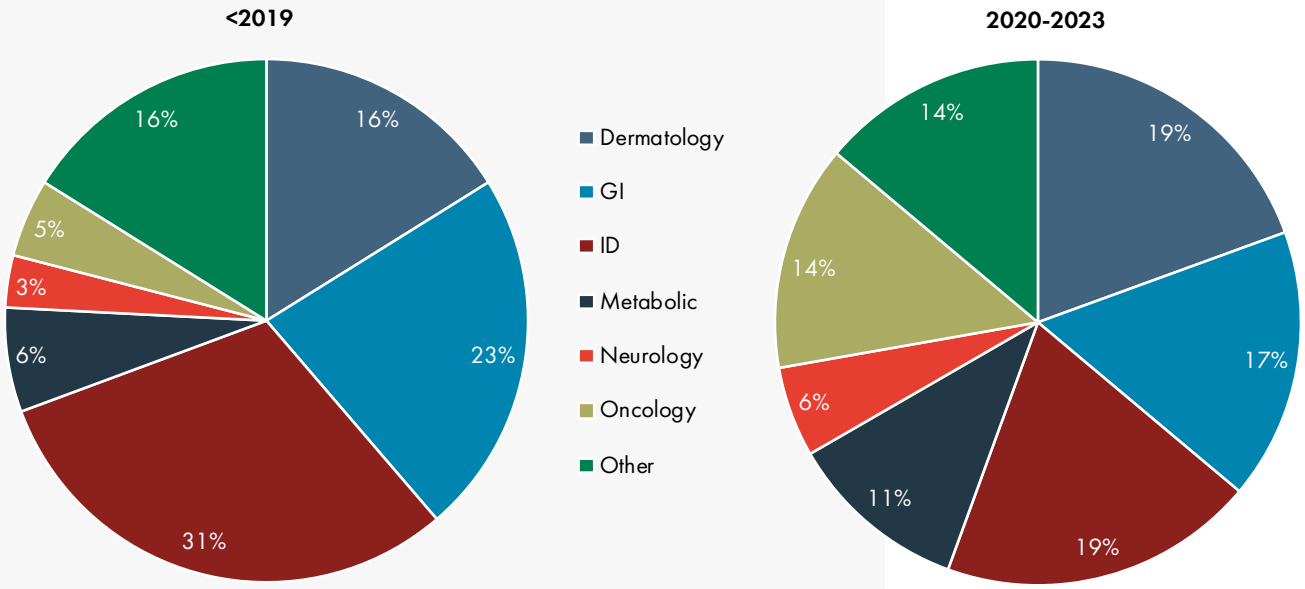



*Figure generated by BBLSA, 2023*

The growth in neurology programs is likely a reflection of the emerging data on the GBA, increased interest from pharmaceutical partners and investors, and significant commercial opportunities in spaces with high unmet need. Additionally, utilization of microbiome therapies for CNS diseases is viewed as an advantage to other therapeutic modalities in development, as microbiome therapies are perceived to be safe with a well-established delivery method through the gut, which is especially advantageous in pediatric and elderly populations.

Given the available data, as well as market opportunity, it is no surprise that ASD, PD, and neuropsychiatric disorders are the most active space within this growing segment of the microbiome. Indeed, as it relates to microbiome modulating therapies, the fastest growing areas of interest within neurological diseases are ASD (n=6), PD (n=5), and neurodegenerative diseases (n=6), and neuropsychiatric disorders including anxiety, depression, and sleep disorders (n=4; Table 1). Based on the interest in these therapeutic areas we assessed the clinical, market, and transactional landscape within these indications.

Table 1.

**List of Neurology Programs in Development**

| Company | Asset | Stage | Indication |
|---|---|---|---|
| AXIAL THERAPEUTICS | AB-2004 | 2 | Autism |
| | AB-2004 PTR | PC | Autism |
| | AB-5006 | PC | Parkinson's |
| NUBIYOTA | MET-2 | 2 | Depression, anxiety |
| Scioto BIOSCIENCES | SB-121 | 1 | Autism |
| | TBD | PC | Autism |
| MaaT | MaaT003 | 1 | ALS |
| FINCH | FIN-211 | PC | Autism |
| KOBIOLABS | KBLP-010 | PC | Autism |
| STELLATE THERAPEUTICS | STL-101 | PC | Parkinson's, Alzheimer's |
| LISCure | LB-P4 | PC | Parkinson's, Alzheimer's |
| | LB-P4E | PC | TBD |
| Artizan BIOSCIENCES | TBD | PC | Parkinson's |
| | TBD | PC | TBD |

| Company | Asset | Stage | Indication |
|---|---|---|---|
| Senda Biosciences | TBD | PC | Parkinson's |
| | TBD | PC | MS |
| YSOPIA bioscience | Yso4 | PC | Mood disorders |
| SeedHealth | TBD | PC | Generalized anxiety disorder |
| BLOOM science | BL-001 | PC | Dravet Syndrome |
| | BL-002 | PC | ALS |
| 4D pharma plc | MRx0006 | PC | Psychiatric disorders |
| | MRx0002 | PC | MS |
| | MRx0029 | PC | Neurodegeneration |
| | MRx0005 | PC | Neurodegeneration |
| KALLYOPE | TBD | PC | Migraine |
| | TBD | PC | TBD |
| Holobiome | TBD | PC | TBD |
| BioPalette | TBD | PC | TBD |

| Autism | Psychiatric | Parkinson's | Other neurodegenerative | Other |
|---|---|---|---|---|

*Table generated by BBLSA, 2023*

# Neurology Indications of Interest

### Autism Spectrum Disorder (ASD)

ASD defines a group of neurodevelopmental disorders characterized by impaired social communications and interactions in addition to repetitive and restrictive patterns of behavior with disturbed anxiety and cognitivist. In the US, there are an estimated 2 million children and 5.4 million adults with ASD, with current standard of care only targeting symptoms and no current options for the core impairments (e.g., social communication / interaction and repetitive behavior).

There is growing evidence supporting the role of the gut and the resident microbiota on the severity of ASD. The hypothesis of a strong correlation between the disruption of gut bacteria and ASD mainly originated from multiple clinical studies demonstrating that children with ASD have distinctive microbiomes and GI problems/symptoms, such as constipation and diarrhea, compared with neurotypical children (Adams et al., 2011; Son et al., 2015; Gondalia et al., 2012). Interestingly, ASD children treated with antibiotic vancomycin showed a reduction in the severity of ASD and demonstrated improvements in behavioral symptoms, suggesting that the gut bacteria may participate in the behavioral disturbances in ASD (Finegold et al., 2002). Several other studies have also found remarkable changes in the gut microbiota composition and in the production of metabolites in children with ASD (Suganya & Koo, 2020). In a small open-label clinical study, microbiota transfer therapy (MTT) in children with ASD significantly improved the gastrointestinal and ASD symptoms.

There are currently 6 microbiome programs for ASD in development, with four programs targeting core autism symptoms and the remaining two focused on GI symptoms (Table 1). Leading the pack is Scioto Biosciences' SB-121, a L. reuteri based therapeutic for ASD patients, with positive topline results to date and swift enrollment in the Phase 1B study, likely representing a significant unmet need in the space. While SB-121 signifies a promising step forward for patients, ASD remains a challenging area for clinical development, due to the patient heterogeneity, lack of optimal disease models, limited validated drug targets, poor understanding of the disease etiology, and hesitation from big pharma to advance R&D (Fierce Biotech, 2 August 2011). These hurdles may contribute to the limited number of ASD transactions. In our dataset, there was only 1 transaction, which was for Finch Therapeutics' licensing of patents from Arizona State University for FIN-211 for ASD and GI symptoms (Table 2).

Table 2.

## List of Transactions for Neurology Based Assets

| Licensee | Licensor | Year | Indication | Stage | Comments |
|---|---|---|---|---|---|
| ASU | FINCH | 2022 | Autism Spectrum Disorders | Preclinical | Finch Therapeutics licenses ASU's patent for microbiome therapeutic, FIN-211, in development for ASD |
| SeedHealth | AXIAL THERAPEUTICS | 2022 | Neuropsychiatric | Discovery | Seed Health launches gut-brain development program with Axial Therapeutics to translate CalTech research into probiotic innovations for neuropsychiatric health |
| FONDAZIONE EDMUND MACH | OptiBiotix | 2021 | Sleep, Stress, Anxiety | Research only | Fondazione launches a new research project exploring the potential role of OptiBiotix's Lactobacillus plantarum LPLDL microbiome modulation drugs on sleep, stress and anxiety |
| MICROBA | Unilever | 2021 | Sleep | Research only | Microba Life Sciences and Unilever to investigate the links between sleep and the human gut with the aim to improve sleep |
| VNIVERSITAT DE VALENCIA | YSOPIA bioscience | 2020 | Depression and Anxiety | Preclinical | Ysopia Biosciences, the first biotech company to harness the therapeutic potential of the Christensenella for disorders such as obesity and inflammatory diseases, to license the University of Valencia's patent for Christensenella in mood disorders |
| MICROBA | Holobiome | 2020 | Depression | Technology | Holobiome and Microba to collaborate on the development of new microbiome therapies for depression |
| UNIVERSITÀ di VERONA | Carbiotix | 2019 | Neuroinflammation | Preclinical | Collaboration agreement to investigate Carbiotix microbiome modulator therapeutics (MMT) applications for addressing neuroinflammation, additionally this collaboration will further validate Carbiotix MMT platform |
| Parkinson's Institute and Clinical Center | AXIAL THERAPEUTICS | 2018 | Parkinson's Disease | Preclinical | Axial and PICC to collaborate on the development of interventions targeting gastrointestinal metabolites that may fuel the development of PD |

*Table generated by BBLSA, 2023*

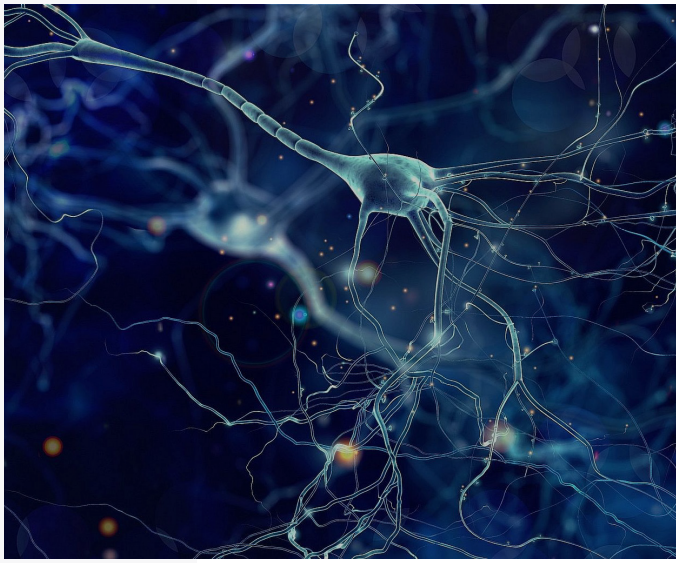
### Parkinson's Disease (PD)

Mounting evidence on gut dysbiosis in PD patients suggests that both qualitative and quantitative changes in the gut microbiota are associated with the disease and its progression, with increased intestinal permeability observed in the early stages of PD. Additionally, GI symptoms are experienced by most PD patients. Various symptoms such as hypersalivation, dysphagia, constipation, nausea, altered bowel habits, and defecatory dysfunction were reported to be present in patients with PD. Several large gut microbiome studies in PD patients in the US found widespread dysbiosis in comparison to controls, notably identifying high levels of bacterial-derived amyloidogenic protein and oxidative stress, both of which have been previously shown to induce alpha-synuclein pathology and inflammation in murine models of PD (Wallen et al., 2022; Sampson et al., 2020; Scudamore & Ciossek, 2018; Boktor et al., 2018).

Since the 1960s, Helicobacter pylori (HP) infection and the related complication (gastric ulcers) have been reported to be associated with PD, and the eradication of HP infection through antibiotics has been shown to ameliorate PD symptoms (Pierantozzi et al., 2001). Supporting evidence from several studies hypothesizes a relationship between the gut, resident microbiota, and PD. However, the precise role, mechanisms, and any causal relationships with microbiota have yet to be fully established (Peterson, 2020).

There are nearly 1 million PD patients in the US and 10 million patients globally. Significant unmet need remains as ~85% of patients will become refractory to standard of care, with some patients experiencing fluctuations of symptoms (Parkinson.org; Beckers et al., 2022).

There are 5 microbiome programs in the pipeline for PD, all of which are still in preclinical development (Table 1). Progress in the field may be slow given the number of rapidly advancing PD programs targeting biomarkers indicative of aberrant lysosomal or mitochondrial function.



However, development in the microbiome is not without its promise for PD. For example, Axial Therapeutics PD asset, AB-5006, an inhibitor of bacterial amyloid proteins aggregation in the gut designed to slow disease progression, comes several years following a collaborative deal struck between Axial Therapeutics' and the Parkinson's Institute and Clinical Center (PICC) (Table 2).

**Psychiatric Disorders**

For psychiatric disorders, multiple recent gut microbiome association studies across several large cohorts, some exceeding 1,000 people, have identified association between multiple microbial taxa and depression and anxiety disorders (Valles-Colomer et al., 2019; Radjabzadeh et al., 2022; Jiang et al., 2018; Butler et al., 2023). Depression is the most common mental illness worldwide, and it has been associated with gut dysbiosis in both human and animal depressive models. Major depressive disorder (MDD) is associated with an increase in the level of proinflammatory cytokines and alteration of gut microbiota composition, with some genera depleted and others abundant in patients with MDD (Limbana et al., 2020).

Whereas for anxiety disorder, it has been estimated that the global incidence is as great as 25%, and up to one-third of people will be affected by anxiety symptoms during their lifetime. In people with social anxiety disorder (SAD), the gut microbiome has been found to be compositionally, particularly in beta diversity, and functionally/metabolically different to that of healthy individuals (Butler et al., 2023).

Five mood disorder-related transactions were identified in our dataset between 2019 and 2023, one of which notably occurred in 2022 when Axial Therapeutics entered into a collaborative agreement with Seed Health (Table 2). This collaboration was established for the development of probiotic innovations targeting the GBA for anxiety, depression, and other neuropsychiatric disorders. Development of these probiotic drugs is built upon groundbreaking research out of California Institute of Technology identifying the critical role of intestinal microbes and microbial metabolites in neuropsychiatric conditions (Yano et al., 2015). Currently, there are 4 microbiome programs in development for mood and psychiatric-related disorders (Table 1). Furthest in development is NuBiyota's Microbial Ecosystem Therapuetic-2 (MET-2), currently in a Phase II trial for patients with major depression. Data from the Phase I study in patients with MDD and Generalized Anxiety Disorder found 75% of participants to have improved symptoms, with limited adverse events and side effects.

**Neurology Transactional Landscape**

Evaluating the transaction landscape for microbiome therapeutics within the last 5 years, most of the deals (~68%) occurred at the discovery or preclinical phases of development, regardless of the indication (Figure 3).

Figure 3.

**Microbiome Transactions Distribution by Top Therapeutic Category & Phase**

*Jan 2018 - Feb 2023*

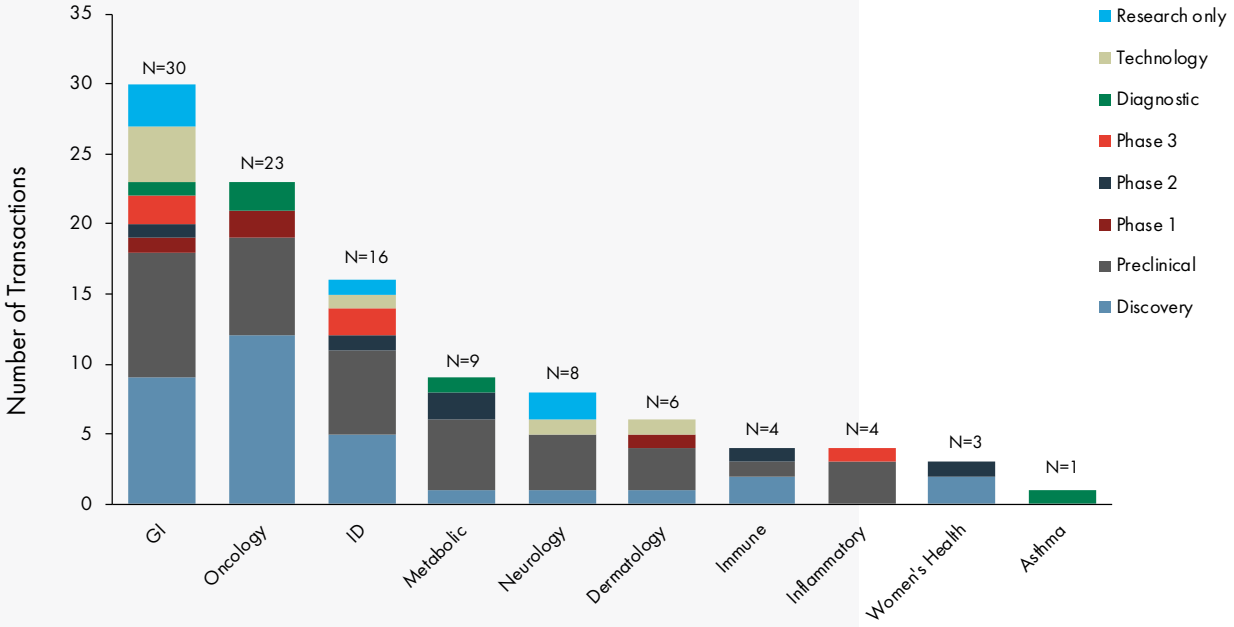



*Figure generated by BBLSA, 2023*

While GI, oncology, and ID transactions lead the space, neurology is a growing area of interest for partners and investors alike. In a separate analysis of M&A transactions across the field of neurology in its entirety, there were 78 deals in 2021, compared to 58 conducted in 2020. This may indicate that as the CNS-microbiome pipeline continues to grow, there will be increasing interest from partners. Of the 8 neurological-based microbiome deals identified, half occurred at the preclinical stage of development (Figure 3). Most of these deals occurred as collaborations or licensing deals to advance an asset by leveraging technologies or know-how of one or both parties, suggesting that partners are seeking to advance CNS focused microbiome pipelines. To date, the number of transactions in this space has remained relatively steady over this period, with 1-2 deals occurring per year (Table 2).

Insights into the GBA have revealed a complex communication system that not only ensures the proper maintenance of GI homeostasis, but is additionally likely to impact affect, motivation, and higher cognitive functions. Since 2020, the majority of transactions (n=5) have been for neuropsychiatric disorders, which may be due to a clearer development pathway and significant need for novel therapies (Table 2). While there is significant interest in ASD and PD within the microbiome space, these remain challenging areas with heterogeneous patient populations – psychiatric disorders may be considered "lower hanging fruit" to demonstrate proof of concept. Further, physicians and patients are actively seeking new drugs for psychiatric conditions that can demonstrate an improvement over the current treatment paradigm, specifically seeking improved efficacy, tolerability and safety, and speed of onset of effect, while avoiding chronic treatments. Additionally, the Street has indicated a surge in focus in neuropsychiatry, due to a number of readouts in the past 2-3 years.

# Conclusions

Over the last decade the field of live biotherapeutic drug development has emerged from an area of intriguing pre-clinical and clinical data to a space with multiple licensed medicines. With both EMA and FDA regulatory frameworks in place for LBPs, emerging regulations for FMTs and late-stage clinical success in CDI, investors and drug developers have begun to cast their eyes beyond the gut. With the emergence of data implicating the GBA in multiple neurologic diseases, there has been increasing interest from early-stage companies and consolidators in biotherapeutic approaches to treat CNS disease. Whether LBPs addressing CNS disease will see the same success and failures as has faced the GI community remains to be seen, but given the preponderance of evidence implicating the GBA in human health and disease there will likely continue to be substantial R&D and investor interest.

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