KPMG

# Harnessing the power of the human microbiome

## An introduction to a nascent market

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# Content

# Executive Summary

## What is the microbiome?

Complex and diverse communities of microorganisms populate each human being. These communities are known as microbiota or microflora, collectively called the microbiome. They play a significant role in our lives, influencing essential processes such as protection against diseases and nutrient absorption. Infections, prolonged use of antibiotics or unhealthy diets can lead to an imbalanced microbiome and compromise our health. Our body may become susceptible to diseases, including skin diseases, gastrointestinal conditions, food allergies, inflammatory and autoimmune disorders, cancer or neurodegenerative diseases.

## What does the market look like and what are future trends?

The human microbiome market still mostly consists of food and beverage products, dietary supplements and cosmetics. However, technological and academic research advances will enable new therapeutics and diagnostics. Indeed, a few medicinal product candidates containing live microorganisms are progressing to phase 3 clinical studies, and the first live biotherapeutic product has been FDA-approved in November 2022. The need for precise diagnostic tests to support healthcare professionals (HCP) in selecting the proper treatment for the right patient will inevitably create a new market segment.

## What are the current challenges and how to successfully enter the human microbiome industry?

The human microbiome industry is rapidly evolving, making it challenging to enter the market successfully. Delineating and implementing the right strategy for entry will be crucial. We identified the critical stages for success:

- Conduct a strategic evaluation of your position in the market
- Establish a precise yet flexible roadmap to realize the value
- Understand the intellectual property landscape and protect your innovation
- Proactively navigate and contribute to shape the immature regulatory processes
- Establish a network of partnerships and alliances to leverage existing capabilities
- Join or establish a microbiome ecosystem

We provide an overview of the human microbiome market, the observed challenges, how to overcome them and introduce future opportunities for pharmaceutical and biotech companies to become pioneers in the microbiome industry.

# The human microbiome

## The human body is populated by the microbiome

The human microbiome refers to the entirety of microorganisms populating the human body. It comprises various species such as bacteria, archaea, fungi, protozoa and viruses that mostly live in symbiotic relationships with us. The population of microorganisms varies depending on the physicochemical conditions, e.g., in the gut, skin, mouth or genital tracts. Recent studies estimate that the number of microbes in the human body exceeds the number of human cells by a factor of 1.3 and encodes for at least 100 times more genes than humans. The microbiome complements the human genome to provide essential functions, such as the ability to degrade fibers or plant polysaccharides, a metabolic process for which the machinery is not encoded by the human genome.

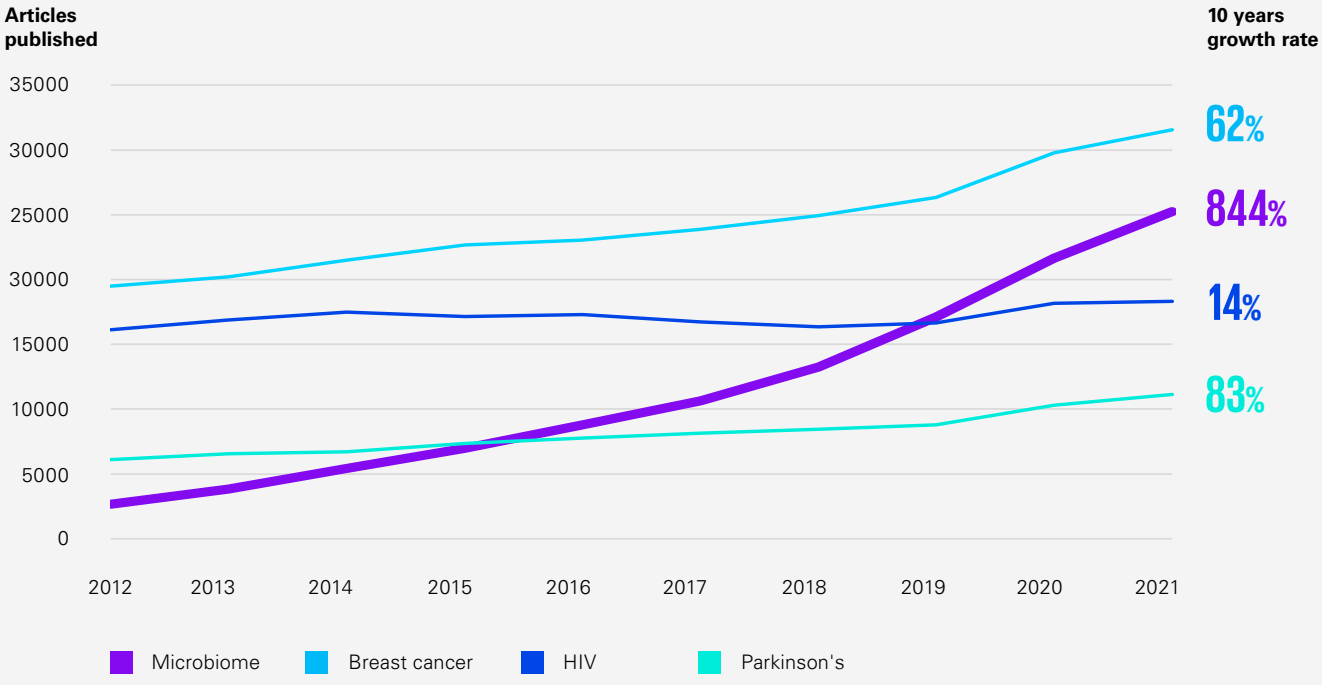
## The dynamic microbiome research field

Technological advancements in genome sequencing have fostered the understanding of the composition and dynamics of the microbiome and its role in human health. Most microbiome-related research focuses on the gut because it contains the largest and most diverse microbial population found in the body. The number of scientific articles published in the microbiome field has strongly increased in the past decade (Figure 1: 844% growth 2012-2021). In comparison, popular research fields, such as Parkinson's disease, breast cancer or HIV, have seen far lower growth rates.

Large-scale research projects such as the "NIH Human Microbiome Project" launched in 2007 significantly contributed to the dynamic of this research filed.

Figure 1:

**Number of scientific articles published in different fields over the 2012-2021 period**




Source: Pubmed database, accessed on 29 August 2022 using the following keywords: "microbiome", "breast cancer", "hiv", "parkinson's"

The Human Microbiome Project characterized the human microbiome and investigated the link between a disrupted microbiome (dysbiosis state) and specific pathologies. Research has demonstrated that a wide range of infectious and non-communicable diseases are linked to a dysfunctional microbiome, such as *Clostridioides difficile (C. difficile)*, recurrent infections, cancer, obesity, inflammatory bowel disease or type 2 diabetes. Furthermore, the gut microbiome influences the immune system and the effect of medication by modulating their uptake. On the other hand, a high diversity of microbe species promotes health and well-being.

Established research platforms or hubs improve scientific collaboration, foster crosstalk and technology transfer between academia and industrial partners and accelerate the clinical development of microbiome-based therapies. KPMG conducted a study for the Microbiome Signature Project and identified 35 such microbiome ecosystems, mainly across Europe and the USA[1]. We found that these ecosystems differ in their mission and goals. While some aim to foster collaboration between science, industry and society or create scientific microbiome communities, others focus purely on fundamental research. Each hub has specific USPs and value propositions. Some are even driven by a consortium of public and private institutions. However, they all have a dedicated management team and external expert support to ensure accelerated success, strong collaborations among stakeholders and a well-defined communication strategy and branding for public outreach.

## The developing microbiome industry

The potential of "microbiome care" interventions to prevent or cure related human diseases is supported by accumulating scientific evidence. For example, a meta-analysis showed that using probiotics reduces healthcare costs and the societal impact of respiratory tract infections in the USA[2]. Thus, companies across the food and beverages, cosmetic and pharmaceutical industries are exploring related market opportunities. Additionally, there are therapeutic needs that are still unmet, such as:

- **Using the human microbiome as an alternative to antibiotics in infection control** by restoring gut colonization resistance and controlling the expansion of resistant strains[3]. The extensive use of antibiotics can contribute to bacteria developing resistance. The treatment of bacterial infections with broad-spectrum antibiotics has severe limitations, as the perturbed microbiome has a decreased ability to control the expansion of antibiotic-resistant pathogens.

- **Leveraging the human microbiome in personalized therapeutics.** The tight interaction between each individual and their microbiome enables the latter to be used as a diagnostic biomarker and in the creation of personalized therapeutics, especially in oncology[4].

- **Providing softer therapeutical alternatives to patients** currently undergoing a heavy treatment journey, who will potentially adopt microbiome-related treatment alternatives to prevent and treat inflammatory bowel disease, obesity or even cancer.

[1] https://mediconvalley.greatercph.com/kpmg_report
[2] https://www.frontiersin.org/articles/10.3389/fphar.2019.00980/full
[3] https://academic.oup.com/jid/article/223/Supplement_3/S283/6134104?searchresult=1
[4] https://onlinelibrary.wiley.com/doi/full/10.1186/s40169-019-0232-y

# The microbiome industry

## Food and dietary supplements

The microbiome food and supplements industry mainly aims to maintain a healthy microbiome with the help of products containing prebiotics, probiotics or their combination (synbiotics). A Canadian survey conducted in 2019 asked consumers which food product features they thought were important for their health. Roughly 70% of the participants either replied with "contains probiotics" or "contains prebiotics"[5], showing that the consumers are aware of their positive effects.

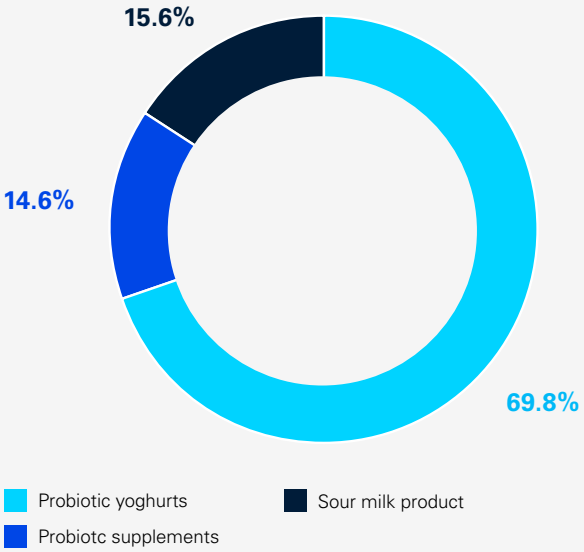
**Prebiotics** are substrates that promote the growth and activity of beneficial bacteria in the host microorganisms. The most common are non-digestible fibers which affect human health by keeping microbial populations balanced. Prebiotics are commercialized in enriched foods or as dietary supplements. The global prebiotics market was valued at $US 6.05 billion in 2021[6] with inulin being the most represented ingredient (40% of the total), followed by fructo-oligosaccharides and galacto-oligosaccharides (20% of the total for each).

**Probiotics** are live microorganisms that can confer health benefits when administered in adequate amounts. They are naturally found in fermented foods such as yogurt and other sour milk products or available from probiotic supplements (Figure 2). Probiotic supplements can contain either a single bacteria strain or a standardized mix of strains and they are used for a variety of health claims, the leading one being digestive health (Figure 3). The global market for probiotic products was valued at $US 47.6 billion in 2021[7]. An established market leader primarily known for its baby and child probiotic products is the Swedish healthcare company BioGaia[8].

[5] https://www.pearl-strategy.ca/2019-health-and-wellness-study
[6] https://www.grandviewresearch.com/industry-analysis/prebiotics-market
[7] https://internationalprobiotics.org/market-trends-the-microbiome
[8] https://www.biogaia.com

Figure 2:

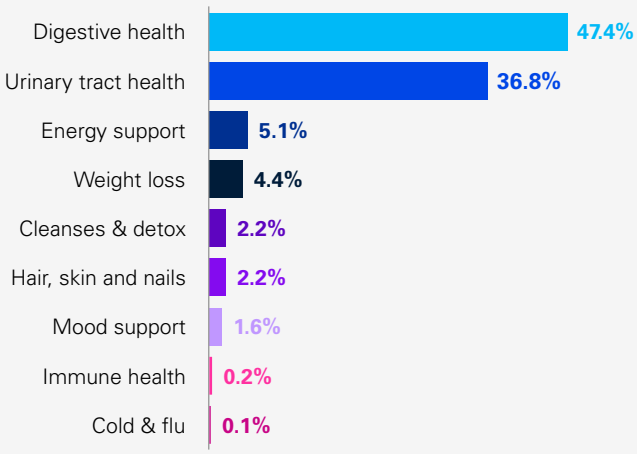
**Probiotics global market by product categories**




Source: https://www.ipaeurope.org/legal-framework/market-data

Figure 3:

**Probiotics supplements by health claim**




Source: https://internationalprobiotics.org/market-trends-the-microbiome

## Cosmetics and skin health

Topical pro- and prebiotics aim to improve the skin microbiome by locally administering selected microbes or establishing favorable conditions for a balanced microbiome. Respective products provide cosmetic benefits or improve skin conditions such as acne, atopic dermatitis or rosacea. The Lancôme Génifique[9] product line is an example of such a skin product. These high-end cosmetic products contain prebiotics and probiotics. AOBiome Therapeutics[10] is another example of a company focusing on probiotic cosmetics. Their technology is based on an ammonia-oxidizing bacterial strain that used to be present in the human skin microbiome but has been eradicated by modern hygiene practices. After successfully launching a line of cosmetics and hygiene products called "Mother Dirt", the company now focuses on clinical applications of its technology and runs several phase-2 clinical trials testing treatments for inflammatory skin conditions.

[9] https://www.lancome.fr/soin/par-gamme/genifique
[10] https://www.aobiome.com
[11] https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse
[12] https://www.enterobiotix.com

## Microbiome-based therapies

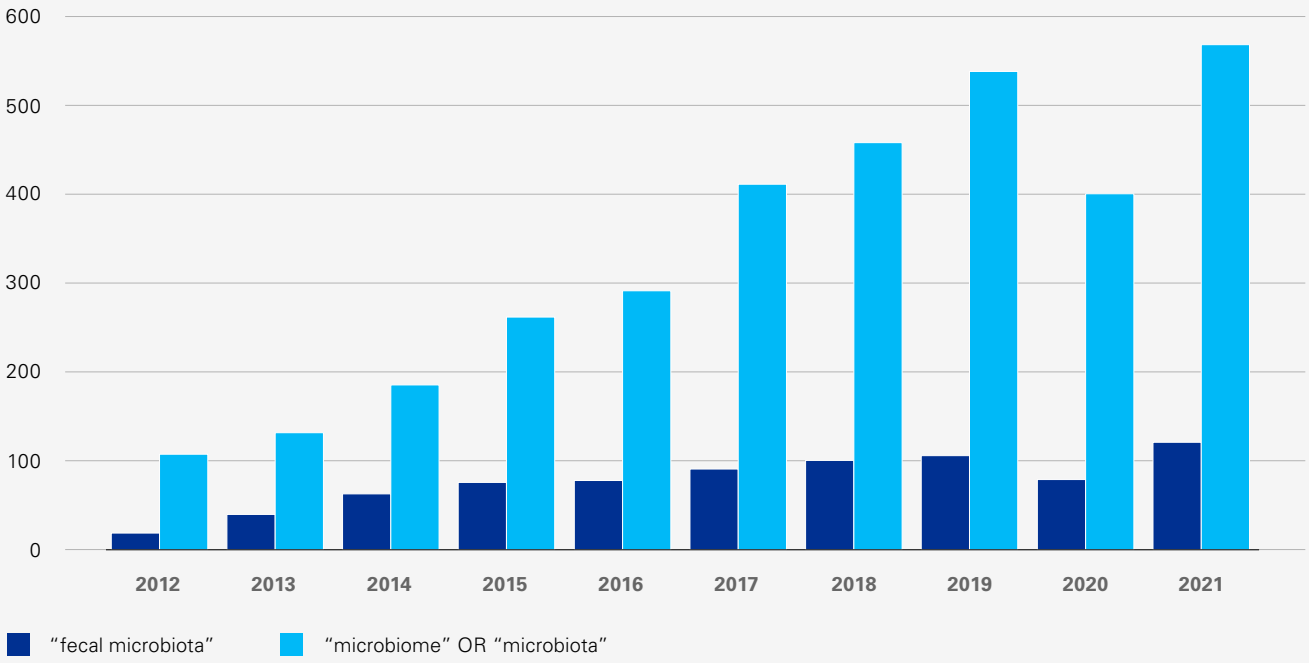
The previously observed increase in research activities is reflected in an increasing number of clinical trials starting each year in the microbiome space (Figure 4). A significant share of the tested interventions is Fecal microbiota transplantations (FMTs). However, more innovative product categories, such as live biotherapeutic products (LBPs) or phage therapies, are also gaining strong interest due to the high unmet need and resulting commercialization potential.

### Fecal microbiota transplantation

The first type of microbiome-based therapeutic intervention developed was fecal microbiota transplantation (FMT). The FMT procedure consists of administering fecal matter from a donor into the intestine of a recipient patient to confer a health benefit. FMT was shown to be effective in preventing recurrent C. difficile infection (CDI). However, FMTs remain difficult to implement due to a challenging donor selection, control of the microbial population composition and contaminations that can be lethal to immuno-compromised patients[11]. Companies such as EnteroBiotix[12] further develop FMT methods to provide safer and more scalable therapeutical products.

Figure 4:

**Number of clinical trials registered on clinicaltrials.gov in the microbiome space**




Source: Clinicaltrials.gov database, accessed on 29 August 2022 using the following keywords: "microbiome OR microbiota", "fecal microbiota"

### Live Biotherapeutic Products

LBPs are biological products that contain live organisms. They prevent, treat or cure diseases[13], distinguishing them from probiotics, which are not authorized to make the same claims[14]. Three companies currently have LBP candidates in clinical phase 3 or beyond (see Table 1). Rebiotix RBX2660 (commercial name Rebyota) became the first LBP to be authorized for commercialization after receiving positive recommendation by an FDA committee in September 2022 and final FDA approval in November 2022. Seres Therapeutics also recently filed a Biologics License Application (BLA) for its SER-109 product candidate that is formulated for oral administration. While the three LBPs presented in Table 1 are developed for the treatment of recurrent CDI, many other indications are entering clinical pipelines, such as LBPs to treat gastrointestinal disorders, mental health conditions, immunological and metabolic diseases, infectious diseases such as Covid-19[15] or to boost cancer treatments based on immunotherapies[16]. Once the first LBPs enter the market, we expect to see increasing investments in various therapeutic areas to leverage on the successes of these frontrunners.

### Dietary supplements repositioned as LBPs

Besides developing new products, some companies are repositioning dietary supplement products to reach the pharmaceutical market with LBPs. One example is Kibow Pharmaceuticals[21], currently investigating a derivative of its Renadyl™ supplement (US-APR2020) in a phase-2/3 clinical trial to support kidney function in patients with chronic kidney disease. The selected live bacteria metabolize toxins as nutrients and are designed as an enteric toxin reduction technology (Intestinal Dialysis™). Another example is BioGaia, which founded the subsidiary BioGaia Pharma[22] in 2017 to translate the company's experience in probiotics into pharmaceutical products. BioGaia Pharma currently runs two clinical trials with a drug candidate for the treatment of Ulcerative Colitis (phase 1) and the treatment of Opioid-Induced Constipation (phase 2).

### Non-live microbiome-derived drugs

Microbiome bacteria naturally produce specific microbial effectors that can be turned into drugs. The biopharmaceutical company Enterome[23] leverages the bioactivity of proteins or peptides produced by the gut microbiome to modulate the activity of epithelial or immune cells in the intestinal tract. The company has four cancer vaccine candidates. Their lead product, EO2401, is currently being tested in combination with

[13] https://www.frontiersin.org/articles/10.3389/fmicb.2019.01047/full
[14] https://www.nature.com/articles/s41467-020-15508-1
[15] https://www.4dpharmaplc.com/en/newsroom/press-releases/clinical-update-phase-ii-covid-19-study
[16] https://www.nature.com/articles/d41586-022-01959-7
[17] https://www.rebiotix.com
[18] https://mybiotics-pharma.com
[19] https://www.serestherapeutics.com
[20] https://www.finchtherapeutics.com
[21] https://kibowpharma.com/about-us
[22] http://biogaiapharma.com
[23] https://www.enterome.com

Table 1:

**Companies with an LBP candidate in pivotal development**

| Company name | Lead product (Phase 3+) | Other products | Collaborator or acquirer |
|---|---|---|---|
| Rebiotix[17] | RBX2660 (Rebyota) | LBP for the treatment of bacterial vaginosis | Ferring Pharmaceuticals (acquired Rebiotix in 2019)<br><br>Partnership with MyBiotics[18] |
| Seres Therapeutics[19] | SER-109 | Product candidate in clinical phase 2b for the treatment of ulcerative colitis | Nestlé Health Science partnership<br><br>Bacthera (support and extension of manufacturing capabilities) |
| Finch Therapeutics[20] | CP-101 | Three product candidates for the treatment of Ulcerative Colitis, Crohn's Disease and Autism Spectrum Disorder in pre-clinical stages | Takeda (deal concluded in 2017 and terminated in 2022) |

nivolumab in a phase-2 clinical trial in collaboration with Bristol-Myers Squibb. Furthermore, Enterome develops microbiome-derived drugs for treating inflammatory and autoimmune diseases and collaborates with Nestlé Health Science to treat food allergies. Evelo Biosciences[24], a biotechnology company, develops products containing extracellular vesicles (EVs) secreted by microbiome bacteria. These vesicles are non-live, present a placebo-like safety and tolerability profile, and can be used as a carrier to deliver microbial effectors. The company expects to initiate clinical trial investigations to treat inflammatory diseases in 2022[25].

### Targeted phage therapy

LBPs are designed to populate the recipient's microbiome with one or more selected microbial strains. However, depletion of other strains might be necessary to manipulate the microbiome's composition in the desired way. The field of phage therapy aims to develop viruses (bacteriophages) that exclusively infect bacteria, not human cells. But no such treatment has been approved in Europe or the US. BiomX[26] develops natural and engineered phage cocktails to kill harmful bacteria in chronic diseases. The company has two drug candidates in clinical phase 1 tested for treating cystic fibrosis and irritable bowel disease. In collaboration with Janssen and Boehringer Ingelheim, BiomX also builds a platform for discovering predictive microbial genomic signatures in the gut microbiome, aiming to develop biomarkers of diseases or responses to treatments based on bacterial gut composition. Eligo Bioscience[27] and SNIPR Biome[28] use bacteriophages as vehicles to genetically modify microbiome bacteria with the CRISPR technology. They develop different applications to kill harmful bacteria or to provide a gain of function by manipulating microbiome bacteria to transiently express one or several exogenous genes. SNIPR Biome initiated a first-in-human clinical trial in 2022 with a cocktail of four bacteriophages designed to reduce E. coli colonization in the gut.

## Diagnostics

Accurately capturing the composition of microbiome samples is essential to understanding the cause of linked pathologies and to develop targeted therapies. Once microbiome-focused treatments will reach the market, HCPs need to be able to select the right drug for the right patient. Accordingly, the need for rapid, affordable and precise diagnostics will increase. However, current next-generation sequencing is limited in this regard, and there is a need for better-suited technologies. Perseus Biomics[29] currently develops a technology based on optical mapping to capture strain-specific signatures from native single DNA molecules. The service will cover diverse microbiome research and drug development applications.

[24] https://evelobio.com
[25] https://www.biospace.com/article/releases/evelo-biosciences-presents-new-preclinical-data-for-extracellular-vesicle-anti-inflammatory-product-candidate-edp2939-at-the-american-association-of-immunologists-meeting
[26] https://www.biomx.com
[27] https://eligo.bio
[28] https://www.sniprbiome.com
[29] https://www.perseusbiomics.com

# What challenges are you facing when entering the microbiome area?

While the probiotics and prebiotics food and supplements category has matured, other categories such as cosmetics and pharmaceuticals are just starting to emerge. Despite the promise of LBPs, challenges remain to be overcome before patients routinely use respective treatments. Frontrunners in the market must protect their innovations, strategically position themselves and ensure manufacturing quality, regulatory compliance and patient acceptance.

## How to protect your innovation?

In the past decade, intense patenting activity has occurred in the microbiome field[30,31]. Academia and start-ups have driven development and own the most valuable microbiome intellectual property (IP) portfolio. However, protecting LBPs can be challenging, especially for products based on single-strain bacteria. Natural phenomena such as bacteria isolated from biological samples cannot be protected[32]. Therefore, respective patent claims are based mainly on the method of treatment. We expect patent challenges to intensify once commercialization begins[33,34]. Innovators should proactively stress-test and future-proof their IP strategy to prevent unforeseen challenges in this new and dynamic industry.

## How to strategically position yourself in this growing market and make sure you are not missing out?

As various products and companies are shaping the microbiome space, entering and navigating the market is challenging. A successful market entry and strategic positioning tailored to the company's potential requires detailed market analysis, including competitor landscape, customer needs and suitable market entry strategies. Companies can decide to invest organically, choose the right partner(s), or develop or join a human microbiome ecosystem.

## How to maneuver and equip yourself in this very specific microbiome manufacturing area?

Manufacturing pharmaceuticals based on the human microbiome is challenging and requires tailored solutions and processes. The products differ from conventional pharmaceutical drugs, and mastering the GxP is a must. For instance, during the LBPs manufacturing process, the selected bacterial strain of interest must survive and remain contaminant-free. Maintaining end-to-end oxygen-free conditions from culture to formulation requires tailored fermentation solutions that differ from food industry practices, where the viability of the stains in products is a lesser concern.

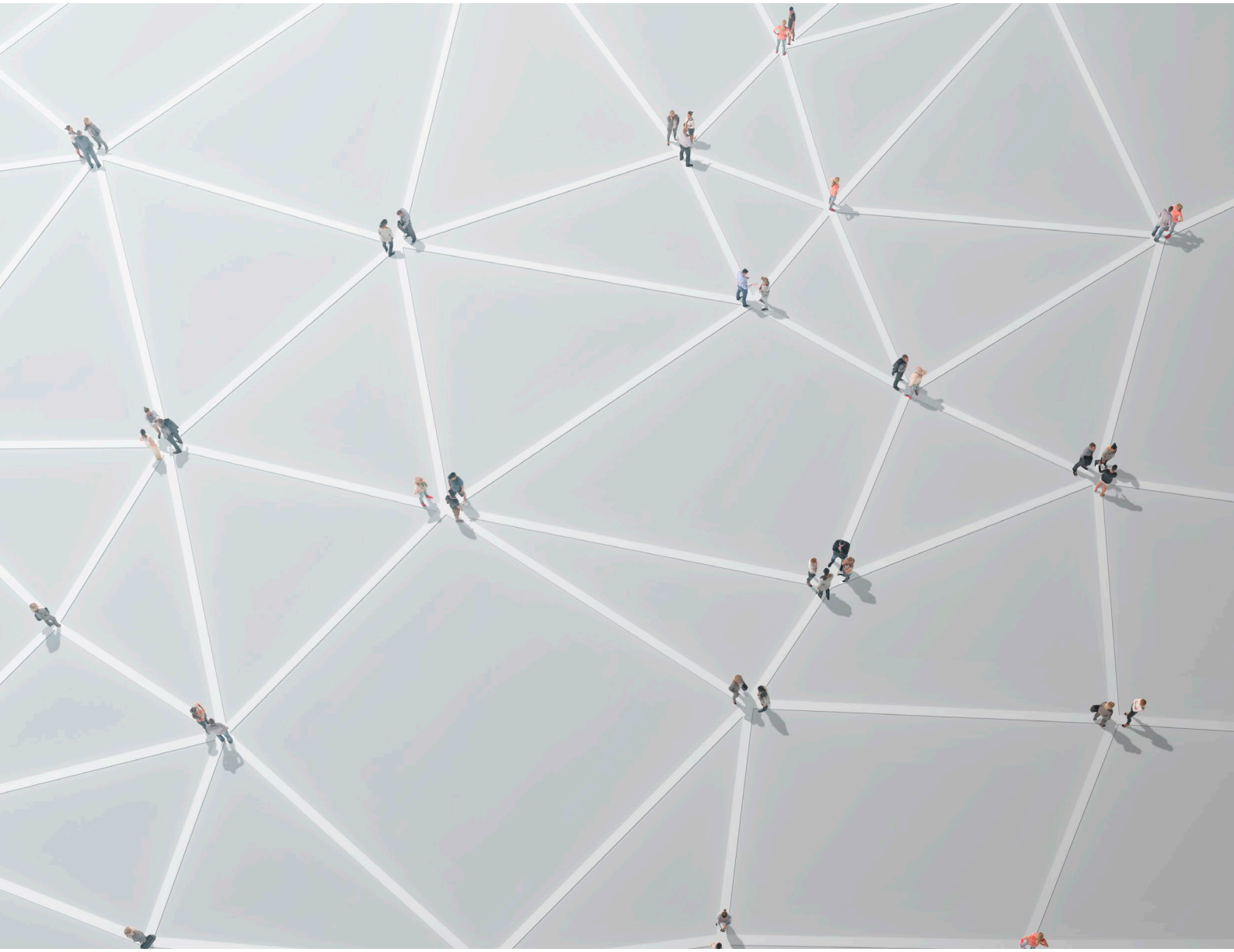
Once successfully grown, LBPs must be formulated and packed, considering their viability requirements and mode of administration. Specialized CDMOs such as Bacthera[35] and Arranta Bio[36] offer dedicated services to support their clients in developing and producing LBPs that meet the required standards. Arranta Bio has notably deployed a US$100 million expansion effort to build in-house microbiome manufacturing capabilities to address the microbiome market[37].

[30] https://www.frontiersin.org/articles/10.3389/fbioe.2018.00084/full
[31] https://www.nature.com/articles/nrd.2016.48
[32] https://www.pharmaceutical-technology.com/comment/live-biotherapeutic-products
[33] https://www.microbiometimes.com/eligo-v-snipr-a-reflection-on-ip-strategies
[34] https://www.iam-media.com/article/pgr-decision-provides-much-needed-clarity-in-fast-growing-microbiome-space
[35] https://www.bacthera.com
[36] https://arrantabio.com/microbiome-lbp-manufacturing
[37] https://www.fiercepharma.com/manufacturing/arranta-bio-splashes-100m-into-clinical-commercial-cdmo-capacity-at-massachusetts

## How to navigate through and be compliant with the microbiome regulatory process?

Due to the innovative nature of most microbiome-based therapeutical treatments, the regulatory framework lacks precedence. LBPs significantly differ from other medicinal products since their biological effect is multifactorial, indirect, complex and not necessarily deciphered. Because the host and microbiome co-evolved, developing relevant animal models is challenging. Risk-based approaches accompanied by tight quality controls are required to ensure the safety of LBPs for human use when entering clinical trials. The FDA officially introduced the LBP category in 2012, and the European Directorate for the Quality of Medicines and Healthcare (EDQM) recognized LBPs as a new category of medicinal products in 2019. Ysopia Bioscience entered the first-in-human clinical study with LBPs[38] and interacted with competent authorities pre-IND to de-risk their approach and clarify expectations. Competent authorities are willing to collaborate with LBP developers, as such early interactions help to identify areas where specific guidelines are needed allowing the LBP regulatory framework to take shape.

[38] https://www.frontiersin.org/articles/10.3389/fmed.2021.716266/full



# Your partner in the nascent human microbiome industry

## Enterprise and portfolio strategy

We help our clients solve their most strategic problems by identifying opportunities for sustainable growth and performance, by finding partners for internal projects or inorganic growth and by conducting asset valuation and commercial due diligence

## Commercial strategy

We support our clients in crafting their go-to-market and launch strategy globally by conducting competitive and market analyses and determining the pricing and market access strategy aligned with their objectives

## Operations strategy

Because different companies and products have different constraints, our practice helps clients determine the most appropriate operating model for their business and helps achieve drastic performance improvement that translates into bottom-line impact

## Who we work with

Large bio-pharma companies

Biotech and clinical-stage start-ups

Medtech and diagnostics providers

Commercial, academic and hospital labs

Investors

## Why KPMG?

**We have extensive experience**
Our practice has worked with clients in the microbiome sector and is highly experienced in supporting biotech companies with commercial strategy and market entry in the EMA region.

**We blend deep scientific expertise with business know-how**
Our team brings together experienced life scientists attuned to the challenges faced by R&D-intensive companies and talented strategy practitioners.

**We bring global strength**
KPMG has access to a network of local teams and subject matter experts working together as a global team to tailor our approach to the specific nuances of each market.

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