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Review Article

Current Regulation and Initial Considerations for Successful Development and Commercialization of Microbiome Therapies

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The gut microbiome is frequently referred to as the "second brain" or "second genome," referring to the impact of the gut microbiota on our health. The microbiome is formed at birth, grows with the host, and is impacted by environmental variables such as nutrition, antibiotics, and lifestyle. Understanding the host health-gut microbiota correlation opens the possibility of modifying the gut microbiome to manage an individual's health. Several techniques, such as probiotic, prebiotic, synbiotic, and faecal microbiota transplantation (FMT), are explored to alleviate the dysbiosis-related negative consequences and restore the gut microbiota in humans. While microbiome-based medicines have made remarkable progress in the last decade, from prebiotics and probiotics to live biotherapeutics, there are still safety concerns and regulatory issues to be addressed. The FMT treatment is currently experimental and lacks authorization, posing numerous ethical, legal, and social challenges that must be resolved as part of an effective regulatory policy response. This study gives an outline of our current understanding of microbiome restoration approaches as well as safety concerns regarding how these approaches are regulated. It presents an outline of the contemporary gut microbiome therapeutic development landscape and an assessment of the commercialization hurdles encountered.

1. Introduction

The microbiota is a bacterial ecology found in the environment and various parts of our body, including our skin, eyes, and gut. The human body contains roughly 10 trillion bacterial cells, 80 percent of which are healthy [1]. The human gut microbiome comprises various microorganisms living in synbiotic relationships with humans. Diet, antibiotic use, and lifestyle choices have all been linked to changes in the gut microbe's ecosystem, which can lead to various clinical disorders [2]. The gut bacteria impact brain function and behaviour via the gut-brain axis, which is mediated by neurological, immunological, and endocrine pathways [2].

Traditional drug development has long overlooked the significance of the human microbiota. This subject has the potential to influence all essential aspects of drug research, including target discovery, more accurate disease animal models, toxicity, and drug metabolism, as well as enhanced patient subtyping for clinical studies and the generation of new treatments [3]. Understanding our cohabitants and the link between the host and the microbiome might reveal light on how microorganisms may influence, treat, modify, or even prevent illness, given that the human body has a nearly equivalent proportion of bacterial cells to human cells [4].

The Human Microbiome Initiative, a five-year project launched by the National Institutes of Health (NIH), was aimed at defining microbial populations at five main body sites and developing a reference database for potential health and disease research using microbiomes. The human microbiome study found that the gut microbiome, which includes microorganisms such as bacteria, fungus, archaea, viruses, and protozoa, numbers over 100 trillion [5]. Humans have the largest concentration of microbial populations in the gut. These gut microbes are a complex ecology of bacteria that may interact with intestinal mucosa and are vital to several physiological functions, such as immunity, absorption, and transport of nutrients. Because of the complicated

synbiotic interaction between gut microbes and their hosts, changes in microbial composition can have a direct influence on physiologic function.

There is convincing evidence connecting alterations in gut microbiota with a range of gastrointestinal (GI) and non-GI disorders. These gastrointestinal conditions include hepatic encephalopathy, enteric infections, Crohn's disease, and enteric illnesses. Obesity, diabetes, other metabolic disorders, autism, autoimmune diseases, infections, and some neurological problems, including Parkinson's disease, are some non-GI diseases linked to gut microbiota alterations [6].

The gut microbiota significantly affects the host's health. It helps with immune response development, infection prevention, nutritional acquisition, and potentially cognitive and nervous system performance. A diverse microbiota is associated to health and long-term stability, and the loss of diversification over time may also be predictive of increasing disease risk. Lack of exercise, a diet heavy in processed carbs and salt, and poor dietary fibre consumption are all linked to gut flora depletion and an increased risk of chronic illness [7].

Various disorders disrupt the gut microbiota, resulting in a condition known as dysbiosis. FMT, probiotic, or live biotherapeutics may correct abnormalities in the gut, its related immune system, and other functions by influencing their development and function. Several illnesses, including obesity, metabolic diseases, both type 1 and type 2 diabetes, allergy, atherosclerosis, and nonalcoholic fatty liver disease (NAFLD), have been associated to dysbiosis (a potentially hazardous alteration of the microbiota's composition) [3].

Microbiota transplantation refers to the transfer of biological material containing a minimally modified collection of microbes from a human donor to a recipient with the intention of improving the microbiota of the recipient [7].

2. Factors which Influence Gut Microbiota

2.1. The Gut Microbiota and Diet. Diet not only provides nutrition but also has an impact on health by influencing the makeup and diversification of the microbiota. According to recent research, some microbial species in the microbes can leave and resurface seasonally based on seasonal food availability [8–10]. As a result of an animal-based diet, bile-tolerant microorganisms, such as *Alistipes*, *Bilophila*, and *Bacteroides*, may become more prevalent, while the number of Firmicutes in the gut may decrease [11]. Studies have shown that people who follow vegetarian diets for extended periods of time may have a greater number of bacteria in their gut that help break down fibre, such as *Clostridium clostridioforme*, *Faecalibacterium prausnitzii*, and *Bacteroides thetaiotaomicron*. The populations of the bacteria *Bifidobacterium*, *Streptococcus*, *Collinsella*, and *Lachnospiraceae* are dense in omnivores; however, the population of the *Subdoligranulum* bacteria is lower [2].

2.2. Antibiotics and Gut Microbiota. Antibiotics have long been used to treat disorders caused by bacterial infection. However, antibiotics have been criticized for their use in treating pathogenic infections, since they may alter the diversity and function of the gut microbiome, resulting in physiological changes. A common example of a medication altering the microbiome and impairing the health of patients is *Clostridioides difficile*-associated diarrhoea (CDAD) [2].

2.3. The Gut Microbiota and Lifestyle. The gut microbiome is also affected by lifestyle. Human gut microbial composition is altered by behaviours such as tobacco consumption and lack of exercise. Stress is another lifestyle element that influences the gut microbiome [12–14]. Stress may reduce Bacteroides but increase *Clostridium* genus levels in the gut, which may impact immunity [9–11].

3. Restoration of the Microbiota

Many therapies have been developed and used to cure diseases caused by dysbiosis. Various strategies to restore gut microbe include the following:

(a) Probiotic, prebiotic, and engineered probiotic treatments

(b) Faecal microbiota transplantation (FMT)

3.1. Probiotic, Prebiotic, and Engineered Probiotic Therapies. In recent decades, the human microbiome has evolved as a biomarker that can describe the condition of one's health, provide a prognosis, and predict how well a medication will work [5]. The word probiotic derives from the Latin word "pro," which means "for," and the Greek adjective "biotikos," which means "suited for life." Together, these two words form the modern English word.

In the 1970s, probiotics were used to promote intestinal microbial balance. The 2001 Expert Committee for the United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO) defines probiotics as "live bacteria that bestow a health benefit on the host" [15].

Probiotics are living microorganisms that provide health advantages to their hosts when given in sufficient amounts. The term also includes well-characterized safe gut synbiotic microorganisms (specific strain or strain combinations) whose absence may seriously affect a host's health [2].

Probiotics have been used safely for generations, but their economic benefit was not recognized until the early twentieth century. By 2020, it was anticipated that the global probiotic market will be valued at $46.55 billion and will be dominated by food corporations, nutraceutical companies, and probiotic production companies. These products include probiotic organisms produced mostly from the gastrointestinal tract or conventionally fermented foods, such as pickle, yoghurt, and kefir grains. Thus, the majority of probiotics supplied and utilized in probiotic research and commercial probiotic manufacturing are sourced from a small number of species, specifically the *Lactobacillus* and *Bifidobacterium* species [2].

In vitro and in animal models have shown that probiotics may exert these benefits in a variety of ways, such as by

suppressing infections or their metabolites, by modulating mucosal immunity, or by improving mucosal integrity [15].

Probiotics are characterized and cultivated in a pure culture which reduces the risk posed by probiotics [16]. According to a recent meta-analysis, probiotics and synbiotics can successfully decrease the fasting levels of blood sugar in diabetics, most likely by restoring the disrupted ecology [17–19]. It has been shown that probiotics can improve health by increasing the barrier of the gut epithelium, producing bacteriocins and lactic acid, lowering the pH of the gut, and modulating the immune response through these pathways [2].

Lactobacillus species, *Bifidobacterium* species, *Escherichia coli*, *Enterococci*, and *Weissella* species are among the numerous commercially available probiotics. The main effects of probiotic administration are improving intestinal barrier function, increasing IgA levels in the gastrointestinal fluid, restoring the gut microbiome homeostasis, and reducing gastrointestinal pathogens by producing antibacterial components and essential molecules [16].

With regard to their intended usage, many probiotic categories have been established around the globe. The United States provides dietary supplements, medicines, live biotherapeutic agents, and medical food as examples of subcategories of probiotics. Japan, India, China, and Malaysia also provide functional foods, Belgium and Germany provide biotherapeutic agents, Italy provides dietetic products, Canada provides natural health products, and some European nations like Denmark, Sweden, and Finland provide food supplements.

A precision probiotic would be a combination of commensal microorganisms and bacteriophages specifically engineered to alter the microbiota from a diseased to a healthy condition [20].

3.1.1. United States, Canadian, and European Regulations on Dietary Supplements. According to the Dietary Supplements Health and Education Act (DSHEA) of 1994, such products are regulated as foods and may claim about their ability to influence the "structure and function" of the body, in addition to claims about general well-being, as they do not claim efficacy in the diagnosis, prevention, or cure of any disease [3].

(1) Declarations of Nutrients. According to the US FDA, nutritional declarations specify the quantity of nutrients in food products. Regulations dictate what nutrients must be included on a label and how they must be presented. For labelling, the Codex has established a percent nutrient reference value; the United States and Canada, a percent daily value; and the European Union, a percent reference intake. The reference values for labelling are typically derived from authoritative assessments of nutrient needs for the generally healthy population (e.g., the DRIs in the United States). Food sources must be evaluated with a reference value prior to being labelled as "good" or "great" sources of a nutrient. Requirements are regulated by legislation in both the United States and Canada.

The European Union has strict requirements for nutritional claims and specifies them in the Claims-Regulation (European Directive 1924/2006) appendix [7]. The FDA classifies items based on the claims made by the marketer, not on the ingredients or any other characteristics of the products themselves. Because the product is classified as a drug, statements that it treats, cures, mitigates, or prevents illness trigger a costly investigational new drug (IND) application procedure. Because of this regulatory framework, probiotics have been sold as dietary supplements. Through this approach, structure-function claims can be made without obtaining FDA approval [21].

(2) Labelling Requirements for Some Dietary Fibres and Prebiotics. Manufacturers need to demonstrate that their isolated or synthetic nondigestible carbohydrate impacts human health before they name it "dietary fibre" on a food product in the US and Canada. These guidelines should be followed when labelling a prebiotic.

(3) Claims about Structure-Function and Function. Structure-function claims (US) or function claims (Canada and EU) are statements that illustrate how a food or dietary component may positively affect the body's normal functioning or physiological activity (e.g., fibre improves gastrointestinal health). No clinical condition or reduction in the risk of illness can be inferred from these statements. Function claims in Europe must be authorized before they may be utilized [7].

(4) Claims of Disease Risk Reduction. Food products and ingredients associated with a lower risk of developing diet-related diseases can claim to reduce disease risk. Scientific evidence supporting claims of disease risk reduction has been approved by regulatory agencies in the United States, Canada, and Europe. Unless listed in Schedule A of the Food and Drug Act, all claims for diseases and health disorders in Canada are subject to premarket review and clearance.

3.1.2. Regulatory Oversight of Live Biotherapeutics. The word probiotic is not used by regulatory agencies in the US. The terms "live microbial ingredients" and "live biotherapeutic agents" can be used interchangeably even though their definitions are explicit [22]. In this sense, commensal microorganisms isolated from the human host and used to treat diseases are categorized as Live Biotherapeutic Products (LBPs). LBPs are regulated by the FDA's Center for Biologics Evaluation and Research (CBER). These products contain living microorganisms (such as bacteria and yeast) which are used for treating diseases or preventing them from occurring. However, it is not a vaccine. The category accommodates a wide range of possible microbiome modulators. LBPs, like vaccines, should be manufactured following Good Manufacturing Practice (GMP) standards. Preclinical and clinical trials should be conducted to evaluate the efficacy, effectiveness, and safety of LBPs [5].

Dietary supplements typically contain living organisms that are not sufficiently characterized for IND submissions (for example, probiotic yoghurts). In order to qualify for human trials, CBER requires that LPBs possess a genotype

or phenotypical characterization, have defined potency (colony-forming units per dose or other assays that predict therapeutic activity), and meet quality acceptance criteria both in-process and in-product, as well as be free of extraneous contaminant organisms [3].

Fermented dairy products, such as yoghurts and kefir beverages, can include various combinations of microbes, such as *Lactobacillus* species and *Bifidobacterium* species, which are said to "support intestinal health" or "keep the balance of intestinal flora" [3].

Live microorganisms are classified as food or dietary supplements in the United States or as LBP agents if used as medications. Based on disease-specific utilization, synbiotic microorganisms isolated from the human host are categorized as LBPs. Most companies in the United States that develop products related to the microbiome choose either one of two routes: (i) FDA-approved therapeutics for specific medical conditions or (ii) the low-cost, low-rigor route of over-the-counter probiotics with wellness claims and claims of structure and function [23].

Microorganisms intended for food and feed applications in the European Union are granted the Qualified Presumption of Safety (QPS) status by the European Food Safety Authority (EFSA). The list does not include any gut-derived NGPs or manufactured probiotics, with the exception of *Bifidobacteria*. Biological and medical products with bacterial or yeast-derived active ingredients need EMA authorization. The Biosimilar Medicinal Products Working Party (BMWP) suggested the creation of the Committee for Medicinal Products for Human Use (CHMP) for biosimilar regulatory reviews [5]. Similarly, the European Directorate for Quality of Medicines (EDQM) formed a LBP Working Party in 2014 to develop a monograph to standardise the quality requirements for LBPs as biological, medicinal products.

(1) Live Biotherapeutic Product Development Pathway. Biological names and strain names are required for LBP applications. As required by FDA regulations, LBP applications should include information about the source of cells from which the product is derived, the culture history of the strains, a description of donor health, phenotype and genotype, and documentation and summary of modifications. The producer must also provide detailed information on the manufacturing process and facility, the materials utilized, and any other products manufactured at that site. As with any other drug substance, LBPs must meet the IND standards. Healthy volunteers are likely to participate in the first human research because of the focus on safety [22].

3.1.3. Next-Generational Probiotic (NGP). Since NGPs are composed of live bacteria and can be used to treat or prevent human disease, they fall under the FDA's definition of a live biological product: a biological product containing live organisms, such as bacteria, that is not a vaccine [22]. While established probiotic and microbiome research facilities can investigate NGPs, commercially motivated start-up biotechnology organizations or pharmaceutical firms are more likely to study LBPs.

3.1.4. Concerns about the Safety of Probiotics, Prebiotics, and Synbiotics. However, despite using probiotics for decades, precautions must be taken to avoid their potential side effects. A major concern is that probiotics might transfer genes for antibiotic resistance to microbial pathogens. Before being employed as food additives, probiotic strains should be screened for undesired genetic makeup, such as antibiotic-resistant genes, using sequence-based identification methodologies. Histamine and tyramine are biogenic amines that can be produced by certain *Lactobacillus* bacteria when they are incorporated into food. Systemic hypotension is a possible side effect of histamine vasodilation. Probiotics should be labelled with information regarding the possible risks they pose to people with health conditions, and this information should be provided to consumers [2].

3.2. Faecal Microbiota Transplantation (FMT). The faecal microbiota is extremely complex, including hundreds of bacteria species. The microbiota makeup varies between people and among persons at various time periods. The microbiota is a living, metabolically active, and extremely dynamic organism that is affected by various environmental factors, including the diet, in various ways [16].

FMT involves the transplantation of minimally modified microbes from human donors to recipients (including autologous transplantation) to influence their microbiota [24].

The goal of FMT is to restore or replace the native microbiota by introducing a full, stable population of microbes. In addition to helping rebuild healthy gut microbiota, FMT has also been found to be a successful therapeutic option for the treatment of *Clostridium difficile* infection (CDI), a serious illness that causes approximately 14,000 deaths each year across the United States and causes over 250,000 hospitalizations [6]. CDI has progressively increased in frequency, morbidity, mortality, and cost over the last decade. It is currently the most common nosocomial infection in the US. An estimated 625,000 cases of CDI occur in the United States and the European Union each year, resulting in inflammation, diarrhoea, and sometimes death. The disease accounts for nearly $1 billion in medical expenses each year. Increasing prevalence of CDIs, such as severe and recurring CDIs (rCDI), has resulted in a rise in the number of harder-to-treat cases [25].

A healthy donor's faecal suspension or purified faecal microbiota can be transplanted into the intestines of a diseased patient via a procedure known as faecal microbiota transplantation. Currently, it is the most effective treatment for rCDI, as well as treating a variety of digestive disorders, including inflammation of the gut, Irritable Bowel Syndrome (IBS), obesity, diabetes, anorexia nervosa, food allergies, and neurodegenerative and neurodevelopmental disorders [4].

FMT poses several moral, social, and regulatory issues. An important concern is to select and screen donors to prevent disease transmission, conduct a long-term study regarding safety and effectiveness, and obtain informed consent from donors. It could also result in the transmission of mental diseases and mood disturbances, such as sadness and anxiety, as well as deceptive claims about the improvement of health and lifespan [6].

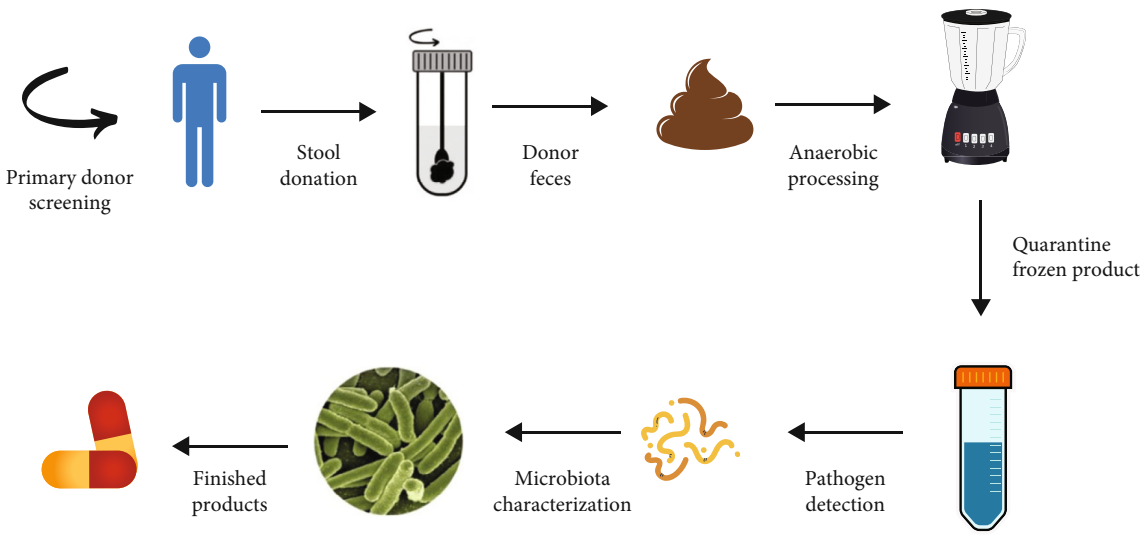

Figure 1: The schematic diagram of the faecal microbiota transplantation process.

FMT is commonly delivered through colonoscopy, enema, or injection into the upper intestinal tract. An ecosystem of gut bacteria with structural and functional equilibrium is transplanted from a pre-screened faecal sample. When the gut flora of a patient is imbalanced, the patient is most likely to develop a health condition, commonly as a result of antibiotic therapy, which removes some bacteria, while allowing others with inherent immunity to the drugs to flourish and overpopulate the gut. *C. difficile* is the bacterium most usually connected with this issue [16].

Frozen faeces, freeze-dried stool, and more advanced items such as capsules containing synthetic stool generated in culture and assembled are all examples of the wide range of products in this category [16].

3.2.1. History of FMT. Since ancient China, faecal solution preparations have been used to treat digestive disorders orally. In 1957, Stanley Falkow, a renowned American microbiologist, and the pioneer of molecular microbial pathogenesis, proposed administering capsules containing preparations of the patients' pre-surgical faeces in order to treat antibiotic-associated diarrhoea. The following year, Ben Eiseman reported in the US that faecal enemas are an effective treatment for pseudomembranous enterocolitis, also referred to as *C. difficile* colitis [4].

However, since the prevalence, the burden of disease, and deaths associated with rCDI have increased over the last decade, the adoption of donor faecal material delivery as a treatment method has gained traction. *C. difficile* strains have become increasingly contagious and virulent as broad-spectrum and strong antibiotics use has increased.

3.2.2. Process of FMT. The complete process for faecal microbiota transplantation is described in Figure 1.

(1) Selection of Donors. To limit and prevent the emergence of adverse effects, FMT donors must undergo rigorous screening procedures. Donors who have been screened should undertake a follow-up interview on the day of their donation to examine any recent potentially lethal behaviours. Standard donor screening processes should be established to reduce the risk of transmission of infection from the donor to recipient, and an eligible donor should undergo blood and stool tests four weeks before donation [26].

(2) Preparation of Faecal Material. Multiple randomized clinical studies and meta-analyses have proven that frozen FMT has the same clinical effectiveness as fresh FMT for treating recurrent or resistant CDI [24–27]. Fresh faeces should be treated within six hours after the donor's discharge and can be maintained at room temperature till further processing [28].

Using a blender, around 50 grammes of faeces is combined with approximately 150 millilitres of sterile normal sodium chloride. The least amount of faeces required is 30 grammes. A filter or gauze is used to filter the mixture to remove any big particle materials that might potentially restrict the endoscope channel. At last, the filtrate is injected into 60 mL syringes, typically 4e5 tubes, and then infused into the gastrointestinal system of the recipient. In a stool bank, the stool is collected from a group of donors who have been pre-screened, the donated faecal material is prepared and divided, and aliquots of the screened faecal material are frozen [29–31]. All these steps are part of the processing. In addition, the final faeces material needs to be meticulously maintained, which includes precisely labelling it, keeping track of it, and storing it at -80 degrees Celsius. On the day of the FMT, the faecal suspensions will be thawed in a water bath maintained at 37 degrees Celsius, and then, the saline solution will be added to get the predicted suspension volume [28].

(3) Recipient Preparation. Patients undergoing FMT require assistance and information before therapy, regardless of the source or method. Before faecal infusion, no antibiotics

should be administered. FMT preparation is comparable to other endoscopic procedures, including bowel preparation. Before the donor faeces infusion, the intestine should be clear of faeces contamination. Some studies recommend using loperamide an hour before FMT to keep transplanted faeces in the intestines for 4 h [28].

(4) Delivery Methods. The current methods for administering faecal material include oral capsules, esophagogastroduodenoscopy (EGD), and nasogastric, nasojejunal, or nasoduodenal tubes for the upper gastrointestinal tract and colonoscopy or retention enema for the lower gastrointestinal tract. Upper gastrointestinal FMT can be provided to patients with an inflammatory colon. However, tube installation pain, aspiration concerns, and inability to assess colon mucosa or collect tissue samples are weak points. FMT via colonoscopy recolonizes the entire colon with beneficial bacteria, and bowel cleansing can minimize the number of remaining organisms and spores in the colon, but it is a hazardous, costly, and intrusive operation. FMT through retention enema is less expensive and intrusive than through colonoscopy; however, donor faeces cannot be distributed to the whole colon. Oral capsule FMT offers low invasion and good patient acceptance, but it is expensive and burdensome [28].

(5) Monitoring Patients and Safety Concerns. In clinical trials and systematic reviews, common temporary adverse effects of FMT include abdominal discomfort, diarrhoea, constipation, and a low-grade fever, whereas uncommon significant side effects are frequently associated with endoscopy and anaesthetic difficulties [23–27]. The exact frequency and duration of follow-up to assess long-term adverse effects following FMT are yet unknown. The European consensus advises an 8-week follow-up period for CDI patients, as well as the collecting of diagnostic and analytical data [28].

3.2.3. Ethical, Judicial, and Social Concerns of FMT. Organ transplants and clinical investigations are morally challenging aspects of the FMT technique. As per FDA guidelines, the use of FMT products to treat *C. difficile* is an experimental procedure, and informed consent is required [6].

There are several morally and socially significant issues regarding informed consent and the vulnerability of patients, defining appropriate healthy donors, the safety of FMT, commercialization, and the possibility of exploiting vulnerable populations.

(1) Informed Consent and Patient Vulnerability. Both research and therapeutic care require the patient's informed, voluntary consent. A lack of information regarding potential side effects, the susceptibility of patients, and the unproven nature of the therapies may make it difficult to obtain informed consent for FMT.

(2) Defining Appropriate Healthy Donor. Donor selection influences FMT effectiveness, at least in part. Identifying, defining, and sourcing ideal donors have evolved into a critical clinical need and a scientific issue requiring multidisciplinary exploration. Screening potential donors and faecal and serum samples is critical for limiting the spread of pathogens and reducing the possibility of recipients being more exposed to chronic problems like obesity or immunological disorders. In several countries, stool banks are established to alleviate the burdens of enrolment of donors and the preparation of their stools. These include OpenBiome and AdvancingBio in the United States, the Taymount Clinic in the United Kingdom, the Netherlands Donor Faces Bank in Netherlands, and the FMT Bank in China.

3.2.4. Risks, Safety, and Privacy concerning FMT. As a general rule, FMT is regarded as safe, although the method in which it is administered (endoscopic surgery) is associated with several short-term hazards. Constipation, bloating, gas, and brief diarrhoea are the most prevalent adverse effects; however, they are usually minor and self-limiting. Some patients had cramping or constipation in the abdomen, fever, or increased C-reactive protein (CRP) within a few hours to a few days following FMT. An increase in severity of illness, interference with current treatment, and development of new infections are all possible dangers. The ethical and social consequences of FMT are of concern. Because of its utilization, there is a potential for privacy violations, especially for donors who have more knowledge about a person than their human DNA. It has been shown that "personal microbiomes include enough differentiating traits to distinguish a person over time" through recent developments in human microbiome research [32].

(1) Safety Concerns. Despite an estimated >70,000 FMT operations performed globally, there has been no single recorded incidence of transmission of infection from FMT. An approved production process or mandatory testing should be implemented for the detection of potential pathogens to ensure a reliable product. The risk of regulatory policy limiting access to this medicine, whether by raising clinical practice hurdles or promoting monopoly pricing, is that desperate patients will seek self-treatment. Only 6% of OpenBiome potential donors complete the whole screening procedure, which involves a 109-item clinical evaluation done by a clinician or physician and 30 stool and blood tests.

Due to the known and unknown risks associated with incorrect donor screening and unsatisfactory patient follow-up, as well as the ease with which patients can prepare and disperse faecal transplants without doctor supervision, any regulatory outcome that restricts access by either reducing supply or significantly increasing the cost of therapy should be implemented with extreme caution [33].

3.2.5. Potential Commercialization and Misuse of FMT. Commercializing FMT raises questions about property rights, data accessibility, and direct-to-consumer (DTC) products. Microbiota profiles that target specific diseases or optimal microbiota profiles that produce valuable goods could be patentable and earn millions of dollars in profit. Pharmaceutical corporations may be interested in "disease-specific stool" samples.

The FDA has concluded that faecal microbiota fits the statutory requirements for both a medication and a biologic product and should be regulated as a drug. In accordance with the Federal Food, Drug, and Cosmetic Act (FDCA), drugs are defined as "articles intended to diagnose, cure, mitigate, treat, or prevent disease, or products (other than foods) intended to affect the structure and function of man or animals." Biological products are defined in the Public Health Service Act as "virals, therapeutic serums, toxin or antitoxin, vaccines, blood, blood components or derivatives, allergenic products, proteins, or comparable products that prevent, treat, or cure disease or condition in humans." Biological products may be regulated under the FDCA, the PHS Act, or both [33].

The FDA's resolution to not impose the IND requirements for rCDI has widened access to the medication by allowing public stool banks like OpenBiome to function. The outcome of patients and the cost of healthcare have improved as a result. Recent research found that faecal transplantation saves $17,000 for each patient [33].

3.2.6. Investigational New Drug (IND) Application Process. An IND application must be submitted to conduct human clinical trials of an experimental or biological drug in the United States. For the use of FMT, a clinician/investigator can file one of the following INDs:

(i) Individuals who do not fit the requirements of an authorized research protocol or for whom no approved study protocol exists may be eligible to submit an emergency IND if the clinical circumstances do not permit the filing of an IND

(ii) Experimental medicines that show potential for serious or life-threatening illnesses in clinical studies can be submitted for greater access as treatment IND. This alternative should be employed by doctors and researchers who plan to treat more than a few participants with rCDI

(iii) FMT that is submitted as research IND can be provided or dispensed under the direct supervision of investigators (with or without subinvestigators). This is the method to employ if the information acquired from patients participating in the protocol will be used for future studies [25].

All acceptable IND applications require a sponsor, a treatment protocol including an informed consent form, and filled FDA forms 1571, 1572, and 3574. All first IND submission documentation should be submitted to the FDA, Therapeutic Biological Product Documents Room, 5901-B Ammendale Road, Beltsville, MD 20705-1266.

(1) Sponsor. A sponsor is required for all IND applications; in the context of FMT, the sponsor would be the person applying. The sponsor's obligations are detailed in 21CFR 312.50-312.70, subpart D. When submitting an IND application, the three forms listed above must be completed. It is required that all forms be provided in triplicate (an original and 2 photocopies are acceptable) [25].

(i) Form 1571: outline of the project's title and objectives. The FDA form 1571 is required for all IND submissions, including the initial IND submission. Preliminary examination of an application will result in an IND number, but study enrolment should not commence before thirty days after the FDA receives an IND or until an earlier communication from the FDA. It contains information about the drug's name, its intended usage, and its potential side effects, as well as information on the study's design

(ii) Form 1572: investigator and sponsor treatment facility description. This section should include information regarding the primary investigator, secondary investigators, and sponsor's site (clinic, hospital, or doctor's office). The name and location of the local Institutional Review Board (IRB) that authorized the FMT treatment protocol should be included

(iii) Form 3674: certification of compliance for clinical trials. In accordance with Title VIII, IND applicants must certify fulfillment of all relevant Public Health Service Act regulations (42 USC 282(j)) prior to filing their IND. These criteria can be completed by submitting FDA form 3674 along with FDA forms 1571 and 1572

FMT's effectiveness and safety will be further supported using an IND, which will allow for further data collection. Prescriptions for FMT for research or treatment of gastrointestinal conditions other than rCDI must be accompanied by an FDA-approved investigational new drug (IND) application [34].

3.2.7. Current FMT Regulatory Environment

(1) United States. FMT is referred to as an unapproved biologic medication by the Food and Drug Administration (FDA). While this is normally the most restricted categorization, the FDA has made an exemption for treating rCDI if the physician receives informed permission. This unique enforcement discretion policy reflects regulatory bodies' difficulties in balancing categorization with patient access. The first randomized controlled study of FMT was published in the New England Journal of Medicine in 2013 after Dutch investigators discovered evidence of its use in the United States. The FDA sponsored a public workshop in May 2013 to explore FMT's regulatory and scientific problems. FMT was classified as an unapproved biologic medication by the FDA at the workshop. It would be necessary for investigators to file an IND application before administering FMT to patients for any reason, and therapy could only be administered in clinical trial settings or during emergency situations.

The IND requirement concerned physicians, patient advocacy organizations, researchers, and medical societies who argued that an alternative regulatory method was needed for patients with rCDI. A discretionary enforcement approach was announced by the FDA in July 2013 in response. The FDA emphasizes in the statement that this is a temporary regulation until they investigate the problem further. Over the years, the FDA has iterated on its FMT regulations in a series of draft guidance [35]. These draft guidelines were submitted for public comment; none has been enacted. In March 2014, the FDA proposed amending the enforcement discretion policy, requiring that both patients and physicians know the stool donor and that all screening must be undertaken under the supervision of the physician administering the FMT. By implementing this plan, hospitals would have been allowed to run their own stool banks while friends and family would be able to contribute directly to public freestanding stool banks like OpenBiome in Cambridge, MA. Concerns about the proposed policy's impact on patient access were raised by a coalition of patient activists and medical professionals. The FDA released a new draft guideline for public comment in March 2016. For the treatment of rCDI, the FDA recommended that clinicians use public stool banks under an IND, according to its draft guideline. No draft or final guidelines have been released after the proposal's period for public comments ended in May 2016. According to healthcare professionals and advocates, the FDA will be better able to strike a balance between patient safety and accessibility by redesignating FMT as a Human Cell, Tissue, or Cellular- or Tissue-Based Product (HCT/P). While the HCT/P paradigm governs diverse treatment applications differently, the biologic therapeutic product classification requires a challenging carve-out for access to rCDI patients [36].

(2) Canada. Clinical Trial Applications (CTA) are required for the study of FMT by Health Canada because it is considered a novel experimental biologic medicine. Health Canada has published an interim policy allowing FMT for rCDI patient populations under specific conditions. Health Canada's usage criteria are more stringent and restrictive than the US. Health Canada's usage guidelines are more demanding and restrictive than those in the United States. Health Canada mandates physicians to get informed consent, establishes recordkeeping criteria, and provides a list of infections and microbiome-mediated illnesses for which donors must be negative. Additionally, the patient or a healthcare professional treating the patient must know the donor. In the absence of these criteria, rCDI patients can only undergo FMT under a CTA [36].

(3) European Union. The EMA has delegated decision-making authority to member states. The Competent Authorities on Substances of Human Origin Expert concluded that faeces do not qualify for inclusion in the European Human Tissue Directive 2004/23/EC and are not HCT/P at the European-level group of 2012 [37]. It was similarly based on a strict definition of directive provisions as the one in the United States. Although FMT contains both human and bacterial cells, it is beyond the scope of the directive due to the postulated active ingredient, which is bacterial. FMT can be regulated in any way that member countries see fit.

(4) Belgium. Stool products utilized in FMT is considered as human body substances, the equivalent of human cells or tissues. In October 2018, the FAMHP implemented the SHC's recommendations after Belgian legislators updated laws in December 2008 to allow stool to be classified as an HCT/P [36].

(5) France. An experimental drug, FMT is listed by the Agency National de Securite du Medicament et des Produits (ANSM). A hospital or pharmacy that manufactures FMT may use it in an approved clinical trial or when it is manufactured under Article L.5121-1 of the French Code of Public Health. FMT should be the last choice, intended for extreme or unusual cases where conventional therapies have failed, and no other therapy options are available [36].

(6) United Kingdom. The Medicines and Healthcare Products Regulation Agency (MHRA) regulates medicines and healthcare products. Many options for patients to get FMT are highlighted in the MHRA's position paper from June 2015. There are three ways in which pharmacies might create FMT for patients: in line with a prescription for a particular patient (known as the "magistral option"), for the pharmacy's patients (the "officinal formula"), or clinical trials. Under the "Specials" framework, a physician may prescribe FMT to an individual patient for use in direct supervision, in line with their requirements [36].

(7) Australia. There are four ways that patients might obtain FMT, which is currently considered an unapproved medicinal product by the Therapeutic Goods Administration (TGA). Patients can obtain FMT under the Special Access Scheme if their prescribing physician deems it necessary in certain rare cases. The TGA's Authorized Prescriber Scheme allows physicians who treat a specific group of patients to seek blanket authorization to perform FMT on all those patients for a specific indication in their treatment. TGA permission is required for patients who wish to import therapeutic items for their use or participate in a clinical study using FMT. The TGA is contemplating changes to the FMT rules. Stakeholders met in October 2018 to discuss the possibility of safely and therapeutically altering FMT regulation while maintaining its long-term availability [38].

3.2.8. Development and Commercialization Challenges

(1) The Paradox of Intellectual Property. Investment in microbiome research can be hampered by a lack of intellectual property and limited patent protection. For example, patent law does not allow natural materials or living organisms to be patented [39].

(2) Considerations for Clinical Development and Trial Design. Developing microbiome treatments is complicated

because a person's microbiome can vary when disrupted, and the specific mix of bacteria delivered clinically (e.g., via faecal microbiota transplantation or FMT) cannot be predicted. These studies have many factors that are hard to control. Additionally, selecting the correct patient group and accurately identifying patients for clinical trials can be difficult.

(3) Regulatory Frameworks. Regulatory systems have not kept up with microbiome-based medicines, and it is unclear which path these therapies will take for evaluation, despite the FDA issuing draft advice and signalling a readiness to dialogue with the industry [40]. It needs to be seen whether this results in developing a new regulatory pathway for microbiome-based treatments inside regulatory authorities. (The FDA has designated both medicines in phase III studies as orphan drugs for rCDI.) Manufacturers will likely charge a premium for these agents to fund their development.

Microbiome-based treatments, particularly those targeting CDI, clearly hold promise in regions of high unfulfilled need and major public health relevance. It is also obvious that the FDA is eager to collaborate with the industry on commercializing FMTs. Whatever the outcome, microbiome-based therapeutics for *C. difficile* infection will lead the way for additional indications, ushering in a new class of medications and treatment techniques into the clinic.

4. Conclusion

Microbiota research is a new therapeutic frontier, with researchers and clinicians anticipating its importance in human health. The FDA ruled that it is not "human" tissue and that any therapies containing microbes intended to affect the functions of the gut microbiome, including stool-based FMT products, must be categorized as drugs/biologics.

Microbiome treatments are a promising new area of medicine for treating a broad variety of conditions. To successfully develop and market these treatments, however, a number of issues must be resolved. The present regulatory landscape is one of the most significant issues. The regulatory environment for microbiome therapeutics is complicated, with specific guidelines needed for everything from the design of clinical trials to the quality control of manufactured products.

The human microbiome presents an additional obstacle because of its complexity. Understanding how these microorganisms interact with one another and with the human body is still an active topic of research since the microbiome is a complex ecosystem of bacteria, viruses, and other microbes. When developing microbiome therapies, it is essential to carefully consider the characteristics of the microbiome, the mode of action of the therapies, as well as the potential risks and benefits of altering the microbiome.

A multidisciplinary strategy will be necessary for the successful development and marketing of microbiome medicines, integrating specialists in microbiology, clinical research, regulatory affairs, and commercialization. To guarantee the efficacy, safety, and accessibility of these treatments, it will be necessary to work closely with regulatory bodies, healthcare professionals, and patients. The potential advantages of microbiome medicines are huge, but their development and commercialization face considerable obstacles. New and innovative microbiome therapies are likely to be developed in the coming years with careful attention to regulatory requirements and scientific rigor.

Comprehending the microbiome and its specific relationship to the host health condition has transformed the paradigm and opened a wide range of species from across the evolutionary spectrum to be studied. Scientific research into the health advantages of certain commensals may result in the discovery of new bacteria that may be researched further to build disease-specific personalized medication.

Microbiome-based therapies have shown significant potential in treating various conditions, but there are still safety concerns that need to be addressed before these treatments can be widely used. Probiotics, prebiotics, and live biotherapeutics have shown promise, but more research is needed to fully understand their benefits and risks. Regulatory measures are also necessary to ensure the safe and effective use of these treatments. As research continues, microbiome-based therapies may become an important tool in managing and treating a wide range of health conditions.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

This graphical abstract provides an overview of the key elements involved in the development and commercialization of microbiome therapies, focusing on current regulations and initial considerations for successful implementation. *(Supplementary Materials)*

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