

## Regulating stool for microbiota transplantation

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### ABSTRACT

In 2017 *Gut Microbes* published “A proposed definition of microbiota transplantation for regulatory purposes,” in which the authors suggest that regulators should draw a line between microbiota transplants and biologic drugs composed of microbial communities (or other products derived from the human microbiome). They develop a definition of microbiota transplantation (MT) to help regulators draw such a line, and suggest that MT need not be, and cannot be, regulated as a biologic drug (a live biotherapeutic product). However, an agency’s regulatory scrutiny of a medical product should be commensurate with that product’s degree of risk to patients. Products for MT, such as stool, are likely to be as or more dangerous than more highly manipulated microbial products that scientists and regulators agree should be regulated as biologic drugs. Therefore, we argue that MT, as defined by the authors, should receive the same regulatory oversight as any other biologic product intended to cure, mitigate, treat, or prevent disease. We also suggest that regulators might not be able to operationalize the proposed definition of MT.

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Clinical practice guidelines now recommend using fecal microbiota transplantation (FMT) as treatment for recurrent *Clostridium difficile* infections (rCDI),<sup>1</sup> and numerous clinical trials are underway testing FMT’s safety and efficacy for other indications. Microbial communities from other human body sites are also being investigated for their therapeutic properties. Yet, the question of how to regulate stool for FMT, and potentially other microbial communities from other body sites, remains contentious. The FDA views stool for transplant as a drug when such transplants are intended to treat a disease,<sup>2</sup> but some commentators have opposed this approach and proposed alternatives.<sup>3,4</sup>

In their *Gut Microbes* commentary, *A Proposed Definition of Microbiota Transplantation for Regulatory Purposes*, Hoffmann *et al.* define microbiota transplantation (MT) as “the transfer of biologic material containing a minimally manipulated community of microorganisms from a human donor to a human recipient... with the intent of affecting the microbiota of the recipient.”<sup>5</sup> They state that such a definition is necessary for agencies to appropriately regulate MT-related products. The authors imply that minimally-manipulated MT products, such as stool

for FMT, should not be regulated as biologic drugs. On the other hand, their working group’s consensus was that microbial communities that have been more-than-minimally manipulated “would not constitute MT, but would be considered a probiotic or other product that FDA would likely regulate as a drug.”<sup>5</sup> According to Figure 1 in the article, stool-derived products such as purified microbial consortia and cultured cocktails of stool-derived microbes would be among the “most manipulated” forms of fecal material, and therefore presumably subject to regulation as a biologic drug (if the sponsor intends them to cure, mitigate, treat, or prevent a disease). When a product is regulated as a drug it undergoes a premarket review process in which an investigational new drug application (IND) is needed for nearly any use of the product unless and until it has been approved for marketing for at least one indication. Even if we agreed that a definition of MT was necessary to promote cogent regulation, we are not convinced that minimally-manipulated microbial products (e.g., stool) should receive minimal regulation.

Hoffmann *et al.* suggest that stool should not be regulated as a biologic drug because it is so complex that it is scientifically and economically

infeasible to fully characterize.<sup>5</sup> Characterization difficulties arise because stool is metabolically active and responsive to the environment; therefore, stool varies from person-to-person and stool from a single individual varies from one batch to another. However, ***if stool composition is dynamic and difficult to characterize, then a minimally-manipulated stool product for allogeneic transplant is possibly the most dangerous type of microbial product for a recipient.*** Compared to highly-manipulated but better characterized stool-derived products, stool from an asymptomatic donor is more likely to contain novel or uncharacterized viruses, bacteria, or protozoa that could be pathogenic, particularly for an already sick recipient. For instance, while conducting donor screening for FMT, Paramsothy and colleagues found a surprisingly large group of asymptomatic people with gastrointestinal parasites.<sup>6</sup>

Paramsothy *et al.* were identifying individuals who should be precluded from donating stool for a FMT study, and after applying their screening criteria they only enrolled approximately 10% of potential donors. The stool bank OpenBiome accepts fewer than 3% of potential stool donors.<sup>7,8</sup> So long as organizations know of relevant pathogens and have the capacity to screen for them, their accidental transmission usually can be prevented. However, not all healthcare organizations that want to undertake FMT have the capacity to conduct in-depth screening.<sup>9</sup> Even when organizations can undertake rigorous screening there is always the potential for novel pathogens to enter human communities and to spread through FMT before we are aware of or able to screen for them. A 2009 report by the Institute of Medicine stated that "...since 1980, new human pathogen species have been discovered at an average rate of over 3 per year."<sup>10</sup> Complicating matters further, the relevant professional communities have not reached consensus on criteria for selecting or screening donors and stool.<sup>8</sup> The FDA is the only federal agency with the authority to enact and enforce regulations to ensure that donors and stool are adequately screened. Without such oversight, some establishments might not adhere to the high standards of Paramsothy *et al.* or OpenBiome.

The FDA uses the concept of minimal manipulation in its tiered, risk-based approach to regulating human cells, tissues, and cellular and tissue-based products (HCT/Ps).<sup>11</sup> The agency assumes that

minimally-manipulated HCT/Ps present fewer risks to patients than highly-manipulated ones. We should not make this assumption for MT products intended for allogeneic transplant. While properly screened MT products might be relatively low risk, they generally will not be lower risk than highly-manipulated microbial products. A highly-manipulated, better-characterized, stool-derived product can be produced in a controlled context free of pathogens. Producers of a stool-derived product will not need to constantly screen donors or anticipate novel pathogens, and the product will have consistency in its numbers and species of microbes so that dose response and side effects will be easier to predict. For all of these reasons, we think a stool-derived product generally will be as safe or safer than stool for FMT, yet Hoffmann *et al.* definitionally separate the two types of product and suggest they should be regulated differently.

Of course, there is no guarantee that a stool-derived product with a limited and well-characterized selection of microbes would be as safe or safer than stool. The stool-derived product might lack important checks and balances found in a more complete microbial community or conferred by the complex matrix of human material in which that community is embedded. Purifying and simplifying the microbial community might permit microbes to become pathogenic. However, we agree with the FDA and Hoffmann *et al.* that stool-derived products meant to treat disease should be regulated as drugs, so significant adverse effects of such products should be identified during clinical trials. We believe it unlikely, therefore, that a risky stool-derived product would enter the market. On the other hand, if stool is regulated less stringently than stool-derived products, then risks associated with FMT generally, or with particular donor and stool screening regimens, might not become evident in a timely manner and many patients could be subjected to unnecessary risks.

Hoffmann *et al.* define minimal manipulation as "processing that does not alter the original relevant biologic characteristics of the transferred community of microorganisms."<sup>5</sup> But what are the original relevant characteristics of stool and how do we know when they have changed? If the scientific community has not adequately characterized the health-related functions of microbes in complex communities, and people's microbial communities are highly dynamic,

then clinicians and regulators lack metrics for determining when a microbial community's relevant properties have been altered by manipulation. Based on current efficacy data, FMT leads to resolution of symptoms of rCDI for over 90% of treated individuals,<sup>12</sup> but we do not know the mechanism by which it produces this effect and which (if any) microbes in the transferred community produce the effect. Given the current state of the science, the FDA may have some difficulties regulating stool as a drug, but it would also have difficulties operationalizing the proposed definition of MT.

If MT products, such as stool, are regulated less stringently than stool-derived products, the regulatory system could disincentivize investment in development of more standardized, better characterized, and possibly higher-quality microbial therapeutics. If FMT becomes widespread with little regulation, manufacturers of stool-derived products might fear that they cannot develop and sell such products at a price patients or payers will accept, even if the stool-derived products would be safer or more effective therapeutics. One could argue that a related phenomenon is already evident for probiotics. Manufacturers can make reasonable returns selling probiotics as dietary supplements and foods, and therefore have little incentive to invest in the costly, high-quality clinical trials and regulatory submissions necessary to prove their products' safety and efficacy as therapeutics.

If regulation should be related to a product's level of risk, and if regulation should incentivize the production of knowledge that patients, clinicians, and payers can use to make treatment decisions, then we do not think any stakeholders would be well served by regulating stool for FMT less stringently than stool-derived products. We acknowledge commentators' concerns that applying drug regulations to stool will reduce patients' access to an effective treatment for rCDI, and possibly for other indications. However, we believe the FDA's 2016 draft guidance<sup>13</sup> strikes a good balance between promoting access to FMT for rCDI and incentivizing the production of safety and efficacy data for both stool and stool-derived products. Ideally, FMT should be an interim solution to the treatment of rCDI or any other disease that might be treated using gut microbes. Patients and the medical community all have an interest in developing products that are safer, effective, and more stable and predictable than stool.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Notes on contributors

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