




Stool for fecal microbiota transplantation should be classified as a transplant product and not as a drug

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Fecal microbiota transplantation (FMT) or donor feces infusion is a therapy that aims to restore a perturbed gut microbiota composition and function. FMT is effective for treatment of patients with (multiple) recurrent *Clostridioides difficile* infections^{1–3} and recommended by current guidelines.^{4–6} In the near future, FMT may also become an accepted treatment option for other intestinal or extra-intestinal diseases.⁷

FMT is performed using suspensions made of donor stool from carefully selected and screened healthy individuals.^{1,7} Donor screening is time consuming and costly. Before the establishment of stool banks, physicians and patients had to find their own donors. This resulted in uncontrolled application of FMT, and the logistical challenge made physicians reluctant to offer FMT to their patients. To overcome these problems, stool banks have been established.^{8,9} The mission of those stool banks is:

- (i) to produce ready-to-use donor feces suspensions for treatment of patients,

- (ii) to improve the quality and safety of FMT by centralization and standardization,
- (iii) to increase the cost effectiveness of FMT, and
- (iv) to facilitate research.

Stool banks are built in concordance with the model of blood banks and should follow quality standards applied to other transplantation products. Most stool banks are non-profit institutions, operating at a local (institution-based), national or international level. Recently, a UEG-funded working group was initiated to define quality standards for stool banking and FMT, which will result in further standardization of this new treatment approach. The current costs to deliver a ready-to-use stool suspension are €1050–1700 in

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Europe.^{9,10} There are also commercial initiatives,¹¹ which may aim for much higher prices.

Driven by the needs of patients, stool banks have emerged as new entities in a landscape without existing regulatory boundaries. This lack of guidance and National or European legislation may become a serious threat to providing the treatment for severely ill patients. This is also illustrated by the recent safety alert in the US about the transmission of multi-drug resistant organisms through FMT,¹² which underlines the need for standardization, quality assurance, and a regulatory framework supporting the activities of stool banks. Legislation requires classification of stool as a product to treat patients. We strongly believe that stool should be considered a transplant product, or be regarded equivalent in status to blood products used for transplantation or transfusion purposes. The EU Tissue and Cells Directive (2004/23/EC) is best suited to guide FMT. Currently, this Directive does not cover FMT because the mechanism of action is not mediated by human cells. An adjustment to align this directive with the new reality of fecal transplantation is thus urgently needed. Only in the case of modification to the donated feces, other than those necessary for the conservation of the microbial community, does the product made of the donated feces become comparable to a drug and is best covered within the European directive for medicinal products intended for human use (2001/83/EC).

Unfortunately, the misclassification of donor feces suspensions as a drug or pharmaceutical product, although difficult to imagine, is still one of the possible outcomes of the current discussion about classification. Currently, stool has already been classified as a drug in countries such as France, Germany, and the United Kingdom. Recently, companies have formed the “Pharmabiotic Research Institute” in Europe and the “Microbiome Therapeutics Innovation Group (MTIG)” in the US. The mission of those groups is “to improve market access,” and to “enhance the regulatory, investment, and commercial environment for microbiome therapeutic drug product development.” Both groups have published statements about the classification of FMT as a drug.^{13,14} MTIG actively collaborates with the Food and Drug Administration for the evaluation of safety parameters related to microbiota-based therapeutic products. Concern has been raised by the MTIG that the existence and accessibility of material from stool banks limits enrollment into clinical trials for microbiome therapeutics. This illustrates how companies are active to influence the current discussion about classification and regulation of FMT. In fact, this discussion has already been troubled by commercial interest in the US some years ago.¹⁵

In this regard, it is important to mention the overall major disadvantages of classification as a drug, which

will result in time-consuming and costly registration processes, and a sharp and unjustified rise in costs. Most importantly, this will negatively impact availability and innovation, obstructing, for example, the future development of single-donor individualized solutions due to the requirements for standardization of active substances. We postulate that stool treatment defined as drug treatment is counterproductive. Stool is not a standardized product that is produced in a factory, but a highly diverse and donor-specific substance of human origin (SoHO) delivered by healthy, usually unpaid, volunteer donors. Therefore, stool suspensions require suitable guidance of quality and safety measures comparable to guidance of other SoHO (blood, tissues, cells and organs) within the EU.

If government authorities seek affordable and quality-assured FMT, a supportive regulatory framework, in combination with appropriate funding or reimbursement, is required for stool banks. This will not only guarantee broad access and safety of FMT, but also enable the future innovation of this new treatment strategy targeting the gut microbiota. If eventually future research results in the replacement of FMT by standardized mixtures of bacteria (or another yet undiscovered stool extract that could theoretically underly the clinical effects of FMT), these should indeed be regulated as a drug or pharmaceutical product.

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