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Regulatory Oversight of Fecal Microbiota Transplantation (FMT)

Considerations for Treating Clinicians

Carolyn Edelstein

Abstract

Fecal microbiota transplantation (FMT) follows a unique model of federal oversight in the United States. Although the U.S. Food and Drug Administration (FDA) considers FMT an investigational new drug, physicians may use FMT to treat patients with recurrent *C. difficile* infection under the agency’s policy of “enforcement discretion.”

This document provides answers to frequently asked questions regarding the regulation of FMT, with an emphasis on the U.S. context.

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Introduction

The Food & Drug Administration (FDA) considers fecal microbiota for transplantation an investigational new drug (IND), a classification that typically requires physicians and scientists to file an IND application if they intend to use the treatment in humans.

However, in 2013, FDA issued [guidance](#) stating that FMT may be used to treat *C. difficile* infection not responsive to standard therapies without filing an IND application, provided that physicians obtain informed consent from the patient or a legal representative that includes informing the patient that FMT is an investigational therapy, and a discussion of its known and potential risks.¹ The FDA stated that they would exercise their “enforcement discretion” for the use of FMT under these circumstances. All other uses of FMT in the U.S. must be performed under IND.

FDA's 2013 guidance is an interim policy to address urgent patient needs associated with life-threatening *C. difficile* infection. The Agency has subsequently published two draft guidance documents, in 2014 and 2016, which have not yet been enacted.

Key Takeaways

- Prevailing FDA guidance allows physicians to perform FMT to treat *C. difficile* infection not responsive to standard therapy without filing an IND.
- Physicians who intend to use FMT to treat *C. difficile* infection not responsive to standard therapy must obtain adequate informed consent from the patient or a legal representative for the use of FMT products.
- FDA does not restrict the use of FMT to any particular route of administration (e.g., colonoscopy, naso-enteric delivery, oral capsule).
- Treatment of indications other than *C. difficile* infection not responsive to standard therapy must be done as part of an IND application to the FDA.
- IND applications may be obtained for clinical trials to treat multiple patients, single patients, and single patients under emergency circumstances.

Frequently Asked Questions

Can physicians perform FMT without an IND application (outside of a clinical trial)?

Yes, physicians may use FMT without an IND application to treat patients with *C. difficile* infections not responsive to standard therapy.

When the FDA announced in May 2013 that it would regulate fecal microbiota as an investigational drug, medical professional societies, physicians, and patients reacted with concern that the policy would limit access to a therapy that has shown promising safety and efficacy in patients with few remaining therapeutic options.²

Responding to these concerns, FDA issued guidance in July 2013 stating that it would exercise “[enforcement discretion](#)” – that is, it would allow doctors to provide FMT (for patients with *C. difficile* infections not responding to standard therapies) without filing an IND application.¹

What are the conditions for performing FMT without an IND application?

- Physicians may only use FMT without an IND application to treat patients with *C. difficile* infection not responsive to standard therapy.
- Physicians must obtain adequate informed consent from the patient or a legal representative, that includes, at minimum, a statement that the use of FMT products to treat *C. difficile* infection is investigational, and a discussion of the therapy's potential risks and alternative options.

FDA has also issued recommendations regarding screening donors for certain pathogens, specifically multi drug-resistant organisms (MDROs), Shiga toxin-producing *E. coli* (STEC) and enteropathogenic *E. coli* (EPEC), and SARS-CoV-2.⁷⁻⁹ Read FDA comments on donor screening of MDROs, STEC, EPEC, and SARS-CoV-2:

- [Screening and testing of stool donors for MDROs](#)
- [Screening and testing of stool donors for STEC and EPEC](#)
- [Screening and testing of stool donors for SARS-CoV-2](#)

Physicians may use material from a donor identified by the patient or physician, or from a stool bank. There are no requirements dictating the route of administration for FMT (e.g. colonoscopy, naso-enteric delivery, oral capsule).

Can physicians perform FMT for indications other than *C. difficile*?

Yes, physicians who would like to use FMT products for any other diseases must file an IND application with the FDA, requesting permission to use an investigational drug in human subjects.

This [publication](#) provides a guide to preparing an IND application for FMT.³ It summarizes the types of INDs that may be appropriate (a research IND, an emergency IND, and a treatment IND), the roles and responsibilities of those applying for an IND, the elements of the IND application itself, and the responsibilities and additional documentation needed to maintain an IND application.

Do stool donors need to be "known" to the physician or patient?

No, under the prevailing guidance the FDA does not require donors to be "known" to either the physician or patient.

In [March 2014](#), the FDA released draft guidance, for public feedback only, concerning two proposed changes to the current policy: (1) that the donor be "known" to the patient or physician and (2) that all donor and stool screening be conducted under the supervision of the physician performing the FMT.⁴ Medical professional societies raised concerns about the proposal's potential to compromise access and safety.

In [March 2016](#), the FDA revised the draft guidance to propose that enforcement discretion be narrowed so that physicians who obtain material from stool banks to treat *C. difficile* infection that is not responsive to standard therapy do so under IND.⁵ This latest draft guidance has not been enacted, and the FDA has not provided updated guidance or announced any timelines for enacting new guidance related to FMT.

I have seen a draft FDA guidance stating that physicians using stool from a stool bank must do so under IND. Is this the new policy?

No: In March 2016, FDA [released its second draft guidance](#) to propose that enforcement discretion be narrowed so that physicians who obtain material from stool banks to treat CDI that is not responsive to standard therapy do so under IND. This document is a draft for discussion purposes, and does not alter current enforcement discretion policy, which allows physicians to use FMT material from a stool bank without submitting an IND application.

The [prevailing FDA guidance](#), published in July 2013, states that physicians may perform FMT outside of an Investigational New Drug (IND) application to treat *C. difficile* infection (CDI) that is not responsive to standard therapy, so long as they obtain informed consent.

What regulations govern FMT outside of the U.S.?

In many countries, as in the U.S., regulation governing FMT is evolving. Strategies include regulating FMT as an unapproved drug or medicine, as a human cell or tissue product, or remaining silent on the topic. This [publication](#) summarizes different international regulatory approaches to FMT across 23 countries.⁶ Physicians or clinical researchers are encouraged to consult with their health regulator for specific and current guidance.

Are there specific regulations governing stool banking?

While there are not regulations specific to stool banking, those who wish to perform FMT for indications beyond *C. difficile* that is not responsive to standard therapies must file an IND application with the FDA. This application includes, among other things, descriptions of the chemistry and manufacturing controls used to produce the FMT material. As examples, the criteria used to determine donor eligibility, stool testing and qualification, material processing, storage and handling, packaging and labeling, and quality controls will be needed.

If an IND sponsor is obtaining material from another manufacturer, the sponsor may cross-reference the regulatory filings of the manufacturer instead of independently providing this information in the IND application. The manufacturer would provide a letter to the FDA authorizing the cross reference. The manufacturer may hold an IND, and may also maintain a [Biologics Master File](#), a document submitted to FDA that describes facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The submission of a Biologics Master File is not required by law or FDA regulation. It is not a substitute for an IND application but may be used to support one or many IND applications or other regulatory filings. Unlike an IND application, a Biologics Master File is not approved or disapproved. The contents are reviewed by the FDA in connection with the review of an IND application or other application that references the Biologics Master File.

FDA has issued recommendations regarding screening donors for certain pathogens, specifically [multi drug-resistant organisms](#),⁷ [Shiga toxin-producing *E. coli* and enteropathogenic *E. coli*](#),⁸ and [SARS-CoV-2](#).⁹

Physicians may use material from a donor identified by the patient or physician, or from a stool bank. There are no requirements dictating the route of administration for FMT (e.g. colonoscopy, naso-enteric delivery, oral capsule).

Conclusion

The FDA has issued a single guidance and two draft guidance documents regarding the regulation of FMT in the United States.

The current guidance, released in 2013, categorizes FMT as an investigational new drug and defines a policy of “enforcement discretion” that allows physicians and researchers to treat *C. difficile* infections using FMT without filing an IND application. Under this guidance, physicians and researchers are required to obtain informed consent before

performing FMT—a process that includes informing the patient that FMT is an investigational therapy, and a discussion of its known and potential risks.¹

Subsequent draft guidance documents, released in 2014 and revised in 2016, proposed additional restrictions on enforcement discretion. These have not been implemented.

Physicians who would like to use FMT products for indications beyond *C. difficile* must file an IND application with the FDA requesting permission to use an investigational drug in human subjects or, if they are obtaining material from another manufacturer, cross-reference the regulatory filing of the manufacturer.

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2067 Massachusetts Avenue
Cambridge, Massachusetts 02140
media@openbiome.org
617-575-2201