

Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridioides difficile* Infection Not Responsive to Standard Therapies

Guidance for Industry

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

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Contains Nonbinding Recommendations

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are informing members of the medical and scientific community and other interested persons of our policy regarding the investigational new drug application (IND) requirements for the use of fecal microbiota for transplantation (FMT) to treat *Clostridioides difficile* (*C. difficile*) infection not responding to standard therapies.¹ At this time, FDA intends to exercise enforcement discretion with respect to such requirements under limited circumstances as described in section II of this guidance. This policy does not apply to FMT that is obtained from a stool bank.

A stool bank is defined, for the purpose of this guidance, as an establishment that collects, prepares, and stores FMT product for distribution to other establishments, health care providers, or other entities for use in patient therapy or clinical research. An establishment that collects or prepares FMT products solely under the direction of licensed health care providers for the purpose of treating their patients (e.g., a hospital laboratory) is not considered to be a stool bank under this guidance.

In development of this policy FDA has considered input from stakeholders, including physicians, scientists, and patients concerned about sufficient access to FMT for patients with *C. difficile* infection not responding to standard therapies. FDA has developed this policy to help facilitate access for such patients, while addressing and controlling the risks that centralized manufacturing in stool banks presents to individuals receiving such products.

¹ FMT administered to treat *C. difficile* infection meets the definition of a biological product, as defined in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)) and the definition of a drug within the meaning of section 201(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)). As a biological product, FMT administered to treat *C. difficile* infection is subject to the licensing requirements set forth in section 351 of the PHS Act (42 U.S.C. 262). It is, however, exempt from these licensing requirements when administered pursuant to an IND and in compliance with the IND regulations set forth in 21 CFR Part 312. (See 42 U.S.C. 262(a)(3)).

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This guidance finalizes the draft guidance entitled “Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies” dated March 2016, and supersedes the guidance entitled “Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies” dated July 2013 (July 2013 guidance).

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. DISCUSSION AND ENFORCEMENT POLICY

Fecal microbiota collected from healthy individuals are being investigated for use in the treatment of *C. difficile* infection. Published data suggest that the use of fecal microbiota to restore intestinal flora may be an effective therapy in the management of refractory *C. difficile* infection.

In this guidance, we are revising the policy described in the July 2013 guidance. Centralized manufacturing in stool banks presents safety concerns related to the number of patients that may be exposed to a particular donor and particular manufacturing practices. These safety concerns include transmission of infectious agents.² Therefore, at this time, FDA does not intend to extend enforcement discretion with respect to the IND requirements for distribution of FMT products obtained from stool banks.^{3,4} The sponsor’s compliance with the IND requirements⁵ in these situations will help to ensure that the stool donor and stool are appropriately qualified by screening and testing and that centralized processing of FMT adheres to appropriate current good manufacturing practice.

² For example, FDA issued a safety alert in March 2020 after becoming aware of patients who developed infections caused by enteropathogenic *Escherichia coli* (two patients) and Shigatoxin-producing *E. coli* (four patients) following receipt of an FMT product supplied by a stool bank. As explained in the safety alert, FDA suspects the infections were due to transmission of these pathogenic organisms from the FMT product. See [Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms](#) (March 12, 2020); [Update to March 12, 2020 Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms](#) (March 13, 2020).

³ The policy outlined in this guidance pertains to minimally processed fecal material obtained from donors to treat *C. difficile* infection not responding to standard therapies. Examples of minimal processing include, sieving, centrifugation, buffer exchange, addition of cryoprotectants, lyophilization and packaging. Some examples of processing procedures that would be considered beyond minimal processing include amplification or reduction of certain enteric species, selection of specific groups of bacteria, or any other intended modification of the microbial composition of the fecal preparations.

⁴ If the FMT is provided by a contract manufacturer, this entity should hold an IND or ship to a sponsor with an active IND. In lieu of providing manufacturing information to the IND sponsor, the contract manufacturing facility may provide a letter, permitting the IND sponsor to cross-reference a master file with this information.

⁵ A sponsor may request FDA to waive applicable requirements under 21 CFR Part 312. The required content and process for submitting a waiver request are described at 21 CFR 312.10.

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In light of the considerations described above, at this time, we intend to exercise enforcement discretion with respect to applicable IND requirements when the FMT product is not obtained from a stool bank and where:

1. The licensed health care provider treating the patient obtains appropriate consent from the patient or his or her legally authorized representative for the use of FMT product. The consent should include, at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of the product's reasonably foreseeable risks.⁶
2. The stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product to treat his or her patient.
3. The use of the FMT product does not raise reported safety concerns or potential significant safety concerns (e.g., concerns regarding inappropriate storage or handling, or concerns regarding administration of product collected without appropriate screening or testing).

FDA will continue to work with sponsors who intend to submit INDs for use of FMT to treat *C. difficile* infection not responding to standard therapies. The Agency will also continue to evaluate its policies concerning the use of such FMT products as scientific evidence in this area evolves.

This enforcement policy does not extend to other uses of FMT. Data related to the use and study of FMT to treat diseases or conditions other than *C. difficile* infection not responding to standard therapies are more limited, and study of FMT for these other uses is not included in this enforcement policy.

We encourage all health care providers administering FMT products to report suspected adverse events to the FDA at 1-800-FDA-1088 or <http://www.fda.gov/medwatch>.

⁶ FDA's regulations require that, in seeking informed consent, an identification of any procedures that are experimental and a description of any reasonably foreseeable risks, among other things, be provided to each subject or the subject's legally authorized representative. 21 CFR 50.25(a)(1)-(2).