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

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Draft Guidance for Industry

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010 or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 or Agency, are informing members of the medical and scientific community and other interested persons that we intend to exercise enforcement discretion under limited conditions, regarding the investigational new drug (IND) requirements for the use of fecal microbiota for transplantation (FMT) to treat *Clostridium difficile* (*C. difficile*) infection not responding to standard therapies. FDA intends to exercise this discretion, provided that: 1) the licensed health care provider treating the patient obtains adequate consent from the patient or his or her legally authorized representative for the use of FMT products. 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 its reasonably foreseeable risks; 2) the FMT product is not obtained from a stool bank; and 3) 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 for treatment of the patient.[1]

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

[1] FMT administered to treat *C. difficile* infection meets the definition of a biological product, as defined in section 351(i) of the PHS Act (42 U.S.C. 262(i)), in that it is a regulated article applicable to the prevention, treatment, or cure of a disease or condition of human beings. It also meets 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)), in that it is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or is intended to affect the structure or any function of the body of man. 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 application and in compliance with the IND regulations set forth in 21 CFR Part 312. (See 42 U.S.C. 262(a)(3)).

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.

FDA does not intend to extend enforcement discretion for the IND requirements applicable to stool banks distributing FMT products. Such distributions are subject to the requirements that a sponsor, typically the stool bank, have an IND in effect before distributing the FMT product to investigators for administration to subjects in accordance with the investigational plan under the Public Health Service (PHS) Act (42 U.S.C. 262(a)(3)) and 21 CFR Part 312. However, as described in this guidance, an IND sponsor may request a waiver of certain IND regulations applicable to investigators for those licensed health care providers receiving FMT product to treat patients with *C. difficile* infection not responsive to standard therapies. (See 21 CFR 312.10).

FDA has developed this policy to assure that patients with *C. difficile* infection not responding to standard therapies may have access to this treatment, while addressing and controlling the risks that centralized manufacturing in stool banks presents to subjects.

FDA intends for this to be an interim policy, while the Agency develops a comprehensive approach for the study and use of FMT products under IND.

This draft guidance replaces the draft guidance of the same title, dated March 2014 (March 2014 Draft Guidance), and when finalized, will supersede the guidance document of the same title, dated July 2013 (July 2013 Guidance).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA'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 FDA's guidances means that something is suggested or recommended but not required.

II. DISCUSSION

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. However, the efficacy and safety profiles of this intervention have not yet been fully evaluated in controlled clinical trials.

In the *Federal Register* of July 18, 2013 (78 FR 42965), following a May 2-3, 2013, public workshop, entitled "Fecal Microbiota for Transplantation," FDA announced the availability of the July 2013 Guidance. During that workshop and in subsequent communications, physicians and scientists expressed concern about the application of the IND regulations (21 CFR Part 312) to the administration of FMT products. Some health care providers stated that applying IND

requirements would make FMT unavailable and suggested that an alternative regulatory approach is needed to ensure the widespread availability of FMT for individuals with *C. difficile* infection unresponsive to standard therapies. The July 2013 Guidance informed members of the medical and scientific community and other interested persons that we intend to exercise enforcement discretion, regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies, provided that the treating physician obtains adequate consent from the patient or his or her legally authorized representative for the use of FMT products. 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 its reasonably foreseeable risks.

In the *Federal Register* of February 26, 2014 (79 FR 10814), we announced the availability of the March 2014 Draft Guidance. The March 2014 Draft Guidance informed members of the medical and scientific community and other interested persons that we intend to exercise enforcement discretion, regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies, provided: 1) the licensed health care provider treating the patient obtains adequate consent from the patient or his or her legally authorized representative for use of the FMT product; 2) the FMT product is obtained from a donor known to either the patient or the licensed health care provider treating the patient; and 3) 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. FDA received many public comments in favor of allowing patient access to FMT to treat *C. difficile*, including access to FMT product from stool banks, but objecting to the provision that the donor be known to the patient or the treating licensed health care provider.

In this guidance, we propose to revise our policy with regard to patient access to FMT product. Centralized manufacturing in stool banks presents safety concerns related to the use of FMT from a limited number of donors administered to multiple patients. These safety concerns include transmission of infectious agents and potentially other unidentified risks related to changes in the microbiome. Therefore, FDA does not intend to extend enforcement discretion with respect to the IND requirements applicable to stool banks distributing FMT products.[2] The sponsor's compliance with the IND requirements 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 conditions.

A stool bank sponsor may identify as the investigator on the IND an individual who is within or affiliated with the stool bank. Health care providers who receive FMT product from the stool bank may be sub-investigators. Sponsors may request waiver of certain IND regulations applicable to investigators. IND sponsors requesting a waiver of certain investigator responsibilities may also include a request for waiver of those regulations related to sub-investigators. (See 21 CFR 312.10).

[2] 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.

III. WHEN FDA INTENDS TO EXERCISE ENFORCEMENT DISCRETION

We will continue to evaluate the enforcement policy concerning the use of FMT products to treat *C. difficile* infection not responding to standard therapies. We are clarifying that we intend to continue to exercise enforcement discretion on an interim basis, provided that:

1. The licensed health care provider treating the patient obtains adequate 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 its reasonably foreseeable risks.

2. The FMT product is not obtained from a stool bank.

3. 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.

Furthermore, during the period of enforcement discretion, 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.

This enforcement discretion 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.