



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 15

[Docket No. FDA-2019-N-3631]

Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies; Public Hearing; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification of public hearing; request for comments.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is announcing a public hearing to obtain input on the use of fecal microbiota for transplantation (FMT) to treat *Clostridium difficile* infection not responsive to standard therapies. FDA will consider scientific data and other information from the public hearing as we continue to consider ways to support the development of FMT to treat *C. difficile* infection not responsive to standard therapies and the impact of the enforcement policy on such development.

DATES: The public hearing will be held on November 4, 2019, from 9 a.m. to 4 p.m. The hearing may be extended or may end early, depending on the level of public participation.

Persons seeking to present or speak at the public hearing must register by October 8, 2019.

Persons seeking to attend but not present at the public hearing must register by October 22, 2019.

Section III of this document provides attendance and registration information. Electronic or written comments will be accepted after the public hearing until January 21, 2020.

ADDRESSES: The public hearing will be held at the FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 31 Conference Center, the Great Room (Rooms 1503B and 1503C),

Silver Spring, MD 20993-0002. Entrance for public hearing participants (non-FDA employees) is through Building 1, where routine security check procedures will be performed. For parking and security information, please refer to <https://www.fda.gov/about-fda/white-oak-campus-information/public-meetings-fda-white-oak-campus>.

You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before January 21, 2020. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of January 21, 2020. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public submit the comment as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions”).

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-2019-N-3631 for “Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The

second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Shruti Modi, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background and Purpose of the Public Hearing

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 *C. difficile* infection not

responsive to standard therapies. However, the efficacy and safety profiles of this intervention have not yet been fully evaluated in adequate and well-controlled clinical trials.

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. FDA has received public comments from some stakeholders suggesting that FMT might be regulated as a human cell, tissue, and cellular and tissue-based product (HCT/P; see 21 CFR part 1271). FMT is a live biotherapeutic product composed of microorganisms. Microorganisms are not human cells or tissues and do not meet the definition of HCT/P (see 21 CFR 1271.3(d)). The hearing will not include discussions about these comments.

In the *Federal Register* of July 18, 2013 (78 FR 42965), following a public workshop, held on May 2 and 3, 2013, entitled “Fecal Microbiota for Transplantation,” FDA announced the availability of a guidance for industry 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” (July 2013 Guidance) (available at: <https://www.fda.gov/media/86440/download>). The July 2013 Guidance, which is still in effect, informed members of the medical and scientific communities and other interested persons that we intend to exercise enforcement discretion regarding the investigational new drug (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 guidance states that

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 potential risks.

In the *Federal Register* of February 26, 2014 (79 FR 10814), we announced the availability of a draft guidance for industry 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” (March 2014 Draft Guidance). The March 2014 Draft Guidance informed members of the medical and scientific communities and other interested persons that we intended 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 healthcare 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 healthcare provider treating the patient; and (3) the stool donor and stool are qualified by screening and testing performed under the direction of the licensed healthcare provider for the purpose of providing the FMT product to treat his or her patient. FDA received many public comments in favor of patient access to FMT to treat *C. difficile*, including access to FMT products from stool banks, but objecting to the provision that the donor be known to the patient or the treating licensed healthcare provider.

After considering the comments on the March 2014 Draft Guidance, in the *Federal Register* of March 1, 2016 (81 FR 10632), FDA announced the availability of a revised draft guidance for industry 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” (March 2016 Draft Guidance) (available at:

<https://www.fda.gov/media/96562/download>). The March 2016 Draft Guidance replaced the March 2014 Draft Guidance and proposed to revise our policy with regard to patient access to FMT product. We noted that centralized manufacturing in stool banks presents safety concerns related to the use of FMT from a limited number of donors administered to multiple patients. Therefore, we stated that FDA does not intend to extend enforcement discretion with respect to the IND requirements applicable to stool banks distributing FMT products. We stated that the sponsor's compliance with the IND requirements would 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. FDA received many public comments on this draft guidance, and we are continuing to evaluate our enforcement policy.

The purpose of this public hearing is to obtain public input on the state of the science regarding FMT to treat *C. difficile* infection not responsive to standard therapies, including the available clinical evidence for safety and effectiveness of FMT for this use and to understand better the impact of FDA's enforcement policy on product development.

II. Issues for Consideration and Request for Data and Information

FDA would like input from stakeholders, including patients, clinicians, research scientists, industry, healthcare providers, and stool banks. We encourage public comments and presentations at the public hearing. If submitting comments, data, and information to the docket, please identify available references for the data and information, as well as the general category area and specific question listed below.

As noted above, 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. To inform FDA's understanding of the current scientific status of FMT, especially as it relates to the use of FMT to treat *C. difficile* infection not responsive to standard therapies, we are interested in obtaining information, including data and studies, from all stakeholders, including patients, clinicians, research scientists, industry, healthcare providers and stool banks on the following topics:

1. Clinical Evidence of Effectiveness
 - What is the strength of the evidence for the use of FMT to treat *C. difficile* infection not responsive to standard therapies?
 - Please identify any published data from rigorously conducted randomized controlled (placebo or non-FMT standard of care comparator) trials that support the use of FMT for:
 - Prevention of recurrent *C. difficile* infection.
 - Treatment of refractory *C. difficile* infection.
2. Safety Evaluation
 - What is the strength of evidence for the safety of FMT in patients with *C. difficile* infection not responsive to standard therapies?
 - Has meaningful safety information been collected under FDA's enforcement policy? How can any deficiencies in safety data collection be remedied?
 - Are there particular safety issues FDA should consider regarding these products (e.g., donor screening/mixing donations)?
3. Impact of FDA's current Enforcement Policy on FMT Product Development

- What impact has FDA’s enforcement policy had on recruitment and ability to conduct clinical trials to assess safety and effectiveness of FMT for *C. difficile* infection not responsive to standard therapies?
 - Can specific examples be cited?
 - How can any negative impacts be remedied?
 - How does the existing availability of FMT affect the incentives for, and the feasibility of, FMT drug-development programs?
 - The use of FMT is addressed in some treatment guidelines (Infectious Diseases Society of America and American Gastroenterological Association). What impact has this had on patient recruitment and conduct of clinical trials?
4. Future and Path Forward
- What additional scientific information is needed to determine the safety and effectiveness of FMT for *C. difficile* infection not responsive to standard therapies?
 - How generalizable are the existing safety and effectiveness data on use of a specific FMT product for *C. difficile* infection not responsive to standard therapies to other FMT products for which safety and effectiveness data are not available?
 - Please comment on how FDA can facilitate patient access, protect patient safety, and include enough flexibility to support innovation for the development and licensure of safe and effective FMT products for *C. difficile* infection not responsive to standard therapies.

III. Participating in the Public Hearing

Registration and Requests to Speak and for Formal Oral Presentations: The FDA Conference Center at the White Oak location is a Federal facility with security procedures and limited seating. Attendance will be free. An agenda for the hearing and any other background materials will be made available on October 25, 2019, at <https://www.fda.gov/vaccines-blood-biologics/news-events-biologics/workshops-meetings-conferences-biologics>. If you need special accommodations because of a disability, please contact Sherri Revell or Loni Warren Henderson at 240-402-8010 at least 7 days before the hearing.

For those interested in speaking at the hearing or presenting at the hearing with a formal oral presentation, please register at <https://www.eventbrite.com/e/use-of-fecal-microbiota-for-transplantation-to-treat-clostridium-difficile-infection-not-responsive-tickets-63906239282> as “In-person presenter.” Speaker and presenter registrations are due October 8, 2019.

FDA will try to accommodate all persons who wish to make a formal oral presentation. Formal oral presenters may use an accompanying slide deck. Individuals wishing to present should identify their name, which stakeholder group they represent (e.g., patient, clinician, research scientist, industry, stool bank), and the number of the specific question, or questions, they wish to address. FDA will consider this information when organizing the agenda. Individuals and organizations with common interests should consider consolidating or coordinating their presentations and request time for a joint presentation. Individual organizations are limited to a single presentation slot. FDA will notify registered presenters of their scheduled presentation times on October 21, 2019. The time allotted for each presentation will depend on the number of individuals who wish to speak. If registered presenters are using an accompanying slide deck, those presenters must submit an electronic copy of their presentation (PowerPoint or PDF) to CBERPublicEvents@fda.hhs.gov on or before October 28,

2019. Persons registered to present are encouraged to arrive at the hearing room early and check in at the onsite registration table to confirm their designated presentation time. Actual presentation times, however, may vary based on how the hearing progresses in real time.

In-person attendance: For those who would like to attend in-person, but who are not making a formal presentation, please register at <https://www.eventbrite.com/e/use-of-fecal-microbiota-for-transplantation-to-treat-clostridium-difficile-infection-not-responsive-tickets-63906239282> as “In-person attendee--no participation.” Seating is limited, and early registration is recommended to allow for broad participation.

Streaming Webcast of the Public Hearing: For those unable to attend in person, FDA will provide a live webcast of the hearing. Please register at <https://www.eventbrite.com/e/use-of-fecal-microbiota-for-transplantation-to-treat-clostridium-difficile-infection-not-responsive-tickets-63906239282> as “online (webcast only)”.

Media: Please register at <https://www.eventbrite.com/e/use-of-fecal-microbiota-for-transplantation-to-treat-clostridium-difficile-infection-not-responsive-tickets-63906239282> as “Media” by October 28, 2019.

Transcripts: Please be advised that as soon as a transcript is available, it will be accessible at <https://www.fda.gov/vaccines-blood-biologics/news-events-biologics/workshops-meetings-conferences-biologics> and <https://www.regulations.gov>. It may be viewed at the Dockets Management Staff (see ADDRESSES).

IV. Notification of Hearing Under 21 CFR Part 15

The Commissioner of Food and Drugs is announcing that the public hearing will be held in accordance with part 15 (21 CFR part 15). The hearing will be conducted by a presiding officer, who will be accompanied by FDA senior management officials. Under § 15.30(f) (21

CFR 15.30(f)), the hearing is informal and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members may question any person during or at the conclusion of each presentation. Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (21 CFR part 10, subpart C).

Under 21 CFR 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. Persons attending FDA's public hearings are advised that the Agency is not responsible for providing access to electrical outlets.

The hearing will be transcribed as stipulated in § 15.30(b) (see section III of this document). To the extent that the conditions for the hearing, as described in this notification, conflict with any provisions set out in part 15, this notification acts as a waiver of those provisions as specified in § 15.30(h).

Dated: September 5, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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