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July 2, 2020

Electronic Submission

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

This Petition is submitted to the U.S. Food and Drug Administration (FDA or the Agency) under 21 C.F.R. § 10.30 on behalf of the Microbiome Therapeutics Innovation Group (MTIG), a coalition of companies leading the research and development of FDA-approved microbiome therapeutics and microbiome-based products to address unmet medical needs, improve medical needs, improve clinical outcomes, and reduce health care costs.[1]

I. INTRODUCTION

The human microbiome exercises a major impact on human health, providing metabolic and synthetic functions such as providing resistance to infectious diseases, regulating the immune system, and aiding in digestion. Disruptions in the microbial ecosystem in the human gut are associated with a range of gastrointestinal and metabolic diseases, including pathogenic infections, inflammatory bowel disease, ulcerative colitis, type 2 diabetes, and autoimmune disorders such as celiac disease. Drug products that regulate the microbiome have the potential to address a number of therapeutic areas, and microbiome modulators are being investigated as potential treatments in areas of infectious diseases, gastrointestinal disorders, metabolic disorders, dermatology, oncology, and neurological disorders.

The most prominent area of research involving the role of the microbiome has thus far been in recurrent *Clostridioides difficile* infection (*C. difficile* or *C. diff.*), which can cause symptoms ranging from mild diarrhea to more serious conditions such as pseudomembranous

[1] Current members of MTIG include Rebiotix Inc., Seed Health, Seres Therapeutics, Inc., Siolta Therapeutics, Takeda Pharmaceutical Company Limited, and Vedanta Biosciences.

colitis, sepsis, and death. [2] Patients with recurrent *C. diff*. are usually on antibiotic therapy and their intestinal microbiota exhibit highly reduced diversity.[3] Research into fecal microbiota transplantation (FMT) has demonstrated that manipulating the human gut microbiome to restore the intestinal flora has therapeutic potential in the treatment of recurrent *C. diff*. FMT involves the administration of a fecal matter solution from a healthy donor into the intestinal tract of a recipient to alter the recipient's gut microbial composition in order to confer a health benefit.[4] Studies have shown that reintroducing normal bacteria via donor feces in patients with recurrent *C. diff.* can correct the imbalance in colon microbiota and restore phylogenetic richness and colonization resistance.[5] FMT has increasingly been administered for the treatment of *C. diff.* infection in patients who have not been successfully treated with traditional antibiotic treatment options, such as vancomycin.[6] Although FMT appears to be an effective therapy in reducing the risk of *C. diff*. recurrence, attaining accurate estimates of efficacy and safety is limited by the quality of published trials.[7]

FDA considers FMT to meet the definition of a drug and biological product and therefore subject to premarket review and approval requirements under the Public Health Service Act (PHSA) and the Federal Food, Drug, and Cosmetic Act (FDCA), including clinical studies to evaluate the safety of FMT are therefore subject to FDA investigational new drug (IND) regulations.[8] In July 2013, FDA issued a guidance document announcing an enforcement discretion policy regarding the IND requirements for the use of FMT to treat *C. diff*. infection not responding to standard therapies while the Agency further considered the matter.[9] The guidance explained that FDA would exercise enforcement discretion provided that the treating physician obtains adequate informed consent explaining that the use of FMT products to treat *C. diff.* is investigational.

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[2] S. Gupta, E. Allen-Vercoe, and E. Petrof, *Fecal Microbiota Transplantation: In Perspective*, 9(2) THER. ADV. GASTROENTOL 229 (Mar. 2016).

[3] W. de Vos and E. de Vos, *Role of the Intestinal Microbiome in Health and Disease: From Correlation to Causation*, 70 (Suppl. 1) NUTRITION REVIEWS S45, S51 (2012).

[4] Gupta et al., supra note 2, at 230.

[5] C. Surawicz, MD et al., *Guidelines for Diagnosis, Treatment, and Prevention of Clostridium difficile Infections*, 108 AM. J. GASROENTEROL 478, 487 (Feb. 2013).

[6] Id.

[7] The potential benefits of FMT must be balanced against risks, as there is a general concern that FMT might lead to unexpected adverse events including metabolic or immune-based disorders. See, Infectious Diseases Society of America (IDSA), *Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)*, 66 CLINICAL INFECTIOUS DISEASES (April 2018), available at: https://academic.oup.com/cid/article/66/7/e1/4855916.

[8] FDA Guidance for Industry, 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), available at: https://www.fda.gov/media/86440/download [hereinafter, "2013 Guidance"].

[9] Id.

FDA has since issued two draft guidance documents to update the 2013 enforcement discretion policy, the most recent of which was issued in 2016. The 2016 draft guidance document narrowed the enforcement discretion policy to exclude FMT products that are obtained from a stool bank and to ensure that the stool donor and stool are qualified by screening and testing under a physician's supervision.[10] While the Agency continues to consider the public comments that were posted in response to the 2016 draft guidance document, it has stated that the enforcement discretion policy as described in the 2013 guidance remains in effect.[11]

By not finalizing the 2016 draft guidance, FDA has allowed commercial-scale stool banks to continue to screen donors, process samples, and commercially distribute FMT treatment products without complying with IND requirements, without adhering to rigorous manufacturing and quality controls, and without establishing the safety and efficacy of their drug products through prospective clinical trials. FDA's failure to actively regulate the manufacture and widespread distribution of FMT products puts the public at risk of serious or life-threatening infections, as evidenced by its issuance of safety alerts in 2019, and which is now amplified because of the novel coronavirus pandemic. This lack of oversight also has led to an unintended consequence that has adversely affected innovation in this vital area of scientific research: the development of approved microbiome therapies has faced substantial delays due to stymied enrollment in clinical trials because of the broad distribution of unapproved FMT.

II. ACTIONS REQUESTED

MTIG respectfully requests that FDA

1. Finalize the 2016 draft guidance and specify that the sponsors and manufacturers of commercial-scale FMT products are required to operate under an IND and must therefore implement and follow the same rigorous clinical, regulatory manufacturing and quality controls applicable to other microbiota drug products that are being developed for licensure under FDA oversight. Holding stool banks and contract manufacturers to IND regulations will assure compliance with the screening and other safety-based precautions outlined in recent FDA safety alerts, which are currently voluntary in nature.

2. Retain the safe harbor for the use of FMT when 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 own patient.

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[10] FDA, Draft Guidance for Industry, Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies (Mar. 2016), available at: https://www.fda.gov/media/96562/download [hereinafter, "2016 Draft Guidance"].

[11] See, e.g. Notification of Public Hearing, Request for Comments, Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies, 84 Fed. Reg. 47,911, 47,913 (Sep. 11, 2019).

3. Provide additional guidance with respect to the comprehensive approach FDA is considering for the study and use of FMT products under an IND.

4. Reiterate that the FMT enforcement discretion policy is an interim policy, and is subject to change or revocation following further evaluation of the policy's effects on patient safety and efficacy. If a sponsor of a microbiota drug for *C. diff.* infection receives marketing approval, MTIG requests that FDA reconsider whether enforcement discretion remains the correct action to ensure safe and effective access to patients.

III. STATEMENT OF GROUNDS

As explained below, the circumstances that existed when the enforcement policy was first announced in the 2013 guidance document are different today. The updated policy announced in the 2016 draft guidance is more suitable for the current environment and it strikes an appropriate balance between patient safety and access. Finalizing the 2016 draft guidance to require stool banks to operate under an IND would advance the public health interest and is supported by the administrative record.

A. The 2013 Enforcement Policy Was Intended to be a Temporary Measure but it is No Longer Appropriate in the Current Environment.

In May 2013, the FDA's Center for Biologics Evaluation and Research (CBER) and the National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID) held a joint public workshop to explore the regulatory and scientific issues associated with FMT with the medical and scientific community. When announcing this workshop, FDA acknowledged that published data "suggest that the use of fecal microbiota to restore gut flora may be an effective therapy in the management of refractory *C. difficile* infection" and that FMT was also being considered as a treatment for inflammatory bowel disease, obesity, and other disorders.[12] FDA explained that controlled trials are necessary to demonstrate the safety and effectiveness of FMT products for *C. difficile* infection and for these other treatment areas and that such clinical trials are subject to regulation by the FDA.[13] The Agency also noted that the "complex nature of FMT products presents specific scientific and regulatory challenges."[14]

The workshop provided the opportunity for stakeholders to make suggestions and comments concerning the future development and regulation of FMT products. FDA took the position that "[w]hen used to cure, treat, mitigate or prevent a disease, fecal microbiota for transplantation meets the legal definition of a drug and biological product" and that an investigational new drug (IND) application was required when FMT is an unapproved new

[12] Notice of Public Workshop, Fecal Microbiota for Transplantation, 78 Fed. Reg. 12,763, 12,764 (Feb. 25, 2013).

[13] Id.

[14] Id.

drug.[15] FDA further explained that controlled clinical studies of FMT can enhance progress in FMT research by assuring subject safety and by developing "good, analyzable, interpretable data regarding outcomes and adverse events as well as other benefits."[16] Following the workshop, FDA stated that it would "continue to develop regulatory pathways and strategies to ensure the safe and effective use of FMT products."[17]

During the workshop and in subsequent communications to FDA, some physicians and scientists expressed concerns that applying IND requirements to individual physicians would affect the availability of FMT products for individuals in their practice with *C. diff.* infection that is unresponsive to standard therapies. FMT products were discussed by some participants in terms of a continuum: at one end of the spectrum were non-physician "home brew" preparations and at the other end of the spectrum were pharmaceutical products made from well-defined individual components. FDA was asked to consider how it would regulate FMT products closer to the home-brew end of the continuum, such as preparations made in a physician's office, without interfering with the practice of medicine.[18] In response to these concerns, FDA issued a guidance document in July 2013 announcing that it would exercise enforcement discretion regarding the IND requirements for the use of FMT to treat such patients while the Agency further considered the matter.[19] The 2013 policy required the treating physician to obtain adequate informed consent from the patient (or the patient's legal representative), including a statement that the use of FMT products is investigational and provide a discussion of its potential risks.[20] The enforcement policy only pertained to the use of FMT for the treatment of patients with *C. diff.* infection that is unresponsive to standard therapies and not to other uses.

The 2013 guidance was an attempt by the FDA to allow practitioners to continue offering FMT to *C. diff.* patients who were unresponsive to standard therapies while it developed parameters for regulatory enforcement over FMT products. At the time the 2013 guidance was issued, guidelines from professional societies had recommended that FMT be performed by specialists with stool from donors who were known to the recipient or treating physician.[21] Since

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[15] FDA Presentation, Fecal Microbiota for Transplantation, https://wayback.archive-it.org/7993/20170113133555/http:/www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM352641.ppt [hereinafter, "2013 FDA Workshop Presentation"].

[16] Id.

[17] FDA, Fecal Microbiome Transplantation Workshop, https://www.accessdata.fda.gov/scripts/fdatrack/view/track_project.cfm?program=cber&id=CBER-All-Fecal-Microbiome-Transplantation-Workshop.

[18] See, e.g., Transcript at 298-301, FDA, Fecal Microbiome Transplantation Workshop (May 3, 2013), available at: https://wayback.archive-it.org/7993/20170113133557/http:/www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM352902.pdf.

[19] 2013 Guidance, supra note 8.

[20] Id.

[21] A consensus guidance on donor screening and stool testing for FMT was provided to FDA in July 2013 by a coalition of medical specialty societies, which recommended that the donor be "an intimate, long-time partner of adult patient or, in the case of a pediatric patient, an adult first-degree relative, close family friend, or well-screened universal donor." Letter from the Presidents of the Infectious Disease Society of America (ISDA), American

the 2013 guidance was issued, use of banked stool from stool donors unknown to the patients or physicians has become increasingly popular. Some health care institutions organized their own internal programs for donor recruitment and screening as well as stool testing and inventory, but because of challenges associated with the development of internal programs, stool for FMT procedures is now increasingly sourced through commercial stool banks that operate separately from the point of care.[22]

In March 2014, FDA issued a draft guidance document proposing to revise its enforcement discretion policy so that it applied only if (1) the stool was obtained from a donor that was known to either the patient or the licensed health care provider treating the patient, and (2) the donor and stool were "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."[23] The informed consent requirement remained the same, and the Agency did not extend the enforcement policy to any uses beyond the treatment of *C. difficile* infection unresponsive to standard therapies because of limited data to support such uses. According to the draft guidance, FDA intended to exercise enforcement discretion on an interim basis while the Agency further considered the matter and developed appropriate policies for the study and use of FMT products under an IND. The draft guidance further stated that the Agency would continue to work with sponsors who intend to submit INDs for use of FMT to treat *C. diff*. that was unresponsive to standard therapies.

Rather than finalize the 2014 draft guidance, FDA issued a revised draft guidance document in 2016 proposing to replace the provision from the 2014 draft guidance that the stool be obtained from a donor that was known to the patient or to the provider with a provision stating that the FMT product could not be obtained from a stool bank.[24] The informed consent provision and the screening and testing provision remained the same as proposed in the 2014 draft guidance. FDA explained its rationale for the change as follows:

> The provision that the donor be known either to the patient or to the treating licensed health care provider, a concept that was used in the March 2014 draft guidance, was subject to difficulties in interpretation, and the revised approach more accurately reflects our intent to mitigate risk, based on the number of patients exposed to a particular donor or manufacturing practice rather than the risk inherent from any one donor. Although

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Society for Gastrointestinal Endoscopy (ASGE), North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), The American Gastroenterological Association (AGA), and the American College of Gastroenterology (ACG) to Wellington Sun, Director, Division of Vaccines and Related Product Applications, CBER, FDA (July 15, 2013), available at: https://web.archive.org/web/20140720012041/https://www.gastro.org/research/Joint_Society_FMT_Guidance.pdf.

[22] M. Woodworth et al., *Laboratory Testing of Donors and Stool Samples for Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection*, 55 J. CLIN. MICROBIOL. 1002 (2017).

[23] FDA, Notice of Availability, Guidance for Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies, 79 Fed. Reg. 10,814 (Feb. 26, 2014).

[24] 2016 Draft Guidance, supra note 10.

FDA acknowledges that directed donations present different risks than stool bank donations, the number of persons exposed through a directed donation will be limited.[25]

The 2016 draft guidance defined "stool bank" 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."[26] Hospital laboratories and other institutions that collect and prepare FMT products solely under the direction of licensed health providers for the purpose of treating their own patients were excluded from the definition of "stool bank." FDA revised the policy in this manner to ensure that patients could continue to have access to FMT treatment, but it drew the line at commercial stool banks because it recognized "the risks that centralized manufacturing in stool banks presents to subjects."[27]

FDA explained that safety concerns associated with centralized manufacturing in stool banks stemming from the administration of FMT to multiple patients from a limited number of donors "include transmission of infectious agents and potentially other unidentified risks related to changes in the microbiome."[28] Requiring stool banks to comply with IND requirements would mitigate these risks by helping to ensure that the stool donor and stool are appropriately screened and tested and that processing adheres to good manufacturing conditions.[29] Consistent with the obligations of many other study sponsors already compliant with FDA's regulations, a stool bank would be the sponsor of an IND and may identify an individual who is within or affiliated with the stool bank as the investigator and may identify the health care providers who receive the FMT product from the stool bank as the sub-investigators.[30] The stool bank would be required to have an IND in effect before distributing the FMT to investigators for administration to subjects in accordance with the investigational plan.[31] The policy explained that the stool bank sponsor could request a waiver of certain IND regulations applicable to investigators and sub-investigators pursuant to 21 C.F.R. 312.10.

In November 2019, FDA held a public hearing on the use of FMT and discussed the impact of the enforcement policy on the development of FMT as a treatment for *C. diff*. not

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[25] FDA, Notice of Availability, 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, 81 Fed. Reg. 10632 (Mar. 1, 2016).

[26] 2016 Draft Guidance, supra note 10, at 1.

[27] Id. at 2.

[28] Id. at 3.

[29] Id.

[30] Id.

[31] Id. at 2.

responsive to standard therapies.[32] Some of the participants advocated for continued enforcement discretion but with a greater use of patient registries to collect data on patients receiving FMT for the treatment of recurrent *C. diff*.[33] An agency panelist clarified, however, that FDA does not have the authority to mandate or require data collection under the enforcement discretion policy and questioned how the process of collecting and analyzing such registry data could lead to decisions regarding safety and efficacy of FMT products outside of clinical trials.[34] Although FDA has acknowledged the need for more data on FMT use, the Agency is rightfully concerned about the potential that safety issues will be under-reported and about the quality of registry data and its utility for regulatory decision making, when such data is collected outside of an IND.[35]

B. The Policy Articulated in the 2016 Draft Guidance Strikes an Appropriate Balance by Allowing FMT Therapy to Continue Under Limited and Controlled Circumstances.

FMT products are now regularly being administered to patients to treat *C. diff*. that is unresponsive to traditional therapies and practitioners are increasingly using FMT in the treatment of other indications. FDA recognizes that the use of FMT has become "accepted as an unlicensed standard-of-care" for recurrent C. diff. but also understands that a standard-of-care does not equate to a "guarantee that any given FMT product will be safe and effective."[36]

MTIG agrees with FDA that FMT meets the legal definitions of a drug product and a biological product and is therefore subject to premarket review and approval requirements under the FDCA and PHSA. Adequate and well-controlled clinical trials are necessary to establish the safety and efficacy of FMT, including trials designed to identify any potential short-term and long-term effects of the transferred microbiota on the recipients and to better understand the components of stool that are responsible for the therapeutic effect.[37]

Like other unapproved new drug and biological treatments, FMT should be studied and developed under an IND to protect the safety and rights of patients and to ensure that clinical

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[32] FDA, Public Hearing, Use of Fecal Microbiota for Transplantation (FMT) to Treat Clostridium Difficile Infection Not Responsive to Standard Therapies (Nov. 4, 2019), https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/use-fecal-microbiota-transplantation-fmt-treat-clostridium-difficile-infection-not-responsive.

[33] See, e.g., Transcript at 76-81, 101-109, 157-158, FDA Part 15 Hearing, Use of Fecal Microbiota for Transplantation to Treat Clostridium Difficile (Nov. 4, 2019), available at: https://www.fda.gov/media/134094/download.

[34] Id. at 86, 106-107.

[35] C Diff Foundation, 7th Annual International *C. diff*. Conference and Health EXPO (Nov. 7, 2019), Presentation by Doran Fink, Deputy Director, Clinical Division of Vaccines and Related Product Applications, CBER, FDA at 28 (Exhibit A) [hereinafter "C Diff Presentation"].

[36] Id. at 27.

[37] See, 2013 FDA Workshop Presentation, supra note 15.

investigations are conducted in accordance with sound scientific principles.[38] The IND process provides a mechanism for FDA to oversee the safety of the investigations as well as assess the scientific quality of the clinical trial and the likelihood that the investigations will yield data that could support marketing approval.[39] Important protections are embedded into the IND framework, such as informed consent and Investigational Review Board (IRB) procedures as well as FDA review of study protocols, patient selection criteria, chemistry, manufacturing, and control (CMC) information, pharmacology and toxicology information, and safety reporting.[40] This is the ideal framework for FMT since it is permissive of research while assuring patient access and maintaining scientific rigor.

Like the 2013 and 2014 policy pronouncements, the enforcement discretion policy proposed in the 2016 draft guidance document was intended to be an interim measure while the Agency developed a comprehensive approach for the study and use of FMT products under an IND. It was the right approach at the time and is the right approach now, since a comprehensive IND regime for FMT products has yet to be established. By not finalizing the 2016 guidance, FDA has permitted stool banks, which widely distribute FMT products to health care providers and institutions, to operate in a virtually unregulated manner under the 2013 policy.

The longer FDA waits to finalize and implement the 2016 guidance, the more prolific the use of unregulated FMT will become and the longer it will take for stool banks to come into compliance with applicable regulations. For example, FDA has had a similar experience with regenerative cell therapy. In November 2017, FDA announced that it would follow a risk-based enforcement policy regarding its IND and premarket approval requirements for cell-based regenerative medicine products until November 2020 and encouraged manufacturers to engage with FDA in the interim to determine if they need to submit a marketing authorization.[41] FDA explained that, pursuant to this risk-based approach, it would take into consideration the use of the products as well as the disease and conditions for which they are intended to be used before deciding whether to enforce its IND and premarket approval requirements during the enforcement discretion period.

FDA subsequently learned about significant deviations from Current Good Tissue Practice (CGTP) and Current Good Manufacturing Practice (CGMP) by a manufacturer of umbilical cord blood-derived products that may have led to microbial contamination and potentially caused serious blood and other infections in numerous patients. In addition to sending a warning letter to the umbilical cord-blood manufacturer, FDA issued letters to other manufacturers and health care providers who offered stem cell treatments to remind them that

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[38] C Diff Presentation, supra note 35 at 20 ("FDA encourages that clinical trials of FMT for CDI be conducted under an IND (for safety oversight and to support development).").

[39] 21 C.F.R. § 312.22.

[40] 21 C.F.R. Part 312.

[41] FDA News Release, "FDA Announces Comprehensive Regenerative Medicine Policy Framework" (Nov. 15, 2017), https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework.

"there is a clear line between appropriate development of these products and practices that sidestep important regulatory controls needed to protect patients."[42] Up to that point, few manufacturers had interacted with the Agency to come into compliance with applicable regulatory requirements.

FDA explained in the 2013 guidance that it considered FMT products to be drug and biologic products subject to IND regulations, and stool banks have been on notice since at least February 2014 when the first draft guidance was issued that FDA did not intend to exercise enforcement discretion over commercially distributed FMT products. Stool banks have had plenty of time to engage with the Agency to develop clinical programs and prepare their IND submissions. Like the regenerative cell therapy manufacturers, however, stool banks will be unlikely to do so without a clear directive from FDA.

The enforcement policy articulated in the 2016 draft guidance document strikes an appropriate balance by allowing FMT therapy to be available to patients who suffer from recurrent *C. diff*. under limited and controlled circumstances while therapeutic products are developed under the drug and biologic pathways to treat this condition. As explained in more detail below, FDA has already become aware of potential safety issues involving the use of FMT. Allowing stool banks to self-regulate while FDA develops a comprehensive framework puts patients at an unreasonable risk.

C. Adopting The Policy Articulated in the 2016 Draft Guidance Document Promotes the Public Health by Holding Commercially Distributed FMT to the Same Safety and Efficacy Standards Governing Other Microbiota Drug Products.

Recent safety issues demonstrate that FDA oversight is necessary to ensure that commercial scale FMT products implement and adhere to rigorous clinical, regulatory manufacturing and quality controls that apply to other microbiota drug products.

In June 2019, FDA issued a safety alert informing health care providers and patients of the "potential risk of serious or life-threatening infections with the use of fecal microbiota for transplantation."[43] The safety alert explained that FDA has become aware of bacterial infections caused by multi-drug resistant organisms (MDROs), which had been transmitted through the use of FMT. In that situation, two immunocompromised adults who received investigational FMT developed invasive extended-spectrum beta-lactamase (ESBL) infections, and one of the individuals died. The FMT that was used in these two individuals was prepared from stool obtained from the same donor. The donor stool and resulting FMT were not tested for ESBL-producing gram-negative organisms prior to use but were later found to be positive. As a result, FDA determined that donor screening and testing of donor stool for MDRO are needed for any

[42] Id.

[43] FDA, Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms (Jun. 13, 2019), https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse.

investigational use of FMT. According to a related FDA press release, the safety communication "underscores the importance of why new therapies are thoroughly studied to ensure the benefits of taking them outweigh the risks to patients, and we will continue to aggressively monitor clinical trials to ensure patients are protected when safety concerns arise."[44]

Not all FMT therapies are being administered through clinical trials, however, and unless an IND is in place, FMT products are not subject to safety reporting regulatory requirements or other safeguards, such as the rigorous CMC controls that apply to other developmental microbiota products. For example, a sponsor of an investigational product under an IND is required to provide safety reports of potential serious risks and must report any suspected adverse reaction that is both serious and unexpected.[45] In contrast, FDA "encourages" health care providers administering FMT products to report suspected adverse events to FDA's Medwatch system. IND sponsors are required to submit detailed CMC information to assure the proper identification, quality, purity, and strength of the investigational drug.[46] Sponsors of clinical trials with live biotherapeutic products are required to provide detailed information about the physical, chemical, or biological characteristics of the drug substance, including a description of the clinical health of the donor(s) as well as the method of manufacture, including procedures used to avoid extraneous microbial contamination.[47] The FDA is "committed to ensuring that FMT-based products used in clinical studies are manufactured appropriately and that clinical trials are designed to determine safety and effectiveness of these products in the treatment of the wide range of indications currently associated with the microbiota."[48] However, due to enforcement discretion, FDA cannot impose specific screening measures on stool banks, nor can the Agency ensure adherence with its recommendations.

FDA issued two safety alerts involving the use of FMT in March 2020. The first alert was issued on March 12 to inform patients and healthcare providers of the potential risk of transmission of pathogenic bacteria by FMT products and the resultant serious adverse reactions

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[44] FDA in Brief, FDA Warns About Potential Risk of Serious Infections Caused by Multi-Drug Resistant Organisms Related to The Investigational Use of Fecal Microbiota for Transplantation (Jun. 13, 2019), https://www.fda.gov/news-events/fda-brief/fda-brief-fda-warns-about-potential-risk-serious-infections-caused-multi-drug-resistant-organisms.

[45] 21 C.F.R. § 312.32.

[46] 21 C.F.R. § 312.23.

[47] FDA Guidance for Industry, Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information (Jun. 2016), https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Early-Clinical-Trials-With-Live-Biotherapeutic-Products--Chemistry--Manufacturing--and-Control-Information--Guidance-for-Industry.pdf.

[48] P. Carlson Jr., *Forum: Regulatory Considerations for Fecal Microbiota Transplantation Products*, 27 ECELHM 2 173-175 (2020).

that may occur.[49] FDA explained that it was aware of infections caused by enteropathogenic Escherichia coli (EPEC) and Shigatoxin-producing Escherichia coli (STEC) that had occurred following investigational use of FMT that the Agency suspected were due to transmission of these pathogenic organisms from FMT product supplied by a U.S. stool bank company. The alert was issued after two patients developed EPEC infection after receiving FMT prepared from stool from two different donors and four patients developed STEC infection after receiving FMT prepared from stool from a single donor. Two additional patients who received FMT prepared from the donor associated with the STEC infections died, but their stool had not been tested for STEC.

The stool bank explained that when it received the first patient reports pertaining to FMT derived from stool from these donors, it placed material from these donors on inventory hold and initiated an investigation.[50] The company further explained that all unused material from these donors had since been recalled and destroyed and that it had revised its screening process in collaboration with FDA. MTIG believes that voluntary, passive patient safety reporting is no longer appropriate given the recent safety issues and that stool banks should instead be required to report any suspected adverse reactions to the FDA in a consistent and regulated manner under the supervision of an IND pursuant to a bona fide clinical study protocol.

The second alert was issued on March 23, 2020 after studies documented the presence of SARS-CoV-2 ribonucleic acid and/or virus in the stool of infected individuals.[51] This information suggested to FDA that there was a possibility that SARS-CoV-2 may be transmitted by FMT, but the risk of such transmission was unknown and the ability to test donors and the stool for SARS-CoV-2 was limited. To mitigate this risk, FDA advised clinicians to use FMT from stool that was donated before December 1, 2019 and that additional protections were necessary for use of FMT derived from stool donated after that date. The additional protections included additional donor screening, testing, development of exclusion criteria, and enhanced informed consent to the FMT recipient that includes information about the potential risks and mitigations strategies related to SARS-CoV-2.

The March 12, 2020 and March 23, 2020 FDA safety alerts underscore the importance of FDA's role in managing the risks involved with the use of unregulated FMT. Allowing commercial stool banks to operate under FDA's 2013 enforcement discretion policy for FMT for recurrent *C. diff.* infection undermines FDA's ability to manage these risks. The 2013 enforcement discretion policy also leaves patient safety exposed to novel risks in the context of

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[49] FDA, Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms (Mar. 12, 2020), https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission.

[50] OpenBiome, OpenBiome Announces Enhanced Donor Screening Protocols Following FDA Alert (Apr. 7, 2020), https://www.openbiome.org/press-releases/2020/3/12/openbiome-announces-enhanced-donor-screening-protocols-following-fda-alert.

[51] FDA, Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Additional Safety Protections Pertaining to SARS-CoV-2 and COVID-19 (Mar. 23, 2020), https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-additional-safety-protections

COVID-19 pandemic. The Agency correctly observed on March 23 that "additional safety protections are needed" for the use of FMT in light of the potential transmission of SARS-CoV-2 virus. Finalizing the 2016 draft guidance will protect patient safety and allow the FDA to fully use its regulatory power, which is especially needed during the current COVID-19 pandemic.

D. Finalizing the 2016 Draft Guidance and Requiring Stool Banks to Operate Under an IND is Supported by The Administrative Record

FDA has heard from a number of stakeholders during public workshops and through public comments posted in response to the 2013 guidance, 2014 draft guidance, and 2016 draft guidance documents. The Agency has had plenty of opportunity to review and consider the various viewpoints offered, and there is ample support in the administrative record and in the information FDA has reviewed related to the safety alerts described above to allow FDA to finalize the draft guidance.

MTIG agrees that FMT should be made available to patients who suffer from recurrent *C. diff.* that is unresponsive to standard therapies under circumstances consistent with the 2016 draft guidance. Until an approved microbiome therapy is available, these patients should be able to access physician-prepared FMT with donor controls and informed consent, but enforcement discretion should not extend to unregulated commercial-scale FMT stool banks that have not established safety and efficacy through FDA-regulated clinical trials.

OpenBiome, the largest stool bank program for FMT preparations in the U.S., has requested that FDA continue to allow stool banks to operate under the 2013 enforcement discretion policy, asserting that the universal stool banking screening and manufacturing protocols are safe because they are "overseen by a panel of experts who are equipped to adapt to emerging evidence, including the addition of donor exclusion criteria as new pathogenic threats emerge, or as other diseases or conditions are linked to the microbiome."[52] The system advocated by OpenBiome is premised on voluntary compliance with these protocols. MTIG does not agree that a program based on voluntary compliance adequately protects patients. FDA has not vetted these screening and manufacturing protocols, nor would it be able to assure that necessary safety measures are taken to protect patients without the stool bank's consent and agreement.

The enforcement discretion policy has enabled stool banks to disseminate large volumes of unregulated stool samples across the country, posing a substantial risk to patient safety particularly in the midst of a global pandemic. OpenBiome alone has distributed more than 50,000 stool samples to over 1,200 hospitals and clinics for use in FMT treatments in the last six years.[53] As long as the 2013 enforcement discretion policy is in place, FDA has no way of monitoring or enforcing a stool bank's compliance with its own protocols or even with industry-

[52] OpenBiome Comment on FDA Enforcement Policy Regarding Investigational New Drug Requirements of the Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies, Draft Guidance for Industry, Docket No. FDA-2013-D-0811-0082 (May 31, 2016).
[53] OpenBiome Comment on "Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies," Docket No. FDA-2019-N-3631.

based consensus standards. As the recent safety alerts highlight, FDA can recommend additional screening and testing criteria, and it can "encourage," but it cannot require, the reporting of adverse events. This is in marked contrast to the rigorous screening, testing, and reporting criteria that are in place for other developmental and approved therapeutic products.

MTIG also disagrees with OpenBiome and other commenters who have argued that compliance with IND regulations can impede patient access or clinical practice in relation to FMT. This claim is belied by FDA's many decades of supporting product innovation across a range of products for the benefit of patients while mitigating risk. There is no reasonable argument that FMT products prepared by stool banks should be exempt from IND requirements when countless of other potential ground-breaking therapies are developed under the rubric of an IND.

IV. CONCLUSION

By not finalizing the 2016 draft guidance document, FDA has permitted commercial stool banks to operate in an unregulated manner widely market and distribute stool samples to practitioners for therapeutic purposes. The safety concerns articulated in the 2016 draft guidance to justify excluding stool banks from the enforcement discretion policy are not theoretical. The risks have already been demonstrated by the recent safety alerts and will likely become more pronounced as a result of the coronavirus pandemic. These risks can be mitigated, and the efficacy of FMT products can be better established, if FDA holds stool banks to the same standards it applies to manufacturers of other drug and/or biological products.

MTIG therefore respectfully requests that FDA finalize the 2016 draft guidance without further delay and develop a comprehensive approach for the study and use of FMT products under an IND. If a sponsor of a microbiota drug for *C. diff.* infection receives marketing approval, MTIG requests that FDA consider withdrawing enforcement discretion except in the case where a physician prepares and administers an FMT to his or her own patient.

V. OTHER REQUIRED INFORMATION FOR FILING OF CITIZEN PETITION

A. Environmental Impact

The relief requested in this petition is categorically excluded under 21 C.F.R. § 25.30(h) and therefore does not require an environmental assessment or an environmental impact statement.

B. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted if requested by the Commissioner following review of this petition.

C. Certification

The undersigned certifies that, to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

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