November 29, 2022

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Sent via email to: pkim@foleyhoag.com

Re: Citizen Petition Docket Number: FDA-2020-P-1633

Dear Mr. Kim:

This letter responds to the Citizen Petition (Petition) you filed with the Food and Drug Administration (FDA, the Agency, or we) on behalf of petitioner, Microbiome Therapeutics Innovation Group (MTIG), which was received by the Agency on July 2, 2020. In your Petition, you request that FDA take certain actions with respect to Fecal Microbiota for Transplantation (FMT) for the treatment of *Clostridium difficile* (or *Clostridioides difficile*) (*C. difficile*) [1] infection. Specifically, you request FDA to take four actions:[2]

1. Finalize the 2016 draft guidance [entitled "Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies (2016 draft guidance)] and specify that the sponsors and manufacturers of commercial-scale FMT products are required to operate under an IND and must therefore implement and follow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.

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.

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

[1] *Clostridium difficile* has been renamed *Clostridiodes difficile*.
[2] Petition at 3-4.

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. difficile*] infection receives marketing approval, MTIG requests that FDA reconsider whether enforcement discretion remains the correct action to ensure safe and effective access to patients.

FDA has reviewed and considered the information submitted in your Petition, including the supporting information provided in and comments submitted to the docket. For the reasons explained below, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Fecal Microbiota for Transplantation

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.

B. Applicable Statutory and Regulatory Framework

An FMT product administered to treat *C. difficile* infection meets the definition of a biological product, as defined in section 351(i) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(i)). 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)). As a biological product, an FMT product 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). Approval of a Biologics License Application (BLA) submitted under section 351(a) of the PHS Act requires a demonstration that the biological product is safe, pure, and potent and that "the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent" (see 42 U.S.C. 262(a)(2)(C)).

Although FMT products administered to treat *C. difficile* infection are subject to the licensing requirements set forth in section 351 of the PHS Act, they are exempt from these requirements when administered pursuant to an investigational new drug application (IND) and in compliance with the IND regulations set forth in 21 CFR Part 312 (see 42 U.S.C. 262(a)(3); 21 U.S.C. 355(i); 21 CFR Part 312).

C. The 2022 FMT Enforcement Policy Guidance

Today, November 29, 2022, FDA announced the availability of the final guidance, "Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridioides difficile* Infection Not Responsive to Standard Therapies" (2022 FMT Enforcement Policy Guidance). The guidance finalizes the above-referenced 2016 draft guidance. It informs members of the medical and scientific community and other interested

persons that FDA intends to exercise enforcement discretion under limited circumstances, regarding the IND requirements described above for the use of FMT to treat *C. difficile* infection not responding to standard therapies.

In light of safety concerns with respect to centralized manufacturing of FMT products in stool banks,[3] the guidance explains that FDA's enforcement policy does not apply to FMT obtained from a stool bank.[4]

II. DISCUSSION

As background, the Petitioner, MTIG, states that it is "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."[5] The Petition states that "[c]urrent members of MTIG include Rebiotix Inc., Seed Health, Seres Therapeutics, Inc., Siolta Therapeutics, Takeda Pharmaceutical Company Limited, and Vedanta Biosciences."[6]

The Petition makes four requests regarding FMT products administered to treat *C. difficile*, each of which is described below.

A. Finalize the 2016 draft guidance and specify that the sponsors and manufacturers of commercial-scale FMT products are required to operate under an IND

Petitioner's first request is to "[f]inalize the 2016 draft guidance and specify that [stool banks][7] 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."[8] Petitioner's second request is for FDA to "[r]etain 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

[3] For purposes of the 2022 FMT Enforcement Policy Guidance and this response, a stool bank is "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." See 2022 FMT Enforcement Policy Guidance, at 1.

[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." 2022 FMT Enforcement Policy Guidance, at fn. 4.

[5] Petition at 1.

[6] *Id.* at fn 1.

[7] Although the list of "actions requested" included on page 3 of the Petition refers to "sponsors and manufacturers of commercial-scale FMT products" and then "stool banks and contract manufacturers," the Petitioner subsequently appears to use the term "stool banks," as defined in FDA's 2016 draft guidance, to refer to these entities.

[8] Petition at 3.

provider for the purpose of providing the FMT product to treat his or her own patient."[9, 10] We interpret the first two requests together as requesting that FDA issue final guidance describing the Agency's intent not to extend enforcement discretion to FMT products obtained from a stool bank and to exercise enforcement discretion with respect to other FMT products consistent with the policy described in the 2016 draft guidance.

In support of these requests, Petitioner raises safety concerns regarding stool banks operating without INDs[11] and highlights protections offered by submission of an IND and compliance with other IND requirements.[12] Petitioner also asserts that the existence of "countless . . . other potential ground-breaking therapies . . . developed under the rubric of an IND" demonstrates that stool banks can comply with IND requirements without "imped[ing] patient access or clinical practice in relation to FMT."[13]

As discussed above, FDA has finalized the 2016 draft guidance. We have concluded this policy appropriately balances considerations regarding patient safety and facilitating access to unapproved FMT products for unmet medical needs. For the reasons explained in the guidance, the enforcement policy described in the 2022 FMT Enforcement Policy Guidance does not extend to the use of FMT product obtained from a stool bank.[14] We therefore grant your request. We do not agree with all of Petitioner's assertions in support of the request; however, because we are granting the request, we will not individually address the assertions in this response.

In addition, to the extent your Petition can be interpreted to request that FDA initiate or take enforcement actions against stool banks, we note that such a request is not a proper subject of a citizen petition. A citizen petition provides a mechanism for interested persons to request that FDA issue, amend, or revoke a regulation or order, or take or refrain from taking any other form of administrative action.[15] However, the definition of administrative action does not include

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[9] *Id.*; see also, id. at 8 ("The Policy Articulated in the 2016 Draft Guidance Strikes an Appropriate Balance by Allowing FMT Therapy to Continue Under Limited and Controlled Circumstances") and *id.* at 13 ("MTIG agrees that FMT should be made available to patients who suffer from recurrent [*C. difficile*] that is unresponsive to standard therapies under circumstances consistent with the 2016 draft guidance.").

[10] To the extent that the Petition's reference to a "safe harbor" is intended to suggest that FDA's enforcement policy regarding FMT products establishes a binding exception from IND requirements, we note that FDA's guidance on this topic does not alter any statutory or regulatory requirements and does not bind the Agency or the public, including stool banks.

[11] For example, the Petition notes that "[r]ecent 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" and describes safety alerts FDA issued in 2019 and 2020. See Petition at 10-12.

[12] See, e.g., *id.* at 9.

[13] *Id.* at 14.

[14] The final guidance includes three bullets to help describe the circumstances in which FDA intends to exercise enforcement discretion, only one of which, that "[t]he 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 inappropriate storage or handling, or concerns regarding administration of product collected without appropriate screening or testing)" is not explicitly included in the 2016 draft guidance. However, this clarification is consistent with the intent described in the 2016 draft guidance with respect to excluding use of FMT that presents safety concerns from the scope of FDA's enforcement policy.

[15] 21 CFR 10.25(a).

enforcement actions,[16] and requests for FDA to initiate enforcement action are outside the scope of our citizen petition regulations.[17] Decisions regarding whether to pursue enforcement action are within the Agency's discretion. Therefore, to the extent you are requesting that FDA initiate or take enforcement actions, we are denying your request under 21 CFR 10.30(e).

B. Provide guidance on the study and use of FMT products under an IND

Petitioner next requests FDA to "[p]rovide additional guidance with respect to the comprehensive approach FDA is considering for the study and use of FMT products under an IND."[18] We acknowledge that the 2016 draft guidance stated that it was intended to be an interim approach while the Agency develops a "comprehensive approach for the study and use of FMT products under IND."[19] At this time, however, we conclude that the policy described in the 2022 FMT Enforcement Policy Guidance strikes the appropriate balance and that additional guidance on a different or more comprehensive approach is not necessary. In addition, other than the general requests we address in this response, Petitioner does not specify what the requested additional guidance on a comprehensive approach should entail or explain why guidance on specific topics would be useful. We therefore deny your request.

C. Reiterate that the FMT enforcement discretion policy is an interim policy, and is subject to change or revocation

Lastly, Petitioner requests FDA to "[r]eiterate 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."[20] In particular, Petitioner requests that FDA consider withdrawing its enforcement policy "[i]f a sponsor of a microbiota drug for [*C. difficile*] infection receives marketing approval . . . except in the case where a physician prepares and administers an FMT to his or her own patient."[21]

With respect to your request that FDA state that its FMT enforcement policy is interim in nature, we have issued the 2022 FMT Enforcement Policy Guidance without such a statement. After a guidance is finalized, FDA may take appropriate action to protect and promote the public health, which may include withdrawal or revision of a guidance, including a guidance communicating an enforcement policy, following further evaluation of the policy. We therefore find it unnecessary to state in the guidance that the policy is interim in nature.

To the extent your Petition can be read to request that FDA specifically address in the guidance if we will withdraw or make any changes to our policy if an FMT product is approved, we also deny your request. Specifically addressing if we will make any changes is premature before we

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[16] As defined in FDA regulations, "administrative actions" include every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner, except that it does not include the referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or an act in preparation of a referral. 21 CFR 10.3(a).
[17] See 21 CFR 10.30(k).
[18] Petition at 4.
[19] 2016 draft guidance at 2.
[20] Petition at 4.
[21] *Id.* at 14.

know what product is approved, how widespread access to and use of that product will be, and what the conditions are for patients at that time. As stated in the 2022 FMT Enforcement Policy Guidance, the Agency will also continue to evaluate its policies concerning the use of FMT products as scientific evidence in this area evolves.

III. CONCLUSION

FDA has considered Petitioner's requests related to FMT products for the treatment of *C. difficile* infection. For the reasons given in this letter, FDA grants your requests in part, and denies the requests in part.

Sincerely,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

cc: Dockets Management Staff