Microbiome Therapeutics Innovation Group Position Statement on FMT

Background

The microbiome is essential to human health providing resistance to infectious diseases, regulating the immune system, and impacting metabolism and digestion.[1] Through a complex and vast network of interacting microbes, the microbiome engages both directly and indirectly with the host to affect neurologic, physiologic and immunologic functions.[2] Disruption of this complex ecosystem is now associated with a multitude of chronic and infectious diseases.

Groundbreaking drug products that modulate the microbiome have the potential to address a wide spectrum of health challenges. The role of the microbiome is best understood in recurrent *Clostridium difficile* (*C. diff.*) infection, but additional clinical research is studying the microbiome's role in other disease states including, for example, inflammatory bowel disease (IBD),[3] irritable bowel syndrome (IBS), liver disease,[4] colon cancer,[5] neurological disorders,[6] and outcomes of cancer immunotherapies[7].

The foundational importance of the microbiome to these diseases and the curative potential of microbiome modulation began with research into fecal microbiota transplantation (FMT). FMT is an investigational procedure that historically consisted of a physician collecting stool from a healthy individual and subsequently administering it to a patient. At present, FMT is most commonly administered for the treatment of *C. diff.* infection in patients who fail other treatment options. Although published data suggests that FMT can be an effective therapy to manage recurrent *C. diff.* infection,[8] the safety and efficacy of FMT have not been fully

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[1] de Vos, WM, de Vos, EAJ. *Role of the intestinal microbiome in health and disease: from correlation to causation*, Nutrition Reviews. 2012;70(Suppl. 1):545-56.

[2] Gupta, S, Allen-Vercoe, E, Petrof, E. *Fecal Microbiota Transplantation: In Perspective*, Therapy Adv. Gastroentology. 2016 Mar;9(2):229-39.

[3] Halfvarson, J., et al., *Dynamics of the human gut microbiome in inflammatory bowel disease*, Nat. Microbiol. 2017 Feb;DOI:10.1038/nmicrobiol.2017.4.

[4] Adolph, TE, et al., *Liver-Microbiome Axis in Health and Disease*, Trends Immunol. 2018 Sep;39(9):712-23.

[5] Miyake, Y, Yamamoto, K. *Role of Gut Microbiota in Liver Diseases*, Hepatol. Res. 2013 Feb;43(2):139-46.

[6] Mayer EA, et al., *Gut Microbes and the Brain: Paradigm Shift in Neuroscience*, J. Neurosci. 2014 Nov;34(46):15490-496.

[7] Elkrief, A, et al., *The intimate relationship between gut microbiota and cancer immunotherapy*, Gut Microbes. 2018 Oct;DOI:10.1020/19490976.2018.1527167.

[8] 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*, (hereinafter, Draft Guidance), at *2, available at

demonstrated in randomized double-blind controlled clinical trials or evaluated by the Food and Drug Administration (FDA).[9]

FDA has determined that FMT administered to treat *C. diff.* infections meets the definitions of a biological product and a drug and is therefore subject to premarket review and approval under the Public Health Service Act ("PHS Act") and the Federal Food, Drug, and Cosmetic Act ("FDCA").[10] Under this determination, clinical trials to demonstrate safety and efficacy are required for FDA approval and commercial distribution of FMT as set forth in the Investigational New Drug ("IND") regulations, 21 CFR Part 312. In 2013, FDA took the position that FMT may be used as an investigational therapy to treat *C. diff.* infections not responding to standard therapies, provided the physician obtains adequate informed consent from the patient, including acknowledgement of the investigational nature and risks of FMT.[11]

In March 2016, FDA issued a Draft Guidance proposing to narrow the IND exemption to the use of FMT to treat *C. diff.* infections not responding to standard therapies, provided that:

- the treating physician obtains informed consent, including a discussion of FMT's "reasonably foreseeable risks";[12]
- the FMT product is not obtained from a stool bank; and
- the stool donor and stool are "qualified by screening and testing" under a physician's supervision in providing the FMT product to treat a patient.[13]

The FDA's decision not to enforce IND requirements under these narrow conditions has created an unintended situation whereby stool bank companies screen donors, process samples, and commercially distribute FMT treatments without complying with IND requirements and without establishing the safety and efficacy of their drug products through prospective clinical trials. At present, this 2016 Draft Guidance has not been finalized.

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https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm488223.pdf (March 2016).

[9] Draft Guidance, at *2.

[10] Draft Guidance, at *1.

[11] 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*, (hereinafter, Guidance), at *1, available at https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM361393.pdf (July 2013).

[12] Draft Guidance, at *3.

[13] Id. at *4.

Patients benefit from products with FDA-approved safety, efficacy, manufacturing controls, and rigorous post-marketing surveillance to ensure long-term safety. FDA approval would also broaden access to a larger patient population through enabling coverage by Medicare and private insurance companies, as well as providing physicians a less burdensome process for administering treatment. At present, the development of approved therapies is facing substantial delays despite extensive outreach, education and recruitment efforts, largely due to stymied enrollment in clinical trials because of the broad distribution of unapproved FMT.

MTIG Position Statement

The Microbiome Therapeutics Innovation Group (MTIG) is a coalition of companies leading the research and development of FDA-approved microbiome therapeutic drugs and microbiome-based products to address unmet medical needs, improve clinical outcomes, and reduce health care costs.

- MTIG agrees with FDA that patients should access FMT treatment through clinical trials and supports continuing patient access to physician-prepared FMT with donor controls and informed consent, consistent with the FDA's Draft Guidance. MTIG also strongly supports FDA's position, as stated in the Draft Guidance, that enforcement discretion should not extend to unregulated commercial-scale FMT stool banks that have not established safety and efficacy through FDA-regulated clinical trials.

- MTIG supports consistent and equitable FDA oversight and regulation to ensure that commercial-scale FMT products implement and adhere to the rigorous clinical, regulatory manufacturing and quality controls to which other microbiota drug products adhere.

- Consistent with years of Agency practice and precedent, MTIG concurs with FDA's regulatory classification of FMT as a drug product that is subject to IND requirements that protect patient safety and assure clinical experiments are conducted in accordance with the law.

- MTIG supports companies in their pursuit of regulatory approvals for microbiome therapeutics and microbiome-based products.

- Streamlining FDA regulatory procedures to increase clarity and decrease development time is the best way to assure that safe and effective microbiome therapeutics reach patients and providers. MTIG encourages the FDA to issue guidance for microbiome therapeutics development topics, such as clinical trial designs, endpoint and biomarker selection, use of expedited review pathways, and product nomenclature.

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