DOES FECAL MATTER?

IMPLICATIONS OF FDA REGULATION ON CURRENT AND FUTURE THERAPEUTIC USES OF FMT

I. Introduction

The next big microbiota therapy might be literal crap. A microbiologist[1] at the Massachusetts Institute of Technology pitched this idea to a group of pharmaceutical executives when he was interrupted and asked if the presentation was a prank.[2] But human feces as a microbiota transplant is no joke. Later that year, that microbiologist, Mark Smith, co-founded OpenBiome and Finch Therapeutics.[3] Open Biome is the largest supplier of donor stool in America and Finch Therapeutics has raised over $77 million dollars to research therapeutic candidates aimed at preventing and curing recurrent Clostridioides difficile infection and other disorders.[4]

The increase use of human feces to treat recurrent Clostridioides difficile has prompted the Food and Drug Administration ("FDA") to increase oversight and regulation. Currently, the FDA has not approved fecal transplants as a treatment but allows the procedure to be administered with certain conditions.[5] This has been the policy since 2013, but in 2016 the FDA issued a draft guidance indicating their intent to regulate fecal transplants as a drug.[6] This would limit the treatment to patients enrolled in clinical trials and therefore limit access to an effective

---

[1] Mark Smith, co-founder of OpenBiome. *See* Andrew Jacobs, *Drug Companies and Doctors Battle Over the Future of Fecal Transplants*, N.Y. TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html.
[2] Andrew Jacobs, *Drug Companies and Doctors Battle Over the Future of Fecal Transplants*, N.Y. TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html
[3] *Id.*
[4] *Id.*; *Recurrent C. Diff*, FINCH, https://finchtherapeutics.com/cp101# (last visited Oct. 25, 2019).
[5] 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, 78 Fed. Reg. 138 (Jul. 18, 2013).
[6] Draft Guidance for Industry: *Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat* Clostridium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*, Food and Drug Administration (Mar. 1, 2016), https://www.fda.gov/media/96562/download.

therapy used to treat recurrent Clostridioides difficile infection.[7] However, the investigative process would ensure the efficacy and safety of fecal transplants in the long-term.[8]

The policy implications are important to pharmaceutical companies, doctors, and patients alike. Opponents to the FDA draft guidance offer an alternative approach of regulating fecal material as a human tissue as opposed to a drug. The FDA is expected to announce a regulatory paradigm soon.[9] In Part II, this Comment begins by examining the uses of fecal microbiota transplant and provides a history of fecal microbiota transplant regulation governed by the FDA.[10] Part III offers ways to define fecal microbiota transplants, competing regulatory schemes, and proposes that the FDA adopt a hybrid approach that mirrors the cord blood regulatory scheme.[11] Under this scheme, the FDA would be regulating fecal material depending on its intended use. In doing so, the FDA would be able to allow efficacious uses of FMT to reach the patient while also regulating exploratory uses that have not been proven safe and effective thereby accommodating patient access concerns without stifling FMT research and innovation.

II. Background

A. What is Clostridioides Difficile?

[7] *Infra* text accompanying note 66.
[8] *Infra* text accompanying note 131.
[9] Samantha DiGrande, *Should Fecal Microbiota Transplants Be Regulated as Drugs or Organ Donations?*, AMERICAN JOURNAL OF MANAGED CARE: IN FOCUS BLOG (Mar. 6, 2019), https://www.ajmc.com/focus-of-the-week/should-fecal-microbiota-transplants-be-regulated-as-drugs-or-organ-donations.
[10] *Infra* Part II
[11] *Infra* Part III

Clostridioides Difficile, or commonly known as c. diff, is a bacterium that causes diarrhea and colitis[12] and causes almost half a million illnesses annually amongst people of all ages.[13] C. diff infections ("CDI") are is characterized by the reduction of necessary gastro-intestinal (GI) bacteria in the gut.[14] Of those affected, 1 in 5 will get contract CDI at least once more[15] and one in 11 people over the age of 65 diagnosed with CDI die within a month.[16] In the aggregate, 30,000 patients die every year from CDI.[17] Most cases of CDI occur after taking antibiotics because broad spectrum antibiotics can suppress harmful *and* beneficial bacteria in the human gut.[18] C. diff can also be contracted through physical contact with surfaces that are contaminated with the feces of an infected person.[19] Given that more than half of hospitalized patients will receive an antibiotic during their hospital stay, c. diff is easily picked up in hospitals and nursing homes that do not implement adequate infection control and where antibiotic use is prevalent.[20] In fact, two-thirds of CDIs were found to be associated with inpatient stays at health care facilities either occurring during the stay or shortly after being discharged.[21]

---

[12] Inflammation of the colon; *See C. Diff Factsheet*, CENTERS FOR DISEASE CONTROL AND PREVENTION, https://www.cdc.gov/cdiff/pdf/Cdiff-Factsheet-508.pdf (last visited Oct. 25, 2019).
[13] *C. Diff Factsheet*, CENTERS FOR DISEASE CONTROL AND PREVENTION, https://www.cdc.gov/cdiff/pdf/Cdiff-Factsheet-508.pdf (last visited Oct. 25, 2019).
[14] Arsalan Ahmed, *Ensuring Safer and More Effective Regulation of Fecal Microbial Transplantation (FMT): A Renewed Understanding)*, 2(1) Col. Med. Rev. (2018).
[15] *C. Diff Factsheet*, CENTERS FOR DISEASE CONTROL AND PREVENTION, https://www.cdc.gov/cdiff/pdf/Cdiff-Factsheet-508.pdf (last visited Oct. 25, 2019).
[16] *Id.*
[17] *Impact*, OPENBIOME, https://www.openbiome.org/impact (last visited Oct. 25, 2019).
[18] Media Release: *Nearly half a million American suffered from Clostridium difficile infections in a single year*, CENTERS FOR DISEASE CONTROL AND PREVENTION (Mar. 22, 2017), https://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html.
[19] *C. Diff Factsheet*, CENTERS FOR DISEASE CONTROL AND PREVENTION, https://www.cdc.gov/cdiff/pdf/Cdiff-Factsheet-508.pdf (last visited Oct. 25, 2019).
[20] Media Release: *Nearly half a million American suffered from Clostridium difficile infections in a single year*, CENTERS FOR DISEASE CONTROL AND PREVENTION (Mar. 22, 2017), https://www.cdc.gov/media/releases/2015/p0225-clostridium-difficile.html.
[21] *Id.*

Ironically, the standard treatment for CDI is to prescribe antibiotics to prevent the bacterium from growing.[22] But 20% of individuals get reoccurring c. diff infections and have limited antibiotic treatment options because, in general, repeating the same therapy used for an initial infection for a recurrent infection is not recommended.[23] Because of the "urgent problems in hospitals, ambulatory surgery centers, inpatient rehab facilities, and skilled nursing facilities and in communities," the Centers for Disease Control and Prevention ("CDC") have partnered with the Centers for Medicare and Medicaid Services ("CMS") to reduce c. diff infections by 30% by 2020.[24] Currently, the CDC has partnered with various research, academic, and federal initiatives to assist in preventing CDI and controlling c. diff bacteria; however, there are less treatment options available for those who contract CDI over and over again.[25]

B. Fecal Microbiota Transplant

A promising treatment option for chronic CDI are fecal microbiota transplants ("FMT"). FMT is a procedure that takes healthy stool from a donor and transplants it into the colon of a patient with CDI. By doing so, necessary and "good" microorganisms are reinstated into a c. diff infected colon and prevents the c. diff bacteria from overgrowing.[26] Not only is FMT an alternative to antibiotic therapies for recurring CDI, it is more effective.[27] Studies have shown

---

[22] *C. difficile infection*, MAYO CLINIC, https://www.mayoclinic.org/diseases-conditions/c-difficile/diagnosis-treatment/drc-20351697 (last visited Oct. 25, 2019).
[23] *The Progression of a* C. Diff *Infection*, CENTERS FOR DISEASE CONTROL AND PREVENTION, https://www.cdc.gov/cdiff/pdf/Cdiff-progression-H.pdf (last visited Oct. 25, 2019).
[24] *What CDC is Doing to Reduce* C. diff *Infections*, CENTERS FOR DISEASE CONTROL AND PREVENTION (Dec. 17, 2018), https://www.cdc.gov/cdiff/reducing.html.
[25] *Innovative Projects: Broad Agency Announcement (BAA)*, CENTERS FOR DISEASE CONTROL AND PREVENTION (Jan. 31, 2019), https://www.cdc.gov/drugresistance/solutions-initiative/innovations-to-slow-AR/projects.html.
[26] Arsalan Ahmed, *Ensuring Safer and More Effective Regulation of Fecal Microbial Transplantation (FMT): A Renewed Understanding)*, 2(1) Col. Med. Rev. (2018).
[27] *Id.*

that 94% of patients with recurrent CDI who underwent FMT were effectively cured and 83% of those patients were cured after a single application.[28] By comparison, patients with recurrent CDI had a 31% recovery rate with antibiotic treatment.[29] However, FMT is only recommended for patients "with multiple recurrences of CDI who have failed appropriate antibiotic treatments."[30]

After the study in 2013, several stool banks were developed internationally to supply donor stool; however, there are no universal guidelines to regulate these facilities.[31] For example, the European Union allows each state to enact its own policy. The Netherlands considers FMT an "unclassified treatment" while several other European countries consider donor stool to be a drug.[32] Therefore, in those countries, FMT must meet active ingredient, dosage form, route of administration, quality, and performance standards, which are very difficult to guarantee from batch to batch.[33] In the U.S., the FDA exercises "enforcement discretion" which allows doctors to treat recurrent CDI outside of clinical trials if certain conditions are met.[34] The primary stool bank in the United States is OpenBiome—a nonprofit organization that is also engaged in FMT research.[35] OpenBiome uses its own screening and testing process because no federal protocols

---

[28] Els van Nood, et al., *Dueodenal Infusion of Donor Feces for Recurrent Clostridium difficile*, 368(5) THE NEW ENG. J. OF MED. 407, 411-12 (2013).
[29] *Id.*
[30] Was noted as a "strong recommendation;" *See Id.*
[31] E.M. Terveer, et al., *How to: Establish and run a stool bank*, 23(12) Clinical Microbiology and Infection 924, 925-26 (2017), https://reader.elsevier.com/reader/sd/pii/S1198743X17302756?token=C687F1F68A5B36ACF27A9CD5AD6A5003134EA5358806A4352955594747DD03D153BBF19947CF07326690420315735116.
[32] *Id.* at 926.
[33] *Id.*
[34] 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; Availability, 78 Fed. Reg. 138, 42965 (Jul. 18, 2013); *See also infra* Part II.C.
[35] *Mission*, OPENBIOME, https://www.openbiome.org/impact (last visited Oct. 25, 2019).

in this context currently exist.[36] However, the organization conducts a rigorous screening process and, since its opening in 2012, has only passed 3% of 3.5 tons of stool.[37]

However, despite the lax formal regulatory framework in place, the use of FMT is met with a variety of safety concerns primarily regarding bacterial infections.[38] The FDA has released a safety alert notifying the risk of adverse reactions due to multi-drug resistance organisms ("MDROs"). Multi-drug resistant bacteria is one of the "most important current threats to public health" and are associated with "increased morbidity, mortality, healthcare costs and antibiotic use."[39] The alert reported two cases of bacterial infections; however, both individuals were both immunocompromised adults who received stool from the same donor which was not tested for extended-spectrum beta-lactamase ("ESBL"), which produces Escherichia coli (E. coli).[40] The donor stool was later tested and found to be ESBL positive.[41] These two adverse events were preventable had proper screening and testing been conducted.

C. FDA Authority and Involvement

---

[36] Bethany Brookshire, *To regulate fecal transplants, FDA has to first answer a serious question: What is poop?*, SCIENCE NEWS SCICURIOUS BLOG (May 18, 2018), https://www.sciencenews.org/blog/scicurious/fecal-transplants-regulation.
[37] *Impact,* OPENBIOME, https://www.openbiome.org/impact (last visited Oct. 25, 2019).
[38] *Important Safety Alert Regarding use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Mutli-Drug Resistant Organisms*, Food and Drug Administration (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.
[39] Davis van Duin and David Paterson, *Multidrug Resistant Bacteria in the Community: Trends and Lessons Learned*, 30(2) Infectious Disease Clinics of N. Am. 377 (2017).
[40] *Important Safety Alert Regarding use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Mutli-Drug Resistant Organisms*, Food and Drug Administration (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.
[41] *Id.*

In 2013, the FDA released its first guidance document announcing its "enforcement discretion" policy regarding the investigational new drug requirements ("IND") of FMT use.[42] The guidance allows FMT to be used to treat CDI when two requirements are met: 1) standard therapies were ineffective and 2) the patient gives informed consent to the potential risks of FMT as an investigational therapy.[43] Discussions at FDA workshops[44] preceding the issuance of the guidance document highlighted the concern that IND regulations would render FMT unavailable to patients who have already exhausted all other treatment options.[45] Therefore, these guidelines were to be the interim guidelines while the agency developed suitable IND policies for the study and use of FMT.[46]

However, despite the concerns about requiring an IND for FMT use, the FDA released a draft guidance that proposed to regulate FMT as a drug the following year.[47] This would require all patients treated with FMT to be enrolled in a clinical trial and limit access to patients who are not eligible for clinical trials.[48] The 2014 draft guidance also intended to exercise "enforcement

---

[42] 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; Availability, 78 Fed. Reg. 138, 42965 (Jul. 18, 2013).
[43] *Id.*
[44] 21 C.F.R. §10.115(g)(1)(i) and (ii) allows the FDA to seek input from individual groups apart from the agency before and after the issuance of a guidance document
[45] 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; Availability, 78 Fed. Reg. 138, 42965 (Jul. 18, 2013).
[46] *Id.*
[47] *Draft Guidance Announcement*, OpenBiome, https://www.openbiome.org/draft-guidance-announcement (last visited oct. 25, 2019).
[48] *Id.;* Samantha DiGrande, *Should Fecal Microbiota Transplants Be Regulated as Drugs or Organ Donations?*, American Journal of Managed Care: in Focus Blog (Mar. 6, 2019), https://www.ajmc.com/focus-of-the-week/should-fecal-microbiota-transplants-be-regulated-as-drugs-or-organ-donations.

discretion" regarding IND requirements given that "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."[49] These provisions were met with favor for allowing patient access to FMT but many objected to the second provision.[50]

In 2016, the FDA rescinded the 2014 draft guidance and issued a new draft guidance that reinstated the FDA's use of "enforcement discretion" under limited conditions regarding relevant IND requirements.[51] The draft guidance would allow the use of FMT to treat recurrent CDI "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, 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."[52] The informed consent must include a statement that acknowledges FMT is an investigational treatment for CDI and a discussion of its "reasonably foreseeable risks."[53] Because this draft guidance prohibits FMT to

[49] 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*, Food and Drug Administration (Mar. 1, 2016), https://www.fda.gov/media/96562/download.
[50] *Id.* at 3.
[51] *Id.* at 2.
[52] *Id.* at 1.
[53] *Id.* at 1.

be obtained from a stool bank, the burden of screening and testing in a centralized location would be dispersed amongst hospitals.[54]

In the 2016 draft guidance, a stool bank is defined 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."[55] But those establishments solely under the direction of licensed health care providers for the purpose of treating their patients are not considered stool banks for purposes of the draft guidance.[56] The draft guidance does not extend enforcement discretion for the IND requirements to stool banks because the FMT products they distribute will have to be covered by the IND the sponsor will have in effect for clinical investigative purposes.[57] Another reason why enforcement discretion will not be extended to stool banks is because these centralized systems pose safety concerns.[58] Such systems use FMT from a limited number of donors but then are administered to multiple patients.[59] The FDA believes that the stool banks' compliance with the sponsor IND will ensure adequate and qualified screening practices.[60]

OpenBiome has highlighted two issues in response to the 2016 draft guidance. The first relates to the challenges that trial enrollment poses to both short and long-term access to

---

[54] Rachel Sachs, *FDA Announces Draft Guidance That Would Limit Enforcement Discretion for FMT*, THE PETRIE-FLOM CENTER (Mar. 1, 2016), http://blog.petrieflom.law.harvard.edu/2016/03/01/fda-announces-draft-guidance-that-would-limit-enforcement-discretion-for-fmt/.
[55] 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*, Food and Drug Administration (Mar. 1, 2016), https://www.fda.gov/media/96562/download.
[56] For example, a hospital lab; *See Id.* at 2.
[57] *Id.* at 2.
[58] *Id.* at 3.
[59] *Id.* at 3.
[60] It is worth noting that IND sponsors may request waivers of certain responsibilities; *Id.* at 3.

microbiome-based therapies.[61] There are three clinical trials focused on studying microbiome-based therapies which have slowed due to enforcement discretion. The second issue is that the proposed policies would unduly limit patients' access to FMT because doctors would only be able to obtain FMT material from a stool bank if their patient were part of a clinical trial.[62]

Other groups point out that the restricting donor stool to be obtained from stool banks contemplate that hospitals are able to collect, prepare, and store FMT for patient's use.[63] However, hospitals are likely unable or unwilling to devote facilities to a bank or personnel necessary to maintain a bank, which would subsequently limit the availability of FMT to patients.[64] "Put another way, stool banks can achieve economies of scale in a way that many hospitals cannot."[65] Furthermore, limiting patient access may force individuals to resort to home FMT remedies because of its "do-it-yourself" potential.[66]

It is worth noting that, though the FDA intends to regulate FMT as a drug, the decentralization of oversight of FMT material from a small number of stool banks to a larger number of hospitals effectively resembles a tissue regulatory system rather than a drug paradigm.[67] A drug paradigm normally consists of a small number of highly-regulated

---

[61] *Proposal For New Draft Guidance*, OPENBIOME, https://www.openbiome.org/comment-to-fda#Proposed-Policy (last visited Oct. 25, 2019).
[62] *Id.*
[63] Rachel Sachs, *FDA Announces Draft Guidance That Would Limit Enforcement Discretion for FMT*, THE PETRIE-FLOM CENTER (Mar. 1, 2016), http://blog.petrieflom.law.harvard.edu/2016/03/01/fda-announces-draft-guidance-that-would-limit-enforcement-discretion-for-fmt/.
[64] *Id.*
[65] *Id.*
[66] *Id.*; *See also* Video: Fecal Transplant (FMT) (May 13, 2013), https://www.youtube.com/watch?v=xLIndT7fuGo.
[67] Rachel Sachs, *FDA Announces Draft Guidance That Would Limit Enforcement Discretion for FMT*, THE PETRIE-FLOM CENTER (Mar. 1, 2016), http://blog.petrieflom.law.harvard.edu/2016/03/01/fda-announces-draft-guidance-that-would-limit-enforcement-discretion-for-fmt/.

manufacturers whereas a tissue paradigm generally consists of a number of facilities regulated for storage and distribution.[68] Given the 2016 draft guidance, which highlighted the medical significance of FMT in treating CDI, and patient access and safety concerns, much discussion has taken place on how the FDA should regulate FMT material. How the FDA chooses to define FMT will substantially influence the regulatory scheme the agency will adopt, which ultimately will impact patient access and FMT research and development. A balanced system able to accommodate FMT's current and future therapeutic benefits is necessary.

III. Analysis

A. Defining FMT

In order to regulate FMT, it must first be defined by regulatory bodies. The Food, Drug, and Cosmetics Act ("FDCA") regulates drugs and defines a drug as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals."[69] The Public Health Services Act ("PHSA") regulates human tissue and defines it as "any tissue derived from a human body which is intended for transplantation to another human for the diagnosis, cure, mitigation, treatment, or prevention of any condition or disease" or "is recovered, processed, stored, or distributed by methods that do not change tissue function or characteristics."[70] Normally, when a tissue's intended use is to treat a disease that affects the structure or function of the body, it is considered a drug.[71] Doing so would not only limit patient access to the treatment, but impose impractical requirements on FMT material.

---

[68] *Id.*
[69] 21 U.S.C. §321(g)(1)
[70] 21 C.F.R. §1270.3(j)(1) and (2)
[71] Erika Lietzan, *Article: Access Before Evidence and the Price of The FDA's New Drug Authorities*, 53 U. Rich. L. Rev. 1243, 1262 (2019).

Regulating FMT like a drug would require FMT material to satisfy uniform standards that it could not possibly meet due to the "community of highly dynamic, metabolically active organisms."[72] Rather, FMT should be regulated as a human tissue like blood and cord blood. For both, the FDA has carved out separate regulatory schemes for blood products as biologics under the PHSA.[73] The regulations primarily focus on ensuring the safety and quality of the blood supply by restricting possible donors.[74] For example, the FDA periodically releases guidance documents with recommendations to reduce the risk of transmitting infectious diseases.[75] Blood banks are required to keep a list of "deferred donors" to ensure that the banks do not collect blood from certain individuals on the list.[76] Additionally, the FDA reviews and approves all test

[72] *Id.* at 1265.
[73] Rachel Sachs, *Ensuring the safe and effective FDA regulation of fecal microbiota transplantation*, 2(2) J. Law. Biosci. 396 (2015).
[74] 21 C.F.R. §630; *See also Keeping Blood Transfusions Safe: FDA's Multi-layered Protections for Donated Blood*, FOOD AND DRUG ADMIN. (Mar., 23, 2018), https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/keeping-blood-transfusions-safe-fdas-multi-layered-protections-donated-blood
[75] For example, in August 1999, the FDA suggested the blood industry avoid donors who had lived in the UK and other European countries because the variant Creutzfeldt-Jakob disease (vCJD), the human form of "mad cow disease," was discovered in the UK. *Variant Creutzfeldt-Jakob Disease (vCJD) and Factor VIII (pdFVIII) Questions and Answers*, FOOD AND DRUG ADMIN.(Jun. 18, 2018), https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/variant-creutzfeldt-jakob-disease-vcjd-and-factor-viii-pdfviii-questions-and-answers; *Keeping Blood Transfusions Safe: FDA's Multi-layered Protections for Donated Blood*, FOOD AND DRUG ADMIN. (Mar., 23, 2018), https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/keeping-blood-transfusions-safe-fdas-multi-layered-protections-donated-blood
[76] *Keeping Blood Transfusions Safe: FDA's Multi-layered Protections for Donated Blood*, FOOD AND DRUG ADMIN. (Mar., 23, 2018), https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/keeping-blood-transfusions-safe-fdas-multi-layered-protections-donated-blood; *See also* Kavita Shah Arora, Righting Anachronistic Exclusions: The Ethics of Blood Donation by MSM, 29(1) J. Gay Lesbian Soc. Serv. 87 (2017) (discussing the controversial practice of blood donor deferral and the ethical goods that must be balanced, including equality and the public's trust in the blood supply, when crafting deferral guidelines).

kits that are administered to each unit of donated blood with the purpose of detecting infectious diseases.[77]

Not only does the FDA regulate the blood supply, it also regulates the blood bank facilities and personnel.[78] The Code of Federal Regulations outlines facility, equipment, and reagent standards to ensure safe and sanitary collection, processing, in addition to proper disposal of blood and blood components procedures.[79] There must be enough personnel at each facility and each are personally required to possess "adequate…educational background, training and experience, including professional training as necessary, or combination thereof, to assure competent performance of their assigned functions."[80]

Blood and FMT material share scientific characteristics that make them distinct from traditional drugs and therefore warrant a special set of regulations. Both have the potential of transmitting diseases while also facing scarcity.[81] Additionally, both the efficacy of blood and efficacy of FMT in treating CDI was known before FDA involvement.[82] But there is one critical distinction: scientists believe that FMT may be able to treat other illnesses that implicate the human microbiome.[83] Illnesses like Crohn's disease, inflammatory bowel diseases, and even non-gastrointestinal disorders like chronic fatigue syndrome may benefit from FMT treatment.[84]

---

[77] *Id.*
[78] 21 C.F.R. §606
[79] 21 C.F.R. §§606.40, 606.60, 606.65
[80] 21 C.F.R. §606.20
[81] Rachel E. Sachs and Carolyn A. Edelstein, *Ensuring the safe and effective FDA regulation of fecal microbiota transplantation*, J. LAW BIOSCI. 396 (2015).
[82] *Id.*
[83] *Id.*
[84] Liang J. Sha et al., *Systematic review: faecal microbiota transplantation therapy for digestive and nondigestive disorders in adults and children*, 39(10) ALIMENTARY PHARMACOLOGY AND THERAPEUTICS 1003, 1004, 1027 (2014); Rachel E. Sachs and Carolyn A. Edelstein, *Ensuring the safe and effective FDA regulation of fecal microbiota transplantation*, J. LAW BIOSCI. 396 (2015).

Because the efficacy of FMT treatment for disorders other than CDI is unknown, further research is necessary but the blood regulatory scheme is unable to accommodate clinical testing. For this reason, another regulatory scheme that allows clinical examination is more suitable.

B. Cord Blood Regulatory Scheme

The development of cord blood—"blood harvested at birth from human placentas and umbilical cords"[85]—and FMT mirror each other. In the 1980's, the benefits of harvesting stem cells from cord blood opposed to the pre-existing painful and costly procedure of harvesting bone marrow stem cells were discovered.[86] This discovery spurred the "biological gold rush" where many biotech entrepreneurships were formed in the cord blood bank business .[87] The immediate clinical utility was profound such that the National Institutes of Health ("NIH") funded a pilot cord blood bank in New York.[88]

The FDA shortly became involved and voiced issues regarding the safety in manipulating cord blood.[89] The agency followed-up with a draft guidance proposal to treat cord blood like experimental new drugs which would impose the IND process.[90] This would have the effect of prohibiting marketing and commercialization of cord blood until the necessary testing was completed.[91] However, the IND requirements for cord blood storage and transplantation are equally compelling. The most effective methods of using cord blood and the long-term safety and efficacy of cord blood transplants were unknown at the time; therefore, any use of cord

[85] Jennifer Kulynych, *Blood As a Biological "Drug": Scientific, Legal, and Policy Issues in the Regulation of Placental and Umbilical Cord Stem Cell Transplantation*, 32 U. RICH. L. REV. 407, 408 (1998).
[86] *Id.* at 409.
[87] *Id.*
[88] *Id.* at 415.
[89] *Id.*
[90] *Id.* at 416.
[91] *Id.*

blood would be considered an investigational use.[92] These concerns led to the contemporary regulatory scheme in which banked cord blood, intended for use by its donor or donor's relatives, is regulated like blood.[93] Similar to blood blanks, cord blood banks must be registered and licensed under the PHSA.[94] However, if cord blood is to be used by a patient who is unrelated to the donor, then it is regulated like a drug and subject to IND regulations.[95]

The paradigm used to regulate cord blood reflects the FDA's point to regulate cord blood based on who the material is for and for what purposes.[96] Likewise, FMT should also be regulated based on its intended use—allowing the FDA to regulate FMT used to treat CDI differently than FMT used to treat other illnesses. There is already strong and convincing evidence that FMT treats CDI effectively and safely[97] and therefore does not require an IND for use in that particular context. On the other hand, FMT used to treat diseases other than CDI for clinical experimentation purposes should be subject to the IND process. For this to happen, the FDA would have to interpret or amend its existing regulations which qualifies fecal materials as a biological product, because the microbes in it can change how the body functions, rather than human tissue.[98]

---

[92] *Id.* at 430.
[93] Rachel E. Sachs and Carolyn A. Edelstein, *Ensuring the safe and effective FDA regulation of fecal microbiota transplantation*, J. LAW BIOSCI. 396 (2015).
[94] *Id.*
[95] *Id.*
[96] *Id.*
[97] Supra [where I talk about the efficacy of FMT in treating CDI]
[98] Bethany Brookshire, *To regulate fecal transplants, FDA has to first answer a serious question: What is poop?*, SCIENCENEWS (May 18, 2018), https://www.sciencenews.org/blog/scicurious/fecal-transplants-regulation.

The FDA's Tissue Reference Group has recommended that fecal material do not meet the definitions of human tissue but did not elaborated on its reasoning.[99] It may be because fecal material is "secreted or extracted human product" which is an explicit regulatory carve-out from under the tissue regulatory scheme.[100] However, the FDA has made an exception to this carve-out in order to categorize semen, a secreted product, as human tissue.[101] Another reason the Tissue Reference Group indicated that FMT is not a human tissue may be because the effectiveness of FMT involves the transplantation of microbial cells or tissue rather than human cells or tissue.[102] However, as long as FMT is sourced from humans, it will contain human cells. Also, this subtle distinction can be overcome by an FDA guidance document clarifying that FMT is an article "containing human cells or tissues."[103]

C. Other Sources and Forms of FMT

A separate recommendation has been proposed for individual FMTs used for the treatment of CDI.[104] Friends or families of patients who donate stool for an individual FMT administered by a doctor should be classified under the "practice of medicine," which the FDA consistently asserts it does not regulate.[105] In this context, doctors would use their expertise and

---

[99] Rachel E. Sachs and Carolyn A. Edelstein, *Ensuring the safe and effective FDA regulation of fecal microbiota transplantation*, J. LAW BIOSCI. 396 (2015).
[100] 21 C.F.R. § 1271.3(d)(3)
[101] *What You Should Know – Reproductive Tissue Donation*, FOOD AND DRUG ADMIN. (Nov. 5, 2010), https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/what-you-should-know-reproductive-tissue-donation.
[102] Rachel E. Sachs and Carolyn A. Edelstein, *Ensuring the safe and effective FDA regulation of fecal microbiota transplantation*, J. LAW BIOSCI. 396 (2015).
[103] Rachel E. Sachs and Carolyn A. Edelstein, *Ensuring the safe and effective FDA regulation of fecal microbiota transplantation*, J. LAW BIOSCI. 396 (2015).
[104]Bethany Brookshire, *To regulate fecal transplants, FDA has to first answer a serious question: What is poop?*, SCIENCENEWS (May 18, 2018), https://www.sciencenews.org/blog/scicurious/fecal-transplants-regulation.
[105] 21 U.S.C. §396

judgment and any treatment that is legally available when treating patients.[106] Proponents of this policy would not require FDA approval or the IND process.[107] This gives the doctor more discretion than the enforcement discretion policy currently adopted by the FDA that allows the doctors to use FMT to treat patients as long as CDI is the illness being treated and the patient has provided informed consent. "Trust [in] the doctor to do what's in the best interest of the patient" underlies the extra leeway granted to doctors under this proposal.[108] Some worry that discretion granted to the doctor may encourage improper FMT use that may result in harm.[109]

Members in the scientific and medical communities indicate that fecal material can be manipulated to varying degrees and therefore should be regulated according to the degree of manipulation.[110] On one end of the spectrum is "fresh stool transferred from the individual donor" which has been manipulated the least; therefore, it mirrors more of a body tissue.[111] On the other extreme are "cultured bacterial cocktail[s] delivered in oral pill form" that has been significantly manipulated.[112] These "modified stool-based products" are derived when the community of microorganisms in the donor stool have been altered and resemble more like a biologic product and thus should be regulated as a drug. [113] This recommendation was designed to promote stool-based products with the goal that companies would be motivated to pursue such

---

[106] Bethany Brookshire, *To regulate fecal transplants, FDA has to first answer a serious question: What is poop?*, SCIENCENEWS (May 18, 2018), https://www.sciencenews.org/blog/scicurious/fecal-transplants-regulation.
[107] *Id.*
[108] *Id.*
[109] *Id.*
[110] *Id.*
[111] *Id.*
[112] *Id.*
[113] Diane Hoffman et al., *Improving regulation of microbiota transplants*, 358(6369) SCIENCE 1390, 1391 (2017).

research and development.[114] However, unless FMTs are rendered ineffective there may not be many incentives for companies to engage in stool-based products because recruitment for the necessary clinical trials might be difficult. After all, "if you have a cheap solution that works and you have a patient with c. diff, that patient will not want to enter a trial with a placebo arm…they want a cure, not a game of roulette."[115]

D. Doctors versus Pharmaceutical Companies

Beyond the medical benefits of FMT material, there is also a tremendous monetary benefit and business interest in fecal material. GlobalData, an analytical firm, reported that the market for drug-based treatments for CDI was worth $360 million in 2016 and is projected to reach $1.7 billion by 2026.[116] The potential for large financial gains has prompted scientists to develop other uses of microbiota with investors pouring in tens of millions of dollars into the research.[117] However, the vast potential the microbiome possesses in treating diseases and its high profitability has contributed to a stand-off between most doctors and pharmaceutical companies.[118]

The disagreement between doctors and pharmaceutical companies primarily split on whether FMT material should be classified as a drug or tissue. Doctors argue that overregulation

---

[114] Bethany Brookshire, *To regulate fecal transplants, FDA has to first answer a serious question: What is poop?*, SCIENCENEWS (May 18, 2018), https://www.sciencenews.org/blog/scicurious/fecal-transplants-regulation.
[115] *Id.*
[116] Andrew Jacobs, *Drug Companies and Doctors Battle over the Future of Fecal Transplants*, THE NY TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html.
[117] Andrew Jacobs, *Drug Companies and Doctors Battle over the Future of Fecal Transplants*, THE NY TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html.
[118] Andrew Jacobs, *Drug Companies and Doctors Battle over the Future of Fecal Transplants*, THE NY TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html.

could "ruin a good thing in health care."[119] If FMT is considered a drug, it will be subjected to the FDA's drug approval process which involves multiple clinical trials and requires a large financial commitment.[120] In return, drug companies are granted the exclusive rights to sell the drug which spends years in clinical trials.[121] Doctors fear that this exclusivity will stifle further FMT innovation and drive up the costs of FMT, making it less accessible to patients.[122] Higher costs have already been reflected in the doubled price of FMT material as a result of the FDA's increased oversight of OpenBiome's production process.[123] These high prices in addition to the fact that most insurances do not cover all costs of investigational treatments, result in high out-of-pocket costs for patients.[124] But, the drug companies currently face a problem: there are not enough patients willing to enroll in clinical trials, which are necessary to get a drug approved by the FDA. If OpenBiome's ability to distribute stool, then patients would be forced to enroll in the drug companies' clinical trials.[125] There's a concern amongst doctors that the FDA will favor the

[119] Andrew Jacobs, *Drug Companies and Doctors Battle over the Future of Fecal Transplants*, THE NY TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html (quoting Dr. Colleen Kelly, a gastroenterologist at Brown University medical school).
[120] *Development & Approval Process*, FOOD AND DRUG ADMIN. (Oct. 28, 2019), https://www.fda.gov/drugs/development-approval-process-drugs; *See also* Drug Approval Process, FOOD AND DRUG ADMIN., https://www.fda.gov/media/82381/download.
[121] Andrew Jacobs, *Drug Companies and Doctors Battle over the Future of Fecal Transplants*, THE NY TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html.
[122] *Id.*
[123] *Id.*
[124] *Frequently Asked Questions*, OPENBIOME, https://www.openbiome.org/patient-faqs.
[125] Andrew Jacobs, *Drug Companies and Doctors Battle over the Future of Fecal Transplants*, THE NY TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html.

"poop drug cartels" or companies that have formed associations and that have raised tens of millions of dollars to advance their interests with the FDA.[126]

Pharmaceutical companies argue that regulating FMT as a drug will "ensure the efficacy and long-term safety of a therapy" that is still "poorly understood."[127] Some doctors agree and note the first principle of medicine is "do no harm," which may result due to the lack of knowledge regarding FMT's adverse effects.[128] The FDA has yet to decide on a regulatory scheme, but the profound prospect of FMT material to doctors and pharmaceutical companies alike call for a new regulatory scheme that is able to accommodate the potential gold mine and ground-breaking nature of FMT material.

IV. Conclusion

Regulating FMT material similar to that of cord blood will allow the FDA to regulate FMT material based on its use. The efficacy of FMT in treating recurrent CDI has been well studied and documented; therefore, it does not require the exhaustive investigative process necessary to approve a new drug. However, the use of FMT for purposes other than CDO would be required to undergo clinical trials. This will allow patients who desperately need treatment access to an effective treatment, while also promoting innovation in other FMT uses. Allowing patient access to FMT procedures will also alleviate the need to resort to "do-it-yourself" FMT.

---

[126] Andrew Jacobs, *Drug Companies and Doctors Battle over the Future of Fecal Transplants*, THE NY TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html (quoting Dr. Alexander Khoruts, a gastroenterologist at the University of Minnesota).

[127] Andrew Jacobs, *Drug Companies and Doctors Battle over the Future of Fecal Transplants*, THE NY TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html.

[128] Andrew Jacobs, *Drug Companies and Doctors Battle over the Future of Fecal Transplants*, THE NY TIMES (Mar. 3, 2019), https://www.nytimes.com/2019/03/03/health/fecal-transplants-fda-microbiome.html (quoting Dr. Sahil Khanna, an associate professor of gastroenterology at the Mayo Clinic).

FDA approval of FMT for purposes of CDI will also encourage insurance companies to cover the procedure; thereby also lowering out-of-pocket costs for patients.

The current enforcement discretion allowing doctors to administer FMT after failed rounds of antibiotics and with the patient's informed consent should be maintained. However, doctors must be required to obtain FMT material from a stool bank—like OpenBiome. These stool banks would be regulated like cord blood banks and must be registered and licensed under the PHSA. The clinical development and biological properties of cord blood highlighted the need to carve-out an exception to the traditional regulatory paradigms—the same is necessary for FMT. To properly develop further uses of FMT while also protecting consumers and overall public health, the FDA must adopt a regulatory scheme that is able to accommodate FMT's current and future therapeutic benefits.