

The Future of Stool Banks: A Premature Death?

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ABSTRACT

This Article examines whether there is a future for stool banks that provide stool for fecal microbiota transplants to treat recurrent *Clostridioides difficile* infection (rCDI), an often-devastating hospital-acquired illness. The authors scrutinize decisions made by FDA regarding the regulation of stool banks and whether alternative regulatory pathways may have been or may be a more promising route for the continued existence of independent, nonprofit stool banks which will likely provide less expensive and, in some cases, more effective therapy than new microbiome-based biologics going through the new drug development pipeline.

I. INTRODUCTION¹

During the past decade, a number of hospital stool banks and a large, nonprofit stool bank were established in response to a need for human stool for the administration of

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¹ This Article is an outgrowth of a series of meetings of a Working Group (WG) that included human microbiome researchers, clinicians, legal academics, food and drug law attorneys, bioethicists, industry representatives, and patient advocates who were brought together to evaluate the regulatory framework for microbiota transplants under an NIH NIAID grant (R21A1119633). While the WG provided insights into the science and regulation of this new area of research and therapeutic product development, neither the WG as a whole nor its individual members approved the content of this Article. The opinions expressed in the manuscript are those of the authors and do not necessarily represent the opinions of the WG. In addition, the Article builds on the groundbreaking article of Rachel Sachs and Carolyn Edelstein, who first wrote about the possible alternative regulatory pathways for FMT and the challenges of the drug/biologics pathway. See Rachel E. Sachs & Carolyn A. Edelstein, *Ensuring the Safe and Effective FDA Regulation of Fecal Microbiota Transplantation*, 2 J.L. & BIOSCIENCES 396 (2015).

fecal microbiota transplants (FMTs).² Such transplants have been offered to patients with recurrent *Clostridioides difficile* infections (rCDI) unresponsive to traditional antibiotic treatment.³ *C. difficile* is a type of bacteria that can cause severe diarrhea and even death.⁴ It is associated with taking antibiotics that disrupt the normal gastrointestinal microbiome.⁵ FMTs are generally performed by a gastroenterologist and call for fresh or frozen “stool product diluted with a liquid, like saline, and then delivered into the intestinal tract of another individual.”⁶ It can be performed via enema, colonoscopy, sigmoidoscopy, or nasogastric tube, and, in some cases, the stool product is encapsulated and taken orally.⁷ In the early days of use of the procedure, stool was often provided by a friend or family member of the patient.⁸ While physicians in most cases prepared the stool for transplant themselves, many preferred not to do so largely due to concerns about their ability to adequately screen donors and resistance to the practice from their hospital leadership.⁹ Some physicians established stool banks at hospitals where they had privileges and relied on laboratory personnel to prepare the stool for transplant, but, over time, most physicians grew to rely on OpenBiome, an independent, nonprofit stool bank (INSB) established in 2012 that provided frozen stool product to physicians all over the country.¹⁰

By 2017, FMTs had become a standard of care in the treatment of rCDI,¹¹ and OpenBiome provided approximately 10,000 units of stool product annually for

² Alexander Khoruts, Diane E. Hoffmann & Francis B. Palumbo, *The Impact of Regulatory Policies on the Future of Fecal Microbiota Transplantation*, 47 J.L., MED. & ETHICS 482, 482 (2019).

³ While there is hope that FMT may be able to treat other ailments from Crohn’s disease to diabetes, evidence of its efficacy as a treatment for other conditions is limited. *Id.* at 483. *See, e.g.*, Simon Mark Dahl Jørgensen, Christian Lodberg Hvas, Jens Frederik Dahlerup, Susan Mikkelsen, Lars Ehlers, Lianna Hede Hammeken, Tine Rask Licht, Martin Iain Bahl & Christian Erikstrup, *Banking Feces: A New Frontier for Public Blood Banks?*, 59 TRANSFUSION 2776, 2777 (2019). “Numerous clinical trials are currently investigating FMT for other indications such as inflammatory bowel diseases, irritable bowel syndrome, hepatic encephalopathy, metabolic syndrome, graft-versus-host disease, and multidrug resistant infections.” *Id.* at 2777.

⁴ *Nearly Half a Million Americans Suffer from C. Difficile Infections in Single Year*, CTRS. FOR DISEASE CONTROL & PREVENTION (Aug. 9, 2018), <https://www.cdc.gov/hai/dpks/deadly-diarrhea/dpk-deadly-diarrhea.html> [<https://perma.cc/HF4F-B2R5>].

⁵ *See infra* note 28 and accompanying text.

⁶ Diane E. Hoffmann, Francis B. Palumbo, Jacques Ravel, Virginia Rowthorn & Erik von Rosenvinge, *A Proposed Definition of Microbiota Transplantation for Regulatory Purposes*, 8 GUT MICROBES 208, 208 (2017).

⁷ *Id.* at 208–09.

⁸ Daryl Ramai, Karl Zakhia, Andrew Ofofu, Emmanuel Ofori & Madhavi Reddy, *Fecal Microbiota Transplantation: Donor Relation, Fresh or Frozen, Delivery Methods, Cost-Effectiveness*, 32 ANNALS GASTROENTEROL. 30, 31 (2019).

⁹ *See infra* notes 101–02 and accompanying text.

¹⁰ *See infra* notes 58–60 and accompanying text.

¹¹ Clifford McDonald, Dale N. Gerding, Stuart Johnson, Johan S. Bakken, Karen C. Carroll, Susan E. Coffin, Erik R. Dubberke, Kevin W. Garey, Carolyn V. Gould, Claran Kelly, Vivian Loo, Julia S. Sammons, Thomas J. Sandora & Mark H. Wilcox, *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 DISEASE 987 (2018).

treatment purposes.¹² Despite its acceptance by the medical profession and evidence of its efficacy and safety, there is great uncertainty about the future of FMT and, more specifically, of INSBs. This comes as OpenBiome announced its inability to continue providing its stool preparation once a new stool-based drug/biologic is approved by FDA.¹³

In this Article, we look at the history of FMT and stool banks, as well as the regulatory decisions made by FDA that both allowed for the operation of stool banks and contributed to their pending obsolescence, including 1) rejecting the proposal that stool and its component gut microbiota be regulated as a tissue; 2) deciding that stool be regulated as a drug/biologic; and 3) exercising enforcement discretion subjecting stool banks to virtually no oversight. We examine alternative regulatory pathways including those for blood, tissues/cells, and cord blood, and argue that these alternative regulatory frameworks may have allowed for the continued operation of an INSB. For each pathway, we speculate about how it would affect patient access to FMT for treatment of rCDI as well as how it would affect product safety and innovation. We conclude that there is likely benefit in permitting INSBs to operate but that they would unlikely be able to survive under FDA's 2016 Draft Industry Guidance,¹⁴ which would require them to go through the investigational new drug (IND) application process and obtain a biologics license. Further, reliance on a system of regional and smaller hospital-based stool banks, which the Guidance contemplates, may not be as safe as having one or two larger INSBs regulated like blood or tissue banks. Finally, we recommend that policy makers consider new rules that would make it possible for INSBs to continue to operate. This, we contend, would either require an alternative regulatory pathway or modifications to the typical IND requirements and subsidies to INSBs, like those recommended for other nonprofit pharmaceutical companies, to allow them to operate in a safe and continuous manner.

II. THE EVOLUTION OF FECAL MICROBIOTA TRANSPLANTS AND STOOL BANKS

A. Early and Recent History of FMT as a Treatment for CDI

Use of stool to treat gut ailments was first described over 1,700 years ago.¹⁵ Called “yellow soup” in the Fourth Century by Chinese researcher Ge Hong, it was used to

¹² OPENBIOME, *Annual Report 2018*, <https://static1.squarespace.com/static/50e0c29ae4b0a05702af7e6a/t/5ea039c598b6d25d07138f20/1587558865331/2018+OpenBiome+Annual+Report.pdf> [<https://perma.cc/73TM-KJZB>].

¹³ See Press Release, OpenBiome, OpenBiome Announces New Direct Testing for SARS-CoV-2 in Fecal Microbiota Transplantation (FMT) Preparations and Release of New Inventory (Feb. 23, 2021), <https://www.openbiome.org/press-releases/2021/2/22/openbiome-announces-new-direct-testing-for-sars-cov-2-in-fecal-microbiota-transplantation-fmt-preparations-and-release-of-new-inventory> [<https://perma.cc/9R4K-9CG3>] [hereinafter OpenBiome Press Release].

¹⁴ U.S. FOOD & DRUG ADMIN., 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 (Mar. 2016), <https://www.fda.gov/media/96562/download> [<https://perma.cc/TD8J-VWS9>] [hereinafter FDA, ENFORCEMENT POLICY (Mar. 2016)].

¹⁵ Hyun Ho Choi & Young-Seok Cho, *Fecal Microbiota Transplantation: Current Applications, Effectiveness, and Future Perspectives*, 49 CLINICAL ENDOSCOPY 257, 257 (2016). See also Blair Merrick,

treat severe diarrhea and was taken orally.¹⁶ Its use was mentioned only sporadically in the literature over the next several centuries. In Western medicine, the first published report of a fecal enema was in 1958¹⁷ for the treatment of “pseudomembranous enterocolitis,” a condition caused by CDI.¹⁸ While hospitals used the therapy in surgical wards for a short period after that, the introduction of the antibiotic, vancomycin, largely replaced the need for the procedure.¹⁹ It was only in cases in which the antibiotic was not effective that the procedure was tried.²⁰ In the last two decades, such cases have significantly increased as more cases of drug-resistant CDI have emerged.²¹ This increase in the overall CDI rate has led to a corresponding increase in cases of rCDI.²² After an initial episode of CDI, 10–30% of patients will experience at least one recurrence, and the risk of additional recurrences increases with each subsequent episode.²³ CDI is one of the most common health care-associated infections in the United States.²⁴ The condition was listed as an Urgent Threat Level Pathogen in the 2014 National Strategy for Combating Antibiotic-Resistant Bacteria.²⁵ The Centers for Disease Control and Prevention (CDC) Emerging Infection Program (EIP) has monitored CDI rates since 2011.²⁶ In 2015, it reported that CDI caused about half a million infections and was associated with approximately

Liz Allen, Nur Masirah M. Zain, Ben Forbes, Debbie L. Shawcross & Simon D. Goldenberg, *Regulation, Risk and Safety of Faecal Microbiota Transplant*, 2 INFECTION PREVENTION IN PRACTICE 100069 (2020).

¹⁶ *From Fourth-Century Soup to 21st-Century Procedure, Fecal Transplantation Proves its Worth Against Stubborn Bacteria*, VA RES. CURRENTS (Jan. 28, 2015), <https://www.research.va.gov/currents/winter2015/winter2015-11.cfm> [<https://perma.cc/AY7Z-PJCV>].

¹⁷ B. Eiseman, W. Silen, G.S. Bascom & A.J. Kauvar, *Fecal Enema as an Adjunct in the Treatment of Pseudomembranous Enterocolitis*, 44 SURGERY 854 (1958).

¹⁸ Khoruts, Hoffmann & Palumbo, *supra* note 2, at 483.

¹⁹ *Id.*

²⁰ *Id.*

²¹ Patrizia Spigaglia, *Recent Advances in the Understanding of Antibiotic Resistance in Clostridium Difficile Infection*, 3 THERAPEUTIC ADVANCES INFECTIOUS DISEASE 23 (2016). Metronidazole is currently the first-line antibiotic treatment for mild CDI owing to its relatively high efficacy, low cost, and concerns about hastening *C. diff.* vancomycin resistance. Ciarán P. Kelly & J. Thomas LaMont, *Clostridium Difficile—More Difficult than Ever*, 352 NEW ENG. J. MED. 1932, 1935 (2008). However, since 2000, metronidazole treatment failure rates have risen from 2.5% to more than 18%. Zain Kassam, Christine H. Lee, Yuhong Yuan & Richard H. Hunt, *Fecal Microbiota Transplantation for Clostridium Difficile Infection: Systematic Review and Meta-Analysis*, 108 AM. J. GASTROENTEROL. 500, 501 (2013). Even with appropriate antibiotic intervention, CDI recurrence occurs with similar rates for metronidazole and vancomycin (20.2% versus 18.4%). Kelly & LaMont, *supra* note 21, at 1936.

²² Jung Hoon Song & You Sun Kim, *Recurrent Clostridium Difficile Infection: Risk Factors, Treatment, and Prevention*, 13 GUT & LIVER 16, 16 (2019).

²³ McDonald et al., *supra* note 11.

²⁴ Becky A. Miller, Luke F. Chen, Daniel J. Sexton & Deverick J. Anderson, *Comparison of the Burdens of Hospital-Onset, Healthcare Facility-Associated Clostridium Difficile Infection and of Healthcare-Associated Infection Due to Methicillin-Resistant Staphylococcus Aureus in Community Hospitals*, 32 INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY 387 (2011).

²⁵ THE WHITE HOUSE, NATIONAL STRATEGY FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA 25 (Sept. 2014), https://www.cdc.gov/drugresistance/pdf/carb_national_strategy.pdf [<https://perma.cc/ EFF3-LU4V>].

²⁶ *Clostridioides Difficile Infection (CDI) Tracking*, CTRS. FOR DISEASE CONTROL & PREVENTION (Mar. 15, 2021), <https://www.cdc.gov/hai/eip/cdiff-tracking.html> [<https://perma.cc/G9YL-KA25>].

29,000 deaths in the United States in 2011.²⁷ This staggering burden of disease prompted increased efforts to prevent CDI, such as hospital antibiotic stewardship programs. A 2020 report of CDC EIP data showed that these efforts have had some apparent success as the national number of CDI cases was estimated to have decreased by 24% between 2011 and 2017.²⁸

CDI recurrence is theorized to result from antibiotic treatment that disrupts the normal diversity of the gut microbiota but mostly spares *C. difficile* spores.²⁹ Once antibiotic treatment is discontinued, the surviving spores germinate, and newly vegetative *C. difficile* proliferate in the absence of selective pressure from a diverse microbiota.³⁰ CDI-produced toxins damage the intestinal lining and make the gut susceptible to further recurrence or re-infection with other CDI strains.³¹ FMT aims to restore normal diversity to the gut microbiota of rCDI patients.³² The rationale behind FMT is that normal gut function can be restored by the reintroduction of a normal microbiota from donor feces infused directly into the patient's gut.³³ The diversity of microorganisms from the donor corrects the microbiota dysbiosis in the patient and puts selective pressure on *C. difficile* proliferation, thus interrupting the disease cycle and preventing CDI recurrence.³⁴

B. Evidence of Effectiveness and Safety

The evidence that rCDI treatment with FMT is safe and effective comes from numerous case series, open-label clinical trials, and, more recently, randomized controlled double-blind clinical trials.³⁵ Multiple systematic reviews of the scientific

²⁷ Fernanda C. Lessa, Yi Mu, Wendy M. Bamberg, Zintars G. Beldavs, Ghinwa K. Dumyati, John R. Dunn, Monica M. Farley, Stacy M. Holzbauer, James I. Meek, Erin C. Phipps, Lucy E. Wilson, Lisa G. Winston, Jessica A. Cohen, Brandi M. Limbago, Scott K. Fridkin, Dale N. Gerding & L. Clifford McDonald, *Burden of Clostridium Difficile Infection in the United States*, 372 NEW ENG. J. MED. 825, 829 (2015).

²⁸ Alice Y. Guh, Y. Mu, L.G. Winston, H. Johnston, D. Olson, M.M. Farley, L.E. Wilson, S.M. Holzbauer, E.C. Phipps, G.K. Dumyati, Z.G. Beldavs, M.A. Kainer, M. Karlsson, D.N. Gerding & L.C. McDonald, *Trends in U.S. Burden of Clostridium Difficile Infection and Outcomes*, 382 NEW ENG. J. MED. 1320 (2020).

²⁹ Yajarayma Tang-Feldman, Susan Mayo, Joseph Silva, Jr. & Stuart H. Cohen, *Molecular Analysis of Clostridium Difficile Strains Isolated from 18 Cases of Recurrent Clostridium Difficile-Associated Diarrhea*, 41 J. CLINICAL MICROBIOLOGY 3413, 3413 (2003).

³⁰ *Id.*

³¹ Johan S. Bakken, Thomas Borody, Lawrence J. Brandt, Joel V. Brill, Daniel C. Demarco, Marc A. Franzos, Colleen Kelly, Alexander Khoruts, Thomas Louie, Lawrence P. Martinelli, Thomas A. Moore, George Russell & Christina Surawicz, *Treating Clostridium Difficile Infection with Fecal Microbiota Transplantation*, 9 CLINICAL GASTROENTEROLOGY & HEPATOLOGY 1044, 1044–45 (2011).

³² Sachs & Edelstein, *supra* note 1, at 399.

³³ *Id.* at 399–400.

³⁴ Bakken et al., *supra* note 31, at 1045.

³⁵ Colleen R. Kelly, Alexander Khoruts, Christopher Staley, Michael J. Sadowsky, Mortadha Abd, Mustafa Alani, Brianna Bakow, P. Curran, Joyce McKenney, Allison Tisch, Steven E. Reinert, Jason T. Machan & Lawrence J. Brandt, *Effect of Fecal Microbiota Transplantation on Recurrence in Multiple Recurrent Clostridium Difficile Infection—A Randomized Trial*, 165 ANNALS INTERNAL MED. 609 (2016) [hereinafter Kelly et al., *Effect of FMT on Recurrence*]. See also Els van Nood, Anne Vrieze, Max Nieuwdorp, Susana Fuentes, Erwin G. Zoetendal, Willem M. de Vos, Caroline E. Visser, Ed J. Kuijper, Joep F.W.M. Bartelsman, Jan G.P. Tijssen, Peter Speelman, Marcel G.W. Dijkgraaf & Josbert J. Keller, *Duodenal Infusion of Donor Feces for Recurrent Clostridium Difficile*, 368 NEW ENG. J. MED. 407 (2013); G. Cammarota, L. Masucci, G. Ianiro, S. Bibbò, G. Dinoi, G. Costamagna, M. Sanguinetti & A. Gasbarrini, *Randomised Clinical Trial: Faecal Microbiota Transplantation by Colonoscopy vs. Vancomycin for the*

literature have examined this data to refine conclusions about FMT safety and efficacy.³⁶ A 2016 literature review by Kassam et al.³⁷ rigorously limited inclusion to peer-reviewed studies that had ten or more patients, laboratory confirmation of CDI pre-treatment, and clinical resolution of diarrhea post-treatment. Eleven studies met these criteria, and the authors concluded that 1) 89.1% of patients achieved clinical resolution with one treatment; 2) there were no adverse events from rectal administration of FMT; and 3) lower gastrointestinal feces delivery was slightly more effective than upper gastrointestinal delivery.³⁸

The first randomized controlled trial of FMT compared to vancomycin treatment was published in 2013 by van Nood et al.³⁹ This landmark trial recruited forty-three patients into one treatment group (i.e., FMT by nasoduodenal tube) and two control groups (i.e., vancomycin alone and vancomycin with bowel lavage).⁴⁰ The study population consisted of patients with rCDI that was unresponsive to metronidazole or vancomycin treatment.⁴¹ Patients in the FMT group achieved 81% cure after the first infusion and, with additional infusions, the cure rate reached 94%.⁴² Cure rates for the two control groups were 31% (vancomycin alone) and 23% (vancomycin with bowel lavage).⁴³ Only minor adverse events were noted in the FMT group.⁴⁴

In 2016, researchers published results of the first randomized controlled double-blind clinical trial comparing FMT with donor stool to FMT using the patient's own stool as a control.⁴⁵ The study by Kelly et al. included forty-six patients who had three or more recurrences of CDI, of which twenty-two were randomized to FMT with donor stool.⁴⁶ Patients in the donor FMT group achieved 91% clinical cure compared to 63% clinical cure in the autologous FMT group.⁴⁷ Minor adverse events did not differ significantly between groups.⁴⁸

As most FMTs have been performed outside of research studies, some have questioned the safety of FMT, especially long-term safety with real-world application.

Treatment of Recurrent Clostridium Difficile Infection, 41 ALIMENTARY PHARMACOLOGY & THERAPEUTICS 835 (2015).

³⁶ A search for "FMT for *Clostridioides difficile*" in PubMed yielded eleven systemic reviews.

³⁷ Kassam et al., *supra* note 21.

³⁸ *Id.* at 500.

³⁹ van Nood et al., *supra* note 35.

⁴⁰ *Id.* at 409.

⁴¹ FMT patients were treated with vancomycin for four to five days before receiving FMT; the two control groups received a standard two-week vancomycin treatment. Fresh fecal preparations from healthy volunteer donors were used for the FMTs. Patients were considered cured if they exhibited no clinical symptoms of CDI within ten weeks following treatment. *Id.* at 408–09.

⁴² *Id.* at 411.

⁴³ *Id.*

⁴⁴ These adverse events included diarrhea, bloating, and abdominal cramping. *Id.* at 412.

⁴⁵ Kelly et al., *supra* note 35.

⁴⁶ All patients were treated with vancomycin two to three days before receiving FMT, and they were permitted to select their donor or receive FMT from a healthy volunteer donor. FMT was performed by colonoscopy and consisted of fresh fecal preparations. *Id.* at 610–11.

⁴⁷ *Id.* at 612.

⁴⁸ Patients were considered cured if they exhibited no clinical symptoms of CDI eight weeks following FMT. *Id.* at 611.

To address the need for additional information on safety, the American Gastroenterology Association Institute, in partnership with other professional organizations, developed the FMT National Registry.⁴⁹ Initial results from the Registry were published in early 2021 and included data on the first 259 participants enrolled since 2017.⁵⁰ Two hundred twenty-two of the patients had completed follow-up at one month and 123 patients at six months.⁵¹ The one month CDI cure rate was 90% and, of those with initial cure followed to six months, only 4% had CDI recurrence.⁵² Severe symptoms reported within one month included diarrhea and abdominal pain, each occurring in 2% of patients, and 1% had hospitalization possibly related to FMT.⁵³ At six months, 1% of patients had a new diagnosis of irritable bowel syndrome and 1% of patients had a new diagnosis of inflammatory bowel disease.⁵⁴ The investigators concluded that the findings “demonstrated high effectiveness of FMT for CDI with a good safety profile.”⁵⁵ The FMT National Registry continues to add participants and plans to follow these patients for up to ten years to assess long-term outcomes and safety.⁵⁶

C. Clinical Application of FMT and Establishment of Stool Banks

The first documented case of rCDI treatment with FMT was in 1983.⁵⁷ It was not until the last decade, however, that FMT came into mainstream medical use for rCDI. The first physicians performing FMT in patients had to both screen the donor and prepare the stool for administration themselves—a time-consuming and not particularly pleasant process, although not difficult in terms of equipment or know-how.⁵⁸ Then, in 2012, an MIT PhD candidate and three colleagues opened a nonprofit stool bank called OpenBiome outside of Boston, MA.⁵⁹ The collaborators founded the

⁴⁹ Colleen R. Kelly, Alison M. Kim, Loren Laine & Gary D. Wu, *The AGA's Fecal Microbiota Transplantation National Registry: An Important Step Toward Understanding Risks and Benefits of Microbiota Therapeutics*, 152 GASTROENTEROLOGY 681, 681 (2017) [hereinafter Kelly et al., *The AGA's FMT National Registry*].

⁵⁰ Colleen R. Kelly, Eugene F. Yen, Ari M. Grinspan, Stacy A. Kahn, Ashish Ateja, James D. Lewis, Thomas A. More, David T. Rubin, Alison M. Kim, Sonya Serra, Yanina Nersesova, Lydia Fredell, Dea Hunsicker, Daniel McDonald, Rob Knight, Jessica R. Allegretti, Joel Pekow, Imad Absah, Ronald Hsu, Jennifer Vincent, Sahil Khanna, Lyn Tangen, Carl V. Crawford, Mark C. Mattar, Lea A. Chen, Monika Fischer, Razvan I. Arsenescu, Paul Feuerstadt, Jonathan Goldstein, David Kerman, Adam C. Ehrlich, Gary D. Wu, & Loren Laine, *Fecal Microbiota Transplantation is Highly Effective in Real-World Practice: Initial Results From the FMT National Registry*, 160 GASTROENTEROLOGY 183 (2021).

⁵¹ *Id.* at 183.

⁵² *Id.*

⁵³ *Id.*

⁵⁴ *Id.*

⁵⁵ *Id.*

⁵⁶ *Id.* at 190.

⁵⁷ Anna Schwan, *Relapsing Clostridium Difficile Enterocolitis Cured by Rectal Infusion of Homologous Faeces*, 2 LANCET 845 (1983).

⁵⁸ Thomas J. Borody & Alexander Khoruts, *Fecal Microbiota Transplantation and Emerging Applications*, 9 NATURE REVIEWS GASTROENTEROLOGY & HEPATOLOGY 88 (2012).

⁵⁹ David Glenn, *Student-Led Project Banks on Promise of Fecal Transplants*, CHRON. HIGHER EDUC. (Feb 3, 2014), <http://chronicle.com/article/Student-Led-Project-Banks-on/144353/> [https://perma.cc/AGE7-NYZ4].

company after “watching [someone close to them] suffer through 18 months of *C. difficile* and 7 rounds of vancomycin before finally receiving a successful, life-changing FMT.”⁶⁰ Their mission was to provide safe, effective, and affordable stool to clinicians and their patients dealing with rCDI and potentially other conditions.⁶¹

OpenBiome was the first INSB in the country. The stool was obtained from healthy donors who were often students at Tufts University,⁶² close to where OpenBiome’s facility was located. Each donor had to complete a 200-question health history with a physician, disclose recent antibiotic use, and answer personal travel history questions.⁶³ If the potential donor passed this initial screening, a sample of their stool was reviewed by a lab for any infectious agents and for the health of the stool bacteria.⁶⁴ The donor’s blood was also tested for standard blood-borne diseases as well as hepatitis A, B, and C, syphilis, and HIV/AIDS.⁶⁵ Each donor received \$40 per sample.⁶⁶

While OpenBiome provided the large majority of stool for FMTs performed in the U.S., some physicians relied on stool from hospital stool banks.⁶⁷ Many FMTs were/are also performed by individuals themselves at home (referred to as “Do it yourself” or DIY FMTs) without the benefit of screening and administration by a health care professional.⁶⁸ The FMT Foundation estimates that approximately 10,000 DIY FMTs per year were performed during OpenBiome’s early years of operation.⁶⁹ Numerous websites provide information about how to do the procedure with minimal equipment or resources.⁷⁰ In addition to the perceived safety and effectiveness of the procedure, individuals may resort to the DIY option because of being unable to find a physician who will do the procedure, the ease of obtaining stool from a friend or relative, the cost of going to a physician or medical center, and the lack of insurance coverage for the treatment. As another alternative, some patients have resorted to

⁶⁰ OPENBIOME, <https://www.openbiome.org/> [<https://perma.cc/258U-FPQP>].

⁶¹ *Id.*

⁶² Rachel Feltman, *You Can Earn \$13,000 a Year Selling Your Poop*, WASH. POST (Jan. 29, 2015), https://www.washingtonpost.com/news/science/wp/2015/01/29/you-can-earn-13000-a-year-selling-your-poop/?utm_term=.5453feec701f [<https://perma.cc/939Z-9UHP>].

⁶³ *Quality and Safety*, OPENBIOME, <https://www.openbiome.org/safety> [<https://perma.cc/3CEZ-UWP8>].

⁶⁴ *Id.*

⁶⁵ *Id.*

⁶⁶ *Donate Your Stool, Earn Money, Save Lives*, OPENBIOME, <https://www.openbiome.org/stool-donation> [<https://perma.cc/HKN4-6EXE>] [hereinafter OPENBIOME, *Donate Your Stool*].

⁶⁷ Khoruts, Hoffmann & Palumbo, *supra* note 3, at 485.

⁶⁸ Brenda Goodman, *The Rise of the Do-It-Yourself Fecal Transplant*, WEBMD (Dec. 9, 2015), <https://www.webmd.com/digestive-disorders/news/20151209/diy-fecal-transplant#1> [<https://perma.cc/DN88-M9JU>].

⁶⁹ *Id.*

⁷⁰ As of May 2015, one such DIY website was accessed over 45,000 times. See Colleen R. Kelly, Stacy Kahn, Purna Kashyap, Loren Laine, David Rubin, Ashish Atreja, Thomas Moore & Gary Wu, *Update on FMT 2015: Indications, Methodologies, Mechanisms and Outlook*, 149 GASTROENTEROLOGY 223, 230 (2015) (citing Michael Hurst, *DIY Fecal Transplants to Cure Yourself of Ulcerative Colitis*, YOUTUBE (June 4, 2013), <https://www.youtube.com/watch?v=WEMnRC22oOs%29>).

“medical tourism” and traveled to other countries for the procedure, but usually do this for indications other than rCDI⁷¹ for which FMT cannot be done in the U.S.

While FMT has reportedly been highly safe and successful in the treatment of rCDI, systematic monitoring and data collection of adverse events has only just begun with the implementation of the FMT National Registry.⁷² Further, in 2019 and 2020, there were eight serious adverse events associated with two institutions performing FMT that were reported to FDA.⁷³

A hospital participating in FMT clinical trials screened donor stool for *C. difficile* toxin and other enteric pathogens but did not screen for extended-spectrum beta-lactamase (ESBL)-producing bacteria (e.g., certain types of *E. coli*)⁷⁴ because it was not the hospital’s protocol at the time.⁷⁵ In 2019, after the hospital administered several rounds of FMT, two patients⁷⁶ became septic with ESBL-producing *E. coli* and one later died.⁷⁷ The hospital reported the adverse events to FDA, and the agency issued a safety alert on June 13, 2019 mandating that donor stool be screened for ESBL-producing organisms in FMT clinical trials and when FMT is used for clinical purposes.⁷⁸

In early 2020, six patients receiving FMT from two different OpenBiome donors developed infections caused by enteropathogenic *E. coli* (EPEC) and Shiga toxin-producing *E. coli* (STEC).⁷⁹ The six patients were being treated with FMT for rCDI and each experienced *E. coli* infection-related symptoms.⁸⁰ Two of the patients had unspecified chronic medical conditions and later died.⁸¹ FDA issued a safety alert on

⁷¹ Kenneth A. Young, *Of Poops and Parasites*, 69 FOOD & DRUG L.J. 555, 557 (2014).

⁷² Kelly et al., *The AGA’s FMT National Registry*, *supra* note 49.

⁷³ See *infra* notes 74–83 and accompanying text.

⁷⁴ Zachariah DeFilipp, Patricia P. Bloom, Mariam Torres Soto, Michael K. Mansour, Mohamad R.A. Sater, Miriam H. Huntley, Sarah Turbett, Raymond T. Chung, Yi-Ben Chen & Elizabeth L. Hohmann, *Drug-Resistant E. Coli Bacteremia Transmitted by Fecal Microbiota Transplant*, 381 NEW ENG. J. MED. 2043, 2044 (2019).

⁷⁵ ESBL-producing organisms are dangerous because they produce enzymes that make antibiotics ineffective. FDA and the researcher had agreed to add ESBL-producing *E. coli* to her screening program, but FDA did not require her to test samples retrospectively, and this material was thus missed. *Id.* at 2047.

⁷⁶ The patients included a sixty-nine-year-old man with liver cirrhosis treated with FMT for refractory hepatic encephalopathy and a seventy-three-year-old man with myelodysplastic syndrome treated with FMT preemptively before and after hematopoietic-cell transplantation. *Id.* at 2044.

⁷⁷ *Id.* at 2046.

⁷⁸ *Information Pertaining to Additional Safety Protections Regarding Use of Fecal Microbiota for Transplantation—Screening and Testing of Stool Donors for Multi-Drug Resistant Organisms*, U.S. FOOD & DRUG ADMIN. (June 18, 2019), <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation> [<https://perma.cc/G43S-MV29>].

⁷⁹ *Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms*, U.S. FOOD & DRUG ADMIN. (Mar. 12, 2020), <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse-events-likely> [<https://perma.cc/TU4T-FJH7>] [hereinafter FDA, *Safety Alert Regarding Use of FMT*].

⁸⁰ *Id.*

⁸¹ *Id.* Tests ultimately showed that one patient who died had been treated with FMT that did not contain STEC and the other patient “died due to cardiorenal failure unrelated to FMT.” Caroline Zellmer, Mohamad R. A. Sater, Miriam H. Huntley, Majdi Osman, Scott W. Olesen & Bharat Ramakrishna, *Shiga*

March 12, 2020⁸² and agency guidance on April 6 requiring prospective and retrospective EPEC and STEC screening of FMT donor stool.⁸³

D. History of Regulation of FMT and Stool Banks

While a few physicians were performing FMTs before 2010, the legal status of the procedure was not clear at that time. A few physicians had made inquiries to FDA as early as 2010 as to whether they needed an IND for research on FMT or to treat patients with rCDI or other serious gastrointestinal conditions.⁸⁴ FDA responded to those inquiries, requiring an IND, but made no public announcement of how it intended to regulate the procedure.⁸⁵

In 2011, Rebiotix, a company that planned to market a stool-based product (specifically, a cryopreserved, filtered microbiota derived from the stool of screened donors and administered through an “off the shelf enema delivery system”) was formed.⁸⁶ In 2012, Rebiotix representatives met with FDA staff to determine whether it would need to go through the “IND process” in order to market its product.⁸⁷ The company also requested that the Tissue Reference Group (TRG) within FDA make a determination as to whether stool could be regulated under the framework for human cells, tissues, and cellular and tissue-based products (HCT/Ps).⁸⁸ In response, the TRG stated that “[m]icrobiota isolated from fecal matter of a donor is not an HCT/P, as defined under 21 CFR 1271.3(d).”⁸⁹ Although the TRG did not provide the rationale

Toxin-Producing Escherichia Coli Transmission Via Fecal Microbiota Transplant, 72 CLINICAL INFECTIOUS DISEASES e876, e879 (2021).

⁸² FDA, *Safety Alert Regarding Use of FMT*, *supra* note 79.

⁸³ *Information Pertaining to Additional Safety Protections Regarding Use of Fecal Microbiota for Transplantation—Testing of Stool Donors for Enteropathogenic Escherichia Coli and Shigatoxin-Producing Escherichia Coli*, U.S. FOOD & DRUG ADMIN. (Apr. 6, 2020), <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation-0> [<https://perma.cc/HC4K-UBDQ>].

⁸⁴ Email correspondence from Alexander Khoruts to Diane Hoffmann (Aug. 11, 2021).

⁸⁵ *Id.*

⁸⁶ *About Rebiotix: Harnessing the Power of the Human Microbiome*, REBIOTIX, <https://www.rebiotix.com/about-rebiotix/> (last visited Oct. 22, 2021) [<https://perma.cc/9LFQ-JV7T>]; see also Lee Jones, *Harnessing the Gut Microbiome: Separating the Hype from the Evidence*, REBIOTIX (Sept. 2015), https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKewjt-PGxnr3vAhXCUjUKHWx-A9QQFjAAegQIAhAD&url=https%3A%2F%2Fwww.rebiotix.com%2Fwp-content%2Fuploads%2FRebiotix-presentation-targeting-the-microbiome.pptx&usq=AOvVaw06XYi9Xn3-EC_JvzMkK0Pq [<https://perma.cc/W52H-RWWD>].

⁸⁷ See *About Rebiotix*, *supra* note 86; see also PART 15 HEARING, *infra* note 121, at 33–34 (statement of Lee Jones, CEO of Rebiotix).

⁸⁸ The Tissue Reference Group includes representatives from FDA’s Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH), and “provides product sponsors with an informal process through which they may obtain an Agency recommendation regarding the application of the criteria in 21 C.F.R. 1271.10(a) to their HCT/Ps for a given indication.” U.S. FOOD & DRUG ADMIN., REGULATORY CONSIDERATIONS FOR HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS—MINIMAL MANIPULATION AND HOMOLOGOUS USE: GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 24 (July 2020), <https://www.fda.gov/media/109176/download> [<https://perma.cc/VF8Y-HR6Y>] [hereinafter FDA, REGULATORY CONSIDERATIONS FOR HCT/PS].

⁸⁹ *Vaccines, Blood & Biologics: Tissue Reference Group*, U.S. FOOD & DRUG ADMIN., <https://web.archive.org/web/20131022042824/https://www.fda.gov/BiologicsBloodVaccines/Tissue/TissueProducts/RegulationofTissues/ucm152857.htm> (last updated July 29, 2013) [<https://perma.cc/2HQP-HB3L>]. The provision defines “[h]uman cells, tissues, or cellular or tissue-based products” as:

for its decision in any public document, it may have determined that such microbiota was not human but rather was composed of independent microorganisms.⁹⁰ In addition, stool would likely meet the definition of “[s]ecreted or extracted human products,” which are exempted from the HCT/P category.⁹¹ Shortly thereafter, FDA told the company that its product would require an IND and must go through the necessary clinical trials for new drug/biologic approval.⁹²

Between 2010 and 2013, more physicians began performing FMTs for treatment of rCDI in patients who were not responding to traditional antibiotic therapy, likely believing it was the practice of medicine. Then, in May 2013 at a public workshop, FDA announced that it was classifying fecal matter as both an investigational new drug and a biologic, and that only physicians currently in possession of an approved IND application would be permitted to continue performing fecal transplants.⁹³

Classification of FMT as a drug/biologic resulted in fewer than twenty physicians in the U.S. being able to perform fecal transplants.⁹⁴ In response, there was a “groundswell of opposition from physicians and patients,”⁹⁵ and, just two months later in July 2013, FDA modified its position and announced that, although it was still classifying stool as a drug and a biologic, it would exercise its enforcement discretion and not enforce the IND requirement for physicians who were performing FMT on patients with rCDI. An IND would be required for any other indication.⁹⁶ The willingness of the agency to suspend the IND requirement was conditional on the treating physician obtaining informed consent from the patient.⁹⁷ At the time, FDA also stated that it intended to exercise its discretion on an interim basis while it further considered the matter.⁹⁸ It was this decision that paved the way for more widespread use of FMT by physicians for the treatment of rCDI.

Less than a year later, in March 2014, FDA published *Draft* Guidance that would add another qualification to the use of FMT for rCDI, i.e., that the FMT product must

articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. . . . The following articles are not considered HCT/Ps: (1) Vascularized human organs for transplantation; (2) Whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter, respectively; [and] (3) Secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P

²¹ C.F.R. § 1271.3(d) (2020).

⁹⁰ Sachs & Edelstein, *supra* note 1, at 411.

⁹¹ 21 C.F.R. § 1271.3(d)(3).

⁹² See PART 15 HEARING, *infra* note 121.

⁹³ ENFORCEMENT POLICY REGARDING INVESTIGATIONAL NEW DRUG REQUIREMENTS FOR USE OF FECAL MICROBIOTA FOR TRANSPLANTATION TO TREAT CLOSTRIDIUM DIFFICILE INFECTION NOT RESPONSIVE TO STANDARD THERAPIES: GUIDANCE FOR INDUSTRY, U.S. FOOD & DRUG ADMIN. 1–2 (July 2013), <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatory/Information/Guidances/Vaccines/UCM361393.pdf> [<https://perma.cc/QL35-UY9P>] [hereinafter FDA, ENFORCEMENT POLICY (July 2013)].

⁹⁴ *What is FMT?*, FECAL TRANSPLANT FOUND., <https://thefecaltransplantfoundation.org/what-is-fecal-transplant/> (last visited Oct. 25, 2021) [<https://perma.cc/S8U4-63BB>].

⁹⁵ *Id.*

⁹⁶ See FDA, ENFORCEMENT POLICY (July 2013), *supra* note 93, at 2.

⁹⁷ *Id.*

⁹⁸ *Id.*

be “obtained from a donor known to either the patient or to the licensed health care provider treating the patient” and that the stool donor and stool must be qualified by screening and testing.⁹⁹ Although the 2014 guidance did not mention stool banks, it would have effectively foreclosed their use. Until the guidance became final, FDA indicated that it would continue to exercise its enforcement discretion and allow physicians to obtain stool from stool banks without an IND.¹⁰⁰

FDA received many public comments on this Draft Guidance in favor of allowing patients access to FMT to treat rCDI, including access to FMT product from stool banks.¹⁰¹ The provision that the donor be known to the patient, or the treating licensed health care provider, was roundly criticized by patients as well as physicians performing the procedure.¹⁰² Despite these comments, in March 2016, FDA issued another draft policy clarifying its position regarding stool from stool banks.¹⁰³ The policy stated that because of safety concerns, it did not intend to continue to exercise enforcement discretion for stool received from independent (non-hospital affiliated) stool banks, i.e., INSBs, and that stool banks would need to submit an IND application and receive FDA approval before their product could be used by physicians.¹⁰⁴ The guidance further stated that health care providers who receive FMT product from a stool bank could be sub-investigators if they wanted to be part of a clinical trial.¹⁰⁵ This would free them from many of the burdens of investigators¹⁰⁶ but would still require them to submit a protocol to their institutional review board and to report adverse events.

Physicians who did not wish to participate in a clinical trial could use stool from a relative or friend of the patient or obtain stool from a hospital stool bank, as long as the donors were screened and the sample stool tested under the direction of the clinician treating the patient.¹⁰⁷ The guidance would allow hospital stool banks to operate without an IND.¹⁰⁸

⁹⁹ 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, U.S. FOOD & DRUG ADMIN. 1 (Mar. 2014), <https://www.fdanews.com/ext/resources/files/02/02-26-14-Guidance.pdf> [<https://perma.cc/9XRL-YZZV>].

¹⁰⁰ *See id.* at 2.

¹⁰¹ *See, e.g.*, Soc’y for Healthcare Epidemiology of America, Comment on Docket No. FDA-2013-D-0811-0003 (May 13, 2014), <https://www.regulations.gov/comment/FDA-2013-D-0811-0015>, [<https://perma.cc/YG2M-K4V7>].

¹⁰² *See* FDA, ENFORCEMENT POLICY (Mar. 2016), *supra* note 14, at 3.

¹⁰³ *Id.* at 1–2.

¹⁰⁴ *Id.* at 3.

¹⁰⁵ *Id.*

¹⁰⁶ *See* 21 C.F.R. § 312.60 (2017) for investigator requirements.

¹⁰⁷ FDA, ENFORCEMENT POLICY (Mar. 2016), *supra* note 14, at 1–2.

¹⁰⁸ *Id.* Presumably, a physician could also obtain access to stool for an individual patient from a stool bank operating under an IND consistent with one of the expanded access provisions under the IND regulations. *See* 21 C.F.R. § 312.310 (2021); *see also* EXPANDED ACCESS TO INVESTIGATIONAL DRUGS FOR TREATMENT USE—QUESTIONS AND ANSWERS: GUIDANCE FOR INDUSTRY, U.S. FOOD & DRUG ADMIN. 3 (June 2016), <https://www.fda.gov/media/85675/download#:~:text=The%20main%20distinction%20between%20expanded,or%20effectiveness%20of%20a%20drug> [<https://perma.cc/H9FV-BHRF>] (“The main distinction between expanded access and the use of an investigational drug in the usual studies covered under an IND is that expanded access uses are not primarily intended to obtain information about the safety or effectiveness of a drug.”).

In public comments on this version of the guidance, all fifty-five of the individuals who responded as patients or potential consumers of FMT criticized the guidance for putting in place barriers to FMT access.¹⁰⁹ Many said they feared lack of access to a life-saving therapy and believed that, if an IND were to be required for stool banks, they would have to meet stringent clinical trial eligibility standards to receive an FMT and might receive a placebo rather than the therapeutic intervention.¹¹⁰ These commenters urged FDA to continue to allow independent stool banks to provide FMT for treatment of rCDI.¹¹¹

Forty-one health care providers (many who had performed FMT) criticized the FDA Draft Guidance because they believed that stool banks “provide a safe, rigorously tested product in a timely manner.”¹¹² They stated that “hospital and local laboratories, especially in rural areas, do not have facilities or training to conduct the same type of screening as stool banks, and are often unable to screen donors quickly.”¹¹³ Finally, they stated that “screening is expensive, not reimbursed by all payers, and hardest on poor patients”¹¹⁴ who cannot afford the out-of-pocket costs. Referring to FDA’s decision that fecal matter is not human tissue,¹¹⁵ several commenters asserted that fecal microbiota should be regulated as tissue not as a drug.¹¹⁶ One commenter stated the decision that fecal matter is not a tissue:

ignores large amounts of scientific evidence that show gut microbiota to be a product of millions of years of co-evolution with their human hosts and an integral part of the human body. It is the same flawed, outdated logic that allows regulation of antibiotic drugs without any consideration of their effects on host microbiota and their long-term effects on the health of the host.¹¹⁷

FDA continued to exercise enforcement discretion after issuing the 2016 Draft Guidance. Subsequently, however, several companies seeking approval for stool-based drugs/biologics began to advocate that FDA put an end to the enforcement discretion policy. These companies had formed an association, the Microbiome

¹⁰⁹ See, e.g., Anna Przychodzki, Comment on Docket No. FDA-2013-D-0811-0022 (Apr. 25, 2016), <https://www.regulations.gov/comment/FDA-2013-D-0811-0057> [<https://perma.cc/57TQ-97JB>].

¹¹⁰ See, e.g., Sheila Neese, Comment on Docket No. FDA-2013-D-0811-0022 (June 20, 2016), <https://www.regulations.gov/comment/FDA-2013-D-0811-0126> [<https://perma.cc/5CKD-YNMY>].

¹¹¹ See Diane Hoffmann, Francis Palumbo, Jacques Ravel, Mary-Claire Roghmann, Virginia Rowthorn & Erik von Roseninge, *Improving Regulation of Microbiota Transplants*, 358 SCIENCE 1390, 1390 (2017) (citing comments on FDA-2013-D-0811).

¹¹² *Id.*

¹¹³ *Id.*

¹¹⁴ *Id.*

¹¹⁵ See *supra* notes 88–90.

¹¹⁶ See, e.g., Ass’n for Pros. in Infection Control and Epidemiology, Comment on Docket No. FDA-2013-D-0811-0022 (Apr. 25, 2016), <https://www.regulations.gov/comment/FDA-2013-D-0811-0062> [<https://perma.cc/D7HG-8DFU>].

¹¹⁷ Alexander Khoruts, Comment on Docket No. FDA-2013-D-0811-0022 (Apr. 25, 2016), <https://www.regulations.gov/comment/FDA-2013-D-0811-0065> [<https://perma.cc/9MK8-PEZA>].

Therapeutics Innovation Group (MTIG), “to advance their interests with the FDA.”¹¹⁸ Chief among their complaints was that, because patients were able to get treatments from OpenBiome for their rCDI, they were unable to attract sufficient human subjects to participate in their Phase II and III clinical trials.¹¹⁹ Perhaps in response, in November 2019, FDA held a Part 15 hearing hoping to obtain feedback from stakeholders on: 1) clinical evidence of effectiveness of FMT for prevention of recurrent CDI and treatment of refractory CDI; 2) strength of data on safety of FMT for rCDI; 3) the impact of FDA’s enforcement discretion policy on FMT product development; and 4) ideas about how the agency might carve out a regulatory path forward that balances patient access with patient safety and allows “enough flexibility to support innovation for the development and licensure of safe and effective FMT products” for treatment of rCDI.¹²⁰

At the hearing, FDA heard from industry representatives, including OpenBiome, as well as researchers, physicians, and patients.¹²¹ Industry representatives working on new drug development with stool-derived products asserted that rigorous and well-controlled, statistically powered studies were needed to establish safety and efficacy¹²² of FMT for rCDI and that the agency’s enforcement discretion policy had had a profound effect on recruitment of subjects for clinical trials. The representative from Rebiotix testified that the company had seen a “four-fold decrease in patient enrollment as measured by patients per site per month” since 2013 when the enforcement discretion policy was put in place.¹²³ She further stated that this decline in enrollment had delayed “access to FDA approved therapies by over two years” and “added 10’s of millions of dollars to [its drug] development costs.”¹²⁴

In contrast to the drug developers, an OpenBiome spokesperson urged that FDA continue its policy of enforcement discretion and stated that “product development for FMT based therapies appears robust and can coexist with Enforcement Discretion” and that perhaps as many as 75% of individuals with rCDI who are eligible for FMT are not eligible for clinical trials.¹²⁵ In addition, the stool bank provided data indicating that there are many patients (approximately 35,000–40,000) who are not being served

¹¹⁸ 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> [<https://perma.cc/8CMH-ACQU>].

¹¹⁹ *See id.*

¹²⁰ Use of Fecal Microbiota for Transplantation to Treat Clostridium Difficile Infection Not Responsive to Standard Therapies; Public Hearing; Request for Comments, 84 Fed. Reg. 47,911, 47,911–14 (Sept. 11, 2019).

¹²¹ U.S. FOOD & DRUG ADMIN., PART 15 HEARING: USE OF FECAL MICROBIOTA FOR TRANSPLANTATION TO TREAT CLOSTRIDIUM DIFFICILE (2019), <https://www.fda.gov/media/134094/download> [<https://perma.cc/W2NV-4DLX>] [hereinafter PART 15 HEARING].

¹²² *Id.* at 33–35 (statement of Lee Jones, CEO of Rebiotix); *see also* Pilar N. Ossorio & Yao Zhou, *FMT and Microbial Medical Products: Generating High Quality Evidence through Good Governance*, 47 J.L. MED. & ETHICS 505, 505 (2019).

¹²³ PART 15 HEARING, *supra* note 121, at 35–36 (statement of Lee Jones, CEO of Rebiotix).

¹²⁴ *Id.* at 36.

¹²⁵ *Id.* at 19–20 (statement of Majdi Osman, CMO of OpenBiome, citing data from Dr. Colleen Kelly: “Seventy-five percent of patients are excluded because of comorbid diseases such as IBD and IBS that are very common in this population.”).

by OpenBiome and who are potential participants for clinical trials.¹²⁶ Finally, he testified that there are two population groups that are particularly well-served by the enforcement discretion policy. The first includes those with severe (i.e., fulminant) CDI—these patients have a very different disease phenotype than those with rCDI—with a mortality rate of 57%.¹²⁷ Data published from a group at Mount Sinai Hospital in New York showed a 77% reduction in the probability of mortality for this group treated with stool provided by OpenBiome.¹²⁸ The second group that has benefitted from the policy is children. Stacy Kahn, a pediatric gastroenterologist, testified that our current antibiotic strategies for treating children with *C. difficile* are not FDA approved for children in most cases.¹²⁹ If institutions stop offering FMT, she said, “the alternative is long term antibiotics which is expensive, can cause adverse events, . . . and may increase vulnerability to [antibiotic-resistant] organisms.”¹³⁰ There are no clinical trials for patients in either of these groups.

E. Safety, Innovation, and Patient Access Under Enforcement Discretion

FDA’s decision to exercise enforcement discretion for FMT to treat rCDI has allowed patients who otherwise may not have been able to access the procedure under a drug regulatory paradigm to do so by making it possible for OpenBiome to remain open.¹³¹ OpenBiome has shipped over 60,000 treatments to physicians for the FMT procedure.¹³²

Some of the individuals who received stool product from OpenBiome may have been eligible for participation in clinical trials currently being conducted by companies pursuing a biological license for a stool-derived microbiota-based therapy; however, many individuals with rCDI would not have been eligible for those trials given their strict exclusion criteria.¹³³ Alternatively, those individuals *may* have been able to obtain access to one of the therapies being tested as part of FDA’s expanded access

¹²⁶ *Id.* at 20–21, 52 (statement of Mark Smith, CEO of Finch Therapeutics, stating that there are “100-fold more rCDI patients than all the industry trials together will enroll”).

¹²⁷ “Fulminant *C. difficile* colitis has been broadly defined as *C. difficile* colitis with significant systemic toxic effects and shock, resulting in need for colectomy or death, and occurs in approximately 3% to 5% of patients with *C. difficile* colitis” Elizabeth A. Sailhamer, Katherine Carson, Yuchiao Chang, Nikolaos Zacharias, Konstantinos Spaniolas, Malek Tabbara, Hasan B. Alam, Marc A. DeMoya & George C. Velmahos, *Fulminant Clostridium Difficile Colitis: Patterns of Care and Predictors of Mortality*, 144 ARCHIVES SURGERY 433, 433 (2009).

¹²⁸ Emily N. Tixier, Elijah Verheyen, Ryan C. Ungaro & Ari M. Grinspan, *Faecal Microbiota Transplant Decreases Mortality in Severe and Fulminant Clostridioides Difficile Infection in Critically Ill Patients*, 50 ALIMENTARY PHARMACOLOGY & THERAPEUTICS 1094, 1094 (2019).

¹²⁹ PART 15 HEARING, *supra* note 121, at 100 (statement of Stacy Kahn).

¹³⁰ *Id.* at 100–01.

¹³¹ We speculate that if OpenBiome had been required to obtain an IND, it would have had to close as the costs of the process would be prohibitive.

¹³² OPENBIOME, <https://www.openbiome.org/impact> (last visited Oct. 25, 2021) [<https://perma.cc/A9LY-VDN9>]; see also OPENBIOME, *Donate Your Stool*, *supra* note 66.

¹³³ See PART 15 HEARING, *supra* note 121, at 20–21.

rules;¹³⁴ however, the industry has claimed that such access would interfere with its investigational trials.¹³⁵

As to safety, the serious adverse events reported by OpenBiome are quite low, i.e., 6/60,000 or .0001, although OpenBiome has only reported serious events that its users have reported to the stool bank.¹³⁶ Under FDA's enforcement discretion policy for FMT, neither physicians nor stool banks are generally required to report adverse events to FDA and any safety reporting is "much less stringent than would be required under FDA supported trials."¹³⁷ As a consequence, critics argue that the enforcement discretion policy has resulted in "over-broad and frequently unsubstantiated safety and efficacy claims"¹³⁸ and a missed opportunity to gather data on outcomes and efficacy that are a standard part of clinical trials under an IND.¹³⁹

Perhaps more concerning, under the current enforcement discretion policy, there is a lack of "uniform standards for comprehensive donor and stool screening."¹⁴⁰ As a result, hospital and independent stool banks and physicians performing FMT with stool from a friend or relative of the patient are not required to follow the same screening standards for donors or donor stool when performing FMT for treatment or clinical trials.¹⁴¹

As regards innovation, although no new stool-based microbiome-based drugs have been approved by FDA, the enforcement discretion policy has allowed several such drugs to proceed along the new drug development pipeline. At least four companies have stool-derived products for the treatment of rCDI in Phase II or III clinical trials, including Finch Therapeutics, Rebiotix, Seres Health, and Vedanta Biosciences.¹⁴²

A final benefit of the enforcement discretion policy is that it has allowed a robust research enterprise in the use of FMT. According to Khoruts et al.:

¹³⁴ See 21 C.F.R. § 312.310 (2021). These rules, however, are also quite restrictive requiring that the patient have a "life-threatening" or "serious disease or condition," that there are no alternative therapies to treat the condition, that the patient cannot enroll in any existing clinical trial, that the benefit to the patient "justifies the potential risks of treatment," and that the patient's receipt of the experimental treatment will not interfere with the ongoing clinical trials. *Expanded Access*, U.S. FOOD & DRUG ADMIN. (Mar. 23, 2021), <https://www.fda.gov/news-events/public-health-focus/expanded-access> [https://perma.cc/V6AQ-H5GG].

¹³⁵ See PART 15 HEARING, *supra* note 121, at 35–39 (statement of Lee Jones, CEO of Rebiotix).

¹³⁶ While stool banks generally were not required to report adverse events under the ED policy, OpenBiome has an agreement with its users that they report adverse events. Also, FDA's March 2020 alert not only requires physicians performing FMT clinical trials to report adverse events but also encourages stool banks supplying stool for FMT for treatment purposes to report them. See *supra* note 79. Users have reported some adverse events to OpenBiome that were not considered caused by the stool product. In some cases, adverse events are caused by the colonoscopy administration or by other underlying morbidities of the patient.

¹³⁷ PART 15 HEARING, *supra* note 121, at 45 (statement of Paul Kim of MTIG).

¹³⁸ *Id.*

¹³⁹ Khoruts, Hoffmann & Palumbo, *supra* note 3, at 493.

¹⁴⁰ PART 15 HEARING, *supra* note 121, at 53 (statement of Mark Smith, CEO of Finch Therapeutics).

¹⁴¹ See Zain Kassam, Nancy Dubois, Bharat Ramakrishna, Kelly Ling, Taha Qazi, Mark Smith, Colleen R. Kelly, Monika Fischer, Jessica R. Allegretti, Shrish Budree, Pratik Panchal, Ciarán P. Kelly & Majdi Osman, *Donor Screening for Fecal Microbiota Transplantation*, 381 NEW ENG. J. MED. 2070, 2070 (2019); see also Bakken et al., *supra* note 31, at 1047–48.

¹⁴² Khoruts, Hoffmann & Palumbo, *supra* note 3, at 486–87.

The relatively light regulatory burden for conducting research¹⁴³ under the enforcement discretion regime, comprised mainly of local IRBs, facilitated a remarkably rapid transition from what used to be a crude procedure that involved preparation and administration of raw, homogenized stool to easily administered purified, cryopreserved microbiota, centrally manufactured from rigorously tested universal donors.¹⁴⁴

In addition, these authors state that the enforcement discretion policy has allowed academic researchers to evaluate safety and effectiveness of fresh versus frozen/thawed stool as well as different routes of administration and dosages.¹⁴⁵ Also, one benefit that is often overlooked is that the policy allowed treatment of rCDI in patients in higher risk groups, “e.g., those with inflammatory bowel disease, advanced liver disease, and organ transplant recipients,” who are “disproportionately represented within the rCDI population, but are excluded in formal clinical trials conducted by commercial developers under IND clinical trial protocols.”¹⁴⁶ Finally, the policy has allowed researchers conducting research on FMT for rCDI, as well as for other indications, to use OpenBiome’s master file that describes the otherwise confidential information about the company’s facilities and its “manufacturing” processes.¹⁴⁷

III. THE REGULATORY PATH NOT TAKEN: REGULATING STOOL AS A DRUG AND BIOLOGIC WITHOUT ENFORCEMENT DISCRETION

A. *A Brief History of the Regulation of Drugs and Biologics*

Without the enforcement discretion policy, FDA would regulate stool product from a stool bank as a biologic/drug. While both biologics and drugs are products that are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease,¹⁴⁸ their statutory history resulted in a somewhat different regulatory framework for each. Although the biologic regulatory pathway offers some flexibility for approval not found in the drug route, it still poses challenges to a natural human product such as stool.

¹⁴³ By “research,” we understand Khoruts et al. to mean innovation in treatment. *See id.* at 492.

¹⁴⁴ Khoruts, Hoffmann & Palumbo, *supra* note 3 at 492–93. Others have echoed these remarks. *See, e.g.,* Jørgensen et al., *supra* note 3, at 2777 (“In recent years, the FMT procedure has undergone drastic improvements, shifting from low-tech applications using kitchen devices and fresh feces obtained from relatives to capsules containing rigorously screened feces from healthy, anonymous donors.”).

¹⁴⁵ Khoruts, Hoffmann & Palumbo, *supra* note 3, at 493.

¹⁴⁶ *Id.*

¹⁴⁷ *See* 21 C.F.R. § 314.420(a) (2020). A drug master file is a voluntary disclosure of confidential and/or protected (e.g., trade secrets) information to FDA for the purpose of the holder (e.g., the IND sponsor or the manufacturer) to 1) incorporate the information by reference when submitting an IND; or 2) authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person it authorized. *Id.*

¹⁴⁸ GENERAL NAVIGATION GUIDE FOR MANUFACTURERS OF FDA-REGULATED PRODUCTS AND START-UPS, U.S. FOOD & DRUG ADMIN. 1–2, <https://www.fda.gov/media/79688/download> (last visited Oct. 25, 2021) [<https://perma.cc/KPG3-WF9Y>].

The original basis for the regulation of biologics was the 1902 Biologics Control Act.¹⁴⁹ The statute was specifically passed to regulate the sale of viruses, serums, toxins, and analogous products.¹⁵⁰ The Biologics Control Act created a Board that was authorized to develop criteria for licensing entities that manufactured and marketed or sold these products in interstate commerce.¹⁵¹ The law prohibited manufacturers from selling or transporting biologics that were not from a licensed facility, but nothing in the statute required that the biologic product be safe or effective.¹⁵² Rather, regulated products had to meet standards for purity and potency.¹⁵³ If a product was found to be “defective,” facility licenses could be revoked or suspended for noncompliance with established requirements.¹⁵⁴

In 1944, the 1902 Act was incorporated into Section 351 of the Public Health Service (PHS) Act.¹⁵⁵ In this process, in addition to requiring a license for biologics manufacturing establishments, the law required a license for biologic products before they could be marketed.¹⁵⁶ This put biologics on par with drugs which had been required to be proven safe prior to marketing since the passage of the 1938 Food, Drug, and Cosmetic Act (FDCA).¹⁵⁷ But, in 1962, the regulatory track of the two product types diverged when Congress passed the Kefauver-Harris Amendment to the FDCA.¹⁵⁸ The Amendment required that drugs, but not biologics, be proven effective prior to marketing.¹⁵⁹

¹⁴⁹ The Act was a response by Congress to the deaths the year before of over twenty children in St. Louis, Missouri, and Camden, New Jersey, from tetanus that arose from injections from a “bad lot” of diphtheria antiserum (St. Louis) and from smallpox antiserum (Camden) made from horse blood. Leslie Boyer, *Viruses and the Biologics Control Act of 1902*, LESLIEBOYERMD (Aug. 17, 2019), <https://scorpiondoc.silvrback.com/viruses-and-the-biologics-control-act-of-1901> [<https://perma.cc/7XKF-QMF4>].

¹⁵⁰ The Act preceded the 1906 Pure Food and Drug Act in part “[b]ecause early vaccines and antitoxins were then administered by direct injection, as compared with drugs, which were largely ingested”; as a result, biologics were regulated earlier and more strictly than drugs. INST. OF MED., BLOOD BANKING AND REGULATION: PROCEDURES, PROBLEMS, AND ALTERNATIVES 5 (Edward A. Dauer ed., 1996).

¹⁵¹ Suzanne White Junod, *Biologics Centennial: 100 Years of Biologics Regulation*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/files/Biologics-Centennial--100-Years-of-Biologics-Regulation.pdf> (last visited Oct. 25, 2021) [<https://perma.cc/PYE2-6MN5>].

¹⁵² Terry S. Coleman, *Early Developments in the Regulation of Biologics*, 71 FOOD & DRUG L.J. 544, 566 (2016).

¹⁵³ *Id.* at 559–65.

¹⁵⁴ *Science and the Regulation of Biological Products*, U.S. FOOD & DRUG ADMIN. (Mar. 28, 2018), <https://www.fda.gov/about-fda/histories-product-regulation/science-and-regulation-biological-products> [<https://perma.cc/X63W-X9VU>] [hereinafter FDA, *Science and the Regulation of Biological Products*]. See also Gary E. Gamerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 FOOD & DRUG L.J. 213, 218 (1994).

¹⁵⁵ Hope E. Hopps, *The Bureau of Biologics; What it is and What it Does*, 33 FOOD DRUG COSMETIC L.J. 198, 198 (1978).

¹⁵⁶ *Id.* at 201.

¹⁵⁷ Gamerman, *supra* note 154, at 219.

¹⁵⁸ Kefauver-Harris Amendment, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended at 21 U.S.C. § 301 *et seq.* (1962)).

¹⁵⁹ *Id.*

It was not until the early 1970s that FDA required “new and previously licensed biologics to be effective.”¹⁶⁰ The agency initially based its decision on the “misbranding provisions of the FDCA” but, in response to criticisms that it was overreaching its authority, switched its rationale stating that it was justified by the “potency requirement” in the PHS Act.¹⁶¹ Since 1973, FDA has required proof of effectiveness for all biologics requesting a license.¹⁶²

Although the regulation put both drugs and biologics products on equal footing in terms of premarket approval, for the next twenty-three years FDA continued to require a separate establishment license for biologics manufacturing facilities.¹⁶³ The focus on the manufacturing process for biologics was justified by the early biological products which “were crude and hard to control for quality.”¹⁶⁴ Biologic products were fundamentally different from the typical drug product, e.g., biologics are “manufactured in a living system” and most are “complex molecules or mixtures of molecules . . . [that are] difficult, and sometimes impossible, to characterize.”¹⁶⁵ In contrast, drugs “generally have well-defined chemical structures, and a finished drug can usually be analyzed to determine all its various components.”¹⁶⁶

Over time and with new technology, biologics came to differ from the older and cruder versions. These newer biologics, such as recombinant proteins, are produced with much greater precision and have a purity that is similar to more traditional chemically manufactured drugs.¹⁶⁷ As a result of these changes in the types of biologics requesting licenses, in 1997 when Congress passed the Food and Drug Administration Modernization Act, it eliminated the need for a separate establishment

¹⁶⁰ Coleman, *supra* note 152, at 597.

¹⁶¹ *Id.* Coleman makes the case that this more recent assertion is at odds with the legislative history of the Act and that “requiring proof of effectiveness as a prerequisite for licensing is arguably as unclear now as it was a century ago.” *Id.* at 598.

¹⁶² Biological Products: Procedures for Review of Safety, Effectiveness and Labeling, 38 Fed. Reg. 4,319 (Feb. 13, 1973).

¹⁶³ See *infra* note 168 and accompanying text.

¹⁶⁴ Kristy Hong, *Breakthrough Biotechnologies: Can the FDA Keep Up with the Speed of Science?*, at 25, 33 (Apr. 27, 2004) (on file with Digital Access to Scholarship at Harvard), <https://dash.harvard.edu/bitstream/handle/1/8889444/Hong.pdf?sequence=1&isAllowed=y> [<https://perma.cc/8HXY-XZTD>].

¹⁶⁵ *How do Drugs and Biologics Differ?*, BIOTECHNOLOGY INNOVATION ORG., <https://archive.bio.org/articles/how-do-drugs-and-biologics-differ#:~:text=Drugs%20versus%20Biologics&text=Most%20biologics%20are%20very%20large,ingredients%20in%20an%20ordered%20process> (last visited Mar. 20, 2021) [<https://perma.cc/U8G2-EPPB>].

¹⁶⁶ *Id.* In addition to these reasons, “biological products are more fragile than drugs . . . , and the composition of biologics is more difficult to standardize. Unlike the chemical compounds that make up a drug . . . , most components of a biologic are highly sensitive to heat, light, contamination, motion, and temperature. Additionally, while drug composition and purity can be determined by chemical analysis, not every component of a biological product can be easily identified or measured.” 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, 422 (1998). As a result of the difficulty in fully characterizing the finished biologic product in the laboratory, “[biologics] manufacturers must ensure product consistency, quality, and purity by ensuring that the manufacturing process remains substantially the same over time. By contrast, a drug manufacturer can change the manufacturing process extensively and analyze the finished product to establish that it is the same as before the manufacturing change.” BIOTECHNOLOGY INNOVATION ORG., *supra* note 166.

¹⁶⁷ Hong, *supra* note 164, at 33.

license for biologics.¹⁶⁸ Thus, biologics manufacturers now can apply for a single Biologics License which covers both product quality and manufacturing compliance with current Good Manufacturing Practices (cGMPs).¹⁶⁹ FDA may grant a biologics license “if the biologic is determined to be ‘safe, pure, and potent’ as defined in § 351 of the PHS Act.”¹⁷⁰ Despite the different statutory language undergirding a requirement of effectiveness, FDA requires the same quantity and quality of evidence of effectiveness for both drugs and biologics.¹⁷¹

B. The Application of the Biologic/Drug Regulatory Framework to Stool Product for FMT

A number of authors have pointed out how stool is very different from a “typical” drug or biologic. In 2013, in an article in *Nature*, Smith, Kelly, and Alm wrote that:

stool is unlike conventional drugs, which are produced under controlled conditions with consistent, known ingredients. Stool is a variable, complex mixture of microbes, metabolites and human cells. It cannot be characterized to the rigorous standards applied to conventional drugs. The material is also widely available—it comes from healthy volunteers, rather than chemical factories or controlled cell cultures.¹⁷²

Sachs and Edelman further elaborated on these observations stating that stool defies the “typical scientific characterization that the FDA has long applied to small molecule and [newer] biologic drugs” and that “[u]nless the active components are identified, purified, and tested, it will not be possible to guarantee that the [stool] product is consistent across batches.”¹⁷³

European authors have made similar arguments about how stool should be regulated in the EU, asserting that:

stool treatment defined as drug treatment is counterproductive. Stool is not a standardized product that is produced in a factory, but a highly diverse and donor-specific substance of human origin (SoHO) delivered by healthy, usually unpaid, volunteer donors. Therefore, stool suspensions require suitable guidance of quality and safety measures comparable to

¹⁶⁸ *FDA Backgrounder on FDAMA*, U.S. FOOD & DRUG ADMIN. (Mar. 28, 2018), <https://www.fda.gov/regulatory-information/food-and-drug-administration-modernization-act-fdama-1997/fda-backgrounder-fdama> [<https://perma.cc/X6UB-EZE5>].

¹⁶⁹ Hong, *supra* note 164, at 33.

¹⁷⁰ *Id.*

¹⁷¹ See U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY PROVIDING CLINICAL EVIDENCE OF EFFECTIVENESS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS 3–4 (1998), <https://www.fda.gov/media/71655/download> [<https://perma.cc/3BDX-V85E>].

¹⁷² Mark B. Smith, Colleen Kelly & Eric J. Alm, *How to Regulate Faecal Transplants*, 506 NATURE 290, 291 (2014).

¹⁷³ Sachs & Edelman, *supra* note 1, at 398, 402.

guidance of other SoHO (blood, tissues, cells and organs) within the EU.¹⁷⁴

Because biologics are inherently variable, especially when derived from different donors, the variation must be controlled during the production process to prevent “changes in key quality attributes that may contribute to clinically meaningful differences.”¹⁷⁵ Also, to meet large commercial demand, the manufacturer must be able to scale up production in such a way that it does not “sacrific[e] product consistency.”¹⁷⁶

Stool has the characteristics of earlier “crude” biologics. It is sourced from different donors and differs from donor to donor as well as from sample to sample from the same donor at different times.¹⁷⁷ The sample consists of a community of microbes that interact with each other, in ways that may be synergistic or antagonistic, and that interact with their host.¹⁷⁸ A single sample obtained for FMT may do different things in different patients or have a different effect depending on the condition for which the patient was given an FMT or the status (microbiological or immunological) of the recipient.¹⁷⁹

Stool used for FMT is also much less manipulated than the typical drug or biologic. The transplanted material consists of organisms that occur naturally at the site and have not been cultivated in the laboratory in a growth environment or medium.¹⁸⁰ Nor is stool like the typical probiotic which is regulated as a dietary supplement and composed of either a monostrain containing one strain of a bacterial species or a multistrain containing “more than one strain of the same [bacterial] species or closely related species.”¹⁸¹

There are a number of ways in which the drug/biologic approval process is not an “easy fit” for stool used for FMT.¹⁸² In order to conduct clinical trials on a new biologic

¹⁷⁴ Josbert J. Keller, Maria J.G.T. Vehreschild, Christian L. Hvas, Simon M.D. Jørgensen, Jouzas Kupciskas, Alexander Link, Chris J.J. Mulder, Simon D. Goldenberg, Ramesh Arasaradnam, Harry Sokol, Antonio Gasbarrini, Christoph Hoegenauer, Elizabeth M. Terveer, Ed J. Kuijper & Perttu Arkkila, *Stool for Fecal Microbiota Transplantation Should be Classified as a Transplant Product and Not as a Drug*, 7 UNITED EUR. GASTROENTEROLOGY J. 1408, 1409 (2019).

¹⁷⁵ Richard Melsheimer, Melissa Calmann, Albert DeRitis, Vinod Philip, Frank Van Gog, Lawrence Doolittle, Kavitha Goya & Donald Neblock, *Ensuring Product Quality, Consistency and Patient Supply over Time for a Large-Volume Biologic: Experience with Remicade®*, 32 BIODRUGS 405, 405 (2018).

¹⁷⁶ *Id.*

¹⁷⁷ Merrick et al., *supra* note 15, at 3.

¹⁷⁸ Alexander Khoruts, *Is Fecal Microbiota Transplantation a Temporary Patch for Treatment of Clostridium Difficile Infection or a New Frontier of Therapeutics?*, 12 EXPERT REV. GASTROENTEROLOGY & HEPATOLOGY 435, 436 (2018).

¹⁷⁹ Khoruts, Hoffmann & Palumbo, *supra* note 3, at 485.

¹⁸⁰ Hoffmann et al., *supra* note 6, at 210.

¹⁸¹ H.M. Timmerman, C.J.M. Koning, L. Mulder, F.M. Rombouts & A.C. Beynen, *Monostrain, Multistrain and Multispecies Probiotics—A Comparison of Functionality and Efficacy*, 96 INT’L. J. FOOD MICROBIOLOGY 219, 221 (2004). *See also* Merrick et al., *supra* note 15, at 4 (stating “[i]t is the lack of characterisation of microbial strains that precludes the classification of FMT as a probiotic according to expert consensus”).

¹⁸² Sachs & Edelstein, *supra* note 1, at 402–08.

product, a manufacturer must submit an IND application to FDA.¹⁸³ That application must include specific information on the physical, chemical, or biological characteristics of the substance, e.g., biological name and strain designations, and the original source of cells from which the substance was derived.¹⁸⁴ Additionally, the manufacturer or biologic sponsor must include a “characterization” of the product.¹⁸⁵ This includes “a description of the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the [biologic] substance.”¹⁸⁶ Also, if there is evidence of the biologic’s mechanism(s) of action, the manufacturer must submit that data to FDA.¹⁸⁷ All of this would be problematic for stool. The FMT process in clinical practice is to transplant a fecal sample containing the whole uncharacterized microbiota because the therapeutic mechanism of FMT is still poorly understood. Without an understanding of the bacterial strains that lead to the desired therapeutic effect, it is problematic to generate reproducible bacterial isolates for FMT.¹⁸⁸

Additional challenges for any individual or company attempting to obtain a biologics license from FDA for stool include the manufacturing requirements and release specifications. Mark Smith, founder of OpenBiome and now CEO of Finch Therapeutics, expressed doubts that the manufacturing process used by OpenBiome today could meet the Biologics License Application (BLA) requirements.¹⁸⁹ The stool-derived products currently in the BLA pipeline all have additional characterization and release specifications and greater control of the manufacturing process than does OpenBiome.¹⁹⁰ And, smaller INSBs and hospital stool banks would be even less likely able to meet the BLA requirements.

¹⁸³ U.S. FOOD & DRUG ADMIN., EARLY CLINICAL TRIALS WITH LIVE BIOTHERAPEUTIC PRODUCTS: CHEMISTRY, MANUFACTURING, AND CONTROL INFORMATION GUIDANCE OF INDUSTRY 7 (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> [<https://perma.cc/VKQ7-TJL9>].

¹⁸⁴ *Id.* Additional requirements include:

- Culture/passage history of the strains;
- If cells were obtained from a clinical specimen, a description of the clinical health of the donor(s), if known . . . ;
- Summary of the phenotype and genotype of the product strains, with special attention to biological activity or genetic loci that may indicate activity or potency; and
- Documentation and summary of modifications, if any, to the LBP, e.g., intentional introduction of foreign genes or mutations, along with details of the genetic construction.

Id.

¹⁸⁵ *Id.* at 8.

¹⁸⁶ *Id.*

¹⁸⁷ *Id.*

¹⁸⁸ Yonghui Ma, Jiayu Liu, Catherine Rhodes, Yongzhan Nie & Faming Zhang, *Ethical Issues in Fecal Microbiota Transplantation in Practice*, 17 AM. J. BIOETHICS 34, 35 (2017).

¹⁸⁹ Email from Mark Smith to Diane Hoffmann (Sept. 3, 2020) (on file with author).

¹⁹⁰ *Id.* For additional challenges of the regulatory framework for stool for FMT, see Magali Cordaillat-Simmons, Alice Rouanet & Bruno Pot, *Live Biotherapeutic Products: The Importance of a Defined Regulatory Framework*, 52 EXPERIMENTAL & MOLECULAR MED. 1397 (2020); see also Kristina Campbell, *Group Examines The Unique Challenges of Clinical Trials for Development of Microbiotic Medicinal Products, Including Live Biotherapeutic Products*, MICROBIOME TIMES (Oct. 29, 2019), <https://www.microbiometimes.com/group-examines-the-unique-challenges-of-clinical-trials-for->

On the other hand, the biologics regulations do not adequately regulate the donor aspects of stool retrieval such as medical history and testing of donors for infectious diseases that may be transferred to recipients.¹⁹¹ Also, the protocol for clinical trials used in the license application would need to be consistently applied and could not be easily modified once a license is granted.¹⁹²

Aside from these challenges, there are additional legislative and regulatory aspects of drug and biologic oversight that are problematic. For example, Sachs and Edelstein describe concerns raised by off-label use and granting data exclusivity to new biologics.¹⁹³ Under the Biologics Price Competition and Innovation Act,¹⁹⁴ new biologics are granted up to twelve years of data exclusivity.¹⁹⁵ During this time, FDA may not approve any “biosimilars” unless the manufacturer or sponsor has done its own safety and efficacy studies.¹⁹⁶ Sachs and Edelstein also argue that granting a stool product manufacturer market exclusivity is problematic when such a manufacturer would be relying on data about processes and effectiveness “that already exists in the public domain.”¹⁹⁷ This lack of fairness assertion, along with an argument that such exclusivity would likely put FMT out of reach for many patients who may not be able to afford it but are desperate for such an effective, life-saving treatment, is compelling.¹⁹⁸

Any type of market exclusivity would be challenging to enforce in the case of FMT because, unlike most other drugs and biologics, as explained above, stool is widely available and individuals may perform an FMT themselves with stool from a friend or family member.¹⁹⁹ FDA would be unable to stop individuals from engaging in such practices.

development-of-microbiotic-medicinal-products-including-live-biotherapeutic-products/
[<https://perma.cc/YV5Q-WBWQ>].

¹⁹¹ Merrick et al., *supra* note 15, at 4. “The safety of FMT highly depends on the selection and screening of the donor because no standardization of the product exists and because pathogen reduction, such as that used for plasma-derived products, is inherently impossible for FMT products.” Jørgensen et al., *supra* note 3, at 2779.

¹⁹² While FDA has recommendations for donor stool and serological testing (*see* Paul E. Carlson, *Regulatory Considerations for Microbiome Based Therapeutics*, U.S. FOOD & DRUG ADMIN. (Feb. 20, 2020), https://isctm.org/public_access/Feb2020/Presentation/Carlson-Presentation.pdf [<https://perma.cc/Q2CX-88LK>]), those recommendations may change after a product is on the market.

¹⁹³ Sachs & Edelstein, *supra* note 1, at 412.

¹⁹⁴ Biologics Price Competition and Innovation Act, Pub. L. No. 111-148, 124 Stat. 804 (2010) (codified as amended at Public Health Service Act § 351(k)(7) (2010)).

¹⁹⁵ Under the Act’s data exclusivity provisions, once a company’s new biologic is approved by FDA, the company is protected for a period of time from competitors’ use of its safety and efficacy data to obtain their own FDA marketing approval. Caroline Park, *Data Exclusivity: What Is it and Why Does it Matter?*, SENSE & SUSTAINABILITY (Jan. 20, 2016), <https://www.senseandsustainability.net/2016/01/20/data-exclusivity-what-is-it-and-why-does-it-matter/> [<https://perma.cc/J6FL-9XDX>].

¹⁹⁶ Biologics may also be considered orphan drugs, in which case they would be eligible for seven years of market exclusivity during which time no product for the same indication can be approved by FDA. Renu Lal, *Patents and Exclusivity*, FDA/CDER SBIA CHRON. (May 19, 2015), at 2, <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf> [<https://perma.cc/4NTL-QE3Q>].

¹⁹⁷ Sachs & Edelstein, *supra* note 1, at 402.

¹⁹⁸ *See* Khoruts, Hoffmann & Palumbo, *supra* note 3, at 497.

¹⁹⁹ *See supra* notes 69–70.

The potential for DIY FMTs also makes the procedure unlike other transplants, which generally require expensive medical equipment and trained health care professionals. Many individuals are performing FMTs at home even though the DIY option poses the risk of transferring harmful bacteria to patients if neither the donor nor the donor stool are screened for transmissible diseases or pathogens.²⁰⁰ This unique fact makes it incumbent on FDA to consider whether strict adherence to treating stool as a drug/biologic, requiring extensive clinical trials, would increase the likelihood of DIY FMTs.

The off-label use of stool for FMT, if it ever were to be approved as a new drug/biologic, is also fraught with problems. In particular, it would likely discourage investment in research into its effectiveness in treating other indications.²⁰¹ While this is true for all newly approved drugs, the nascent field of microbiome-based therapies and uncertainties about long term side effects, such as obesity and auto-immune disorders, make this a particularly serious concern in the context of FMT.²⁰² This risk/benefit trade-off may make sense in the context of rCDI where FMT can be life-saving, but such a trade-off may not be appropriate in its use for other indications.

C. The Impact on Stool Banks if FDA Were to Have Regulated Stool as a Drug/Biologic, and the Resulting Effect on Patient Access, Safety, and Innovation

If FDA had either initially decided not to exercise its enforcement discretion and finalize its 2016 industry guidance document, OpenBiome may have been forced to close as it would need considerable investment capital to go through the IND process. As a nonprofit, it could not raise equity financing.²⁰³ But, even if it were to have pursued for-profit status, such funding was unlikely given the uncertainty of obtaining a biologics license for stool and of any return on investment if its product were to receive a license. This uncertainty is due to the lack of intellectual property obtainable in stool,²⁰⁴ the variation among stool samples, and the DIY option that patients have. If OpenBiome had closed, it likely would have cut off the ability of thousands of individuals to obtain FMTs. While some of these individuals may have been able to obtain stool product from hospital stool banks,²⁰⁵ these banks would likely have had to scale up significantly to meet the demand for stool product.

Whether patient safety would have improved if OpenBiome had closed its doors is highly unlikely. OpenBiome appears to have had a virtually unblemished safety record until the adverse events reported in 2020, which remain of uncertain origin.²⁰⁶ Also, safety issues have arisen under clinical trials overseen by FDA as illustrated by the

²⁰⁰ Goodman, *supra* note 68.

²⁰¹ See Sachs & Edelstein, *supra* note 1, at 402; Khoruts, Hoffmann & Palumbo, *supra* note 3, at 498; Merrick et al., *supra* note 15, at 4.

²⁰² Ma et al., *supra* note 188, at 40–41.

²⁰³ 26 U.S.C. § 501(c)(3) (2011).

²⁰⁴ Mark J. FitzGerald & Erik J. Spek, *Microbiome Therapeutics and Patent Protection*, 38 NATURE BIOTECHNOLOGY 806 (2020).

²⁰⁵ Under the 2016 industry guidance, FDA would continue to exercise its enforcement discretion for local, hospital-based stool banks. FDA, ENFORCEMENT POLICY (Mar. 2016), *supra* note 14, at 1.

²⁰⁶ See *supra* notes 79–86 and accompanying text.

two adverse events reported in 2019.²⁰⁷ It is also likely that due to lack of access to stool for FMT via stool banks, more patients would have engaged in DIY FMT without any donor screening.

Industry advocates claim there would have been faster development and approval of a new stool microbiome-based drug/biologic if FDA had not exercised its enforcement discretion because the companies with products currently in the IND pipeline would have been able to attract more patients to their clinical trials.²⁰⁸ The claim is hard to evaluate given that their study inclusion criteria are quite narrow.²⁰⁹ Keller et al., in contrast, assert that requiring stool banks to go through the drug approval process would “negatively impact [both] availability and innovation, obstructing, for example, the future development of single-donor individualized solutions due to the requirements for standardization of active substances.”²¹⁰ Finally, strict enforcement of the IND requirement and related closure of stool banks would likely reduce research into use of FMT for other indications. Some researchers would not want to screen donors, test the stool, or prepare the stool for administration, which would be required if they were not able to obtain the product directly from OpenBiome or a hospital stool bank.

Patient access to an effective therapy may also have diminished even if a stool-derived microbiome-based drug/biologic product were to have been approved because it would have been much more costly than the stool provided by OpenBiome.²¹¹ Although insurance coverage typically follows approval by FDA, not everyone has drug coverage, and biologics are often not fully covered by insurance given their extremely high costs.²¹² These high costs would also have been a reason for more individuals attempting to do the procedure themselves with unscreened stool from a friend or family member. Moreover, once a new biologic/drug is approved for rCDI, it would likely have twelve years of data exclusivity as a biologic and seven years of market exclusivity as an orphan drug,²¹³ adding to the ability to charge supra-competitive prices.

IV. ALTERNATIVE REGULATORY PATHWAYS AND THEIR RELEVANCE FOR STOOL BANKS

Alternative regulatory options for stool and stool banks would primarily be those for transplanted procedures and products. Like other transplantation procedures, FMT has features of both a product, i.e., stool, and a procedure in that it is taken from one human being and is transferred into the bowel of another. In this section, we explore

²⁰⁷ See *supra* notes 74–78 and accompanying text.

²⁰⁸ See PART 15 HEARING, *supra* note 121; *supra* notes 122–24 and accompanying text.

²⁰⁹ See PART 15 HEARING, *supra* note 121 (referencing a study by Dr. Colleen Kelly).

²¹⁰ Keller et al., *supra* note 174, at 1409.

²¹¹ See Sachs & Edelstein, *supra* note 1, at 406; Khoruts, Hoffmann & Palumbo, *supra* note 3, at 497.

²¹² See Khoruts, Hoffmann & Palumbo, *supra* note 3, at 497.

²¹³ FDA may award market exclusivity to an orphan drug that overlaps traditional data exclusivity for biologics to “bar[] any sponsor from making the same drug for the same indication – even if the sponsor does not rely on the innovator’s data.” Gregory J. Glover, *The Enduring Role of Orphan Drug Exclusivity for Biologics*, PHARM. L. GRP. (Dec. 28, 2020), <https://www.pharmalawgrp.com/blog/13/the-enduring-role-of-orphan-drug-exclusivity-for-biologics/> [<https://perma.cc/E5Y4-8M3W>].

the possibility of stool being regulated like blood (a biologic for which the IND requirement was waived), or tissues and cells (for which no IND is required), or like cord blood (in some cases regulated as an HCT/P and in others regulated as both an HCT/P and a biologic).

A. *The Blood Regulatory Pathway and Its Application to Stool*

1. *History of Blood Transfusion and Its Regulation*

The original basis for the regulation of blood was the 1902 Biologics Control Act.²¹⁴ While blood later became a regulated commodity under the law, blood products were not initially regulated under the Biologics Control Act because they were not sold in interstate commerce.²¹⁵ Additionally, the Biologics Control Act was not clear about which product classes were to be licensed and did not explicitly mention blood.²¹⁶ It was not until 1970 that Congress amended the PHS Act by adding “blood, blood component or derivative” to the list of products that had to be licensed.²¹⁷

In 1972, FDA issued several regulations to tighten controls over biological products, including blood and blood banks.²¹⁸ Among the efforts to invigorate FDA oversight were blood bank registration and a “Biologics Efficacy Review.”²¹⁹ Prior to this time, the large majority of blood banks were not licensed under the PHS Act because they operated exclusively intrastate.²²⁰ Because drug manufacturing facilities²²¹ were required to register with FDA,²²² and blood was now considered a drug/biologic, in 1973 all blood banks were required to register with FDA.²²³ The two requirements—licensure and registration—were and continue to be distinct. The difference at the time was described in the Federal Register:

The licensing procedure under section 351 of the [PHS] Act involves the submission of a license application for both an establishment and a product detailing all phases of manufacture and requires a pre-licensing inspection as well as annual inspections thereafter. So long as a licensee meets the prescribed standards, . . . the licensee may ship licensed biologics in interstate commerce Registration, on the other hand, involves the submission of a form containing ownership and location

²¹⁴ See *supra* note 150 and accompanying text.

²¹⁵ FDA, *Science and the Regulation of Biological Products*, *supra* note 154.

²¹⁶ Coleman, *supra* note 152, at 576.

²¹⁷ Act of Oct. 30, 1970, Pub. L. No. 91-515, § 291, 84 Stat. 1297, 1308.

²¹⁸ Gamerman, *supra* note 154, at 220.

²¹⁹ *Id.*

²²⁰ Of 3,000–5,000 blood banks and blood collection facilities thought to exist in 1972, only 165 were licensed. Human Blood or Blood Products. 37 Fed. Reg. 17,419, 17,419 (Aug. 26, 1972).

²²¹ FDA considered banks to be manufacturing facilities because they collected, stored, packaged, and labeled blood. 21 C.F.R. § 606.3(h) (2020).

²²² Section 510(b) of the PHS Act, passed in 1962, requires that each drug establishment register on an annual basis with the Food and Drug Administration. There is no exemption for such establishments operating intrastate, either under the statute (Sec. 510(g)) or by administrative interpretation of the statutory exemptions. 21 C.F.R. § 132.51.

²²³ Registration of Blood Banks and Other Firms Collecting Manufacturing, Preparing, or Processing. 38 Fed. Reg. 2,965, 2,967 (Jan. 31, 1973).

information on an annual basis and requires a biennial inspection, but does not permit the registrant to ship blood or other biological products out of the State in which they are registered.²²⁴

As a result, FDA was able, for the first time, to obtain information about all the blood banks operating in the country. Licensure was still required for facilities transporting blood across state lines.²²⁵

During the 1970s, in response to concerns about the safety of the U.S. blood supply, FDA established “safeguards to protect the health of the donor, ensure product potency, and create standards for blood collection.”²²⁶ The agency also issued a final rule in 1975 requiring “that all facilities that process blood or blood components adhere to current good manufacturing practices (cGMP).”²²⁷ In these regulations, FDA made clear its position that blood was both a biologic/drug and a tissue²²⁸ and subject to regulation under both the PHS Act and the FDCA.

As part of its Biologics Efficacy Review, FDA convened a series of expert panels to review the efficacy of biologics under its purview that had been permitted on the market without FDA premarket approval.²²⁹ Manufacturers were required to “provide information substantiating that each of [its] products [was] safe, effective and properly labeled.”²³⁰

The expert panel on blood products concluded its work in 1985.²³¹ Although the panel had anticipated a problem-free review because of the “well developed, widely distributed, and accepted group of technologies” associated with blood and blood component retrieval, transport, storage, and administration, the panel members soon

²²⁴ *Id.* at 2,966. As of 1995, there were “188 FDA-licensed [blood collection or storage entities] at 790 locations” in the U.S. and 2,900 registered entities. INST. OF MED., HIV AND THE BLOOD SUPPLY: AN ANALYSIS OF CRISIS DECISIONMAKING 49 (Lauren B. Leveton, Harold C. Sox, Jr. & Michael A. Stoto eds., 1995).

²²⁵ In 1973, FDA stated that there was “currently [] no statutory authority to license intrastate blood banking.” Registration of Blood Banks, 38 Fed. Reg. at 2,966 (referring to Section 351 of the PHS Act). However, one year later, it announced in proposed regulations for good manufacturing practices for blood banks that:

[t]he jurisdiction of the [FDCA] is not limited to situations where the drug itself has been or is to be introduced into interstate commerce. Consistent with section 201(g)(1)(D) of the act, if one of a drug’s essential components . . . has moved in interstate commerce, the entire drug is subject to the requirements of the act and the FDA may regulate the final drug product.

Current Good Manufacturing Practice for Blood and Blood Components, 39 Fed. Reg. 18,614, 18,614 (May 28, 1974). Those regulations were finalized in 1975 and allowed FDA to regulate blood transported within a state if, for example, the container it was collected, stored, or transported in crossed state lines. See Final Regulations for Collection, Processing, and Storage, 40 Fed. Reg. 53,532 (Nov. 18, 1975). Despite this authority, FDA does not require blood banks that operate intrastate to be licensed. *Id.*

²²⁶ Mark Weinstein, *Regulation of Plasma for Fractionation in the United States*, 3 ANNALS BLOOD 1, 3 (2018).

²²⁷ *Id.*

²²⁸ Final Regulations for Collection, Processing, and Storage, 40 Fed. Reg. at 53,532 (stating “[b]lood is considered a tissue by the scientific community and is classified as such by most histology textbooks”).

²²⁹ Hopps, *supra* note 155, at 200.

²³⁰ *Id.*

²³¹ Biological Products; Blood and Blood Derivatives; Implementation of Efficacy Review, 50 Fed. Reg. 52,602, 52,604 (proposed Dec. 24, 1985).

discovered that many of the older products lacked scientifically defensible safety and efficacy data.²³² As a result, the panel relied on “consensus based upon common experience” to determine whether certain products should remain licensed.²³³ Further, because the decentralized blood banking system lacked standardized protocols for safety and efficacy, the panel had to rely on “years of experience with [blood and blood products], publications in the literature, submissions of procedures and standards of large blood bank organizations, data available in license applications, generic procedures specified by good manufacturing practices and standards of accreditation”²³⁴ to make its determinations about the safety and efficacy of blood products.²³⁵ The panel also stated there were obstacles to its obtaining adequate clinical investigational data due to a lack of commercial sponsorship and the inability of researchers to obtain sufficient funding or recruit sufficient subjects to complete clinical investigations that had been started.²³⁶

In its final report, the panel recommended which products should retain their license (Category I—safe, effective, not misbranded), which should lose their license (Category II—unsafe, ineffective, or misbranded), and which required further testing to warrant licensing (Category III). The panel made Category I recommendations for the vast majority of blood products, including whole blood with anticoagulants, red blood cells, frozen red blood cells, and single donor plasma.²³⁷

Because these blood products were technically “grandfathered” into the licensing requirement for biologics, FDA has never required “blood banks to submit INDs or to provide premarket safety and effectiveness data for blood intended for transfusion.”²³⁸ Blood banks, however, must comply with other regulations for biologics/blood products. For example, manufacturers must comply with cGMP.²³⁹ And, like other biologics facilities, they must notify FDA about changes made in the manufacturing of the product. These include changes in the “production process, quality control,

²³² *Id.*

²³³ *Id.*

²³⁴ *Id.*

²³⁵ The panel made particular note of the challenges of decentralization stating it “had to deal with a situation rather different from that which has confronted previous panels which have reviewed . . . biological therapeutic materials. The bulk of the products it reviewed were:

produced widely throughout the country in installations which range[d] from large centralized blood banks, through smaller units, down to the size of a blood bank supported by an individual hospital. There [were] no large industrial ‘manufacturers’ whose submissions and protocols [could] be reviewed as the basis for safety and efficacy determinations for therapeutic materials produced by blood banks. Thus, in this area, a manufacturer-by-manufacturer review of the Panel of every blood bank product [was] . . . impossible.

Id.

²³⁶ *Id.*

²³⁷ See Biological Products; Blood and Blood Derivatives; Implementation of Efficacy Review, 50 Fed. Reg. 52,602, 52,604 (proposed Dec. 24, 1985).

²³⁸ Kulynych, *supra* note 166, at 424. However, new blood products intended to treat, cure, mitigate, or prevent disease must submit an IND to FDA’s Office of Blood Research and Review. U.S. FOOD & DRUG ADMIN., FDA REGULATION OF BLOOD AND BLOOD COMPONENTS IN THE UNITED STATES Slide 2, <https://www.fda.gov/media/81654/download> [<https://perma.cc/AW46-B9TJ>] [hereinafter FDA REGULATION OF BLOOD AND BLOOD COMPONENTS].

²³⁹ 21 C.F.R. § 606 (2020).

equipment, facilities, responsible personnel, or labeling established in the approved license application(s).”²⁴⁰ Establishments are inspected by FDA at regular intervals to ensure compliance with regulations. During inspections, records are reviewed including documents related to quality assurance and quality control, personnel training records, information about donors such as adverse reactions, and testing for infectious disease.²⁴¹ Although FDA had earlier declared blood a tissue,²⁴² and its regulation has much in common with human tissue, in 1997 when FDA issued its “Proposed Approach to Regulation of Cellular and Tissue-Based Products,” it explicitly excluded transfusable blood products.²⁴³

2. Application of the Blood Regulatory Framework to Stool and Stool Banks

The process for blood transfusion is similar to that of FMT in that it is donor-based and relies on thorough screening of donors to determine safety.²⁴⁴ Like stool, blood is unique to each donor and each donation must be screened for pathogens.²⁴⁵ As a result, FDA requires screening of donors and screening and testing of each unit of blood received.²⁴⁶ Blood is also like stool used for FMT in that it is highly reproducible and “minimally manipulated.”²⁴⁷

Blood regulations fall into the following categories: recruiting donors, qualifying donors, blood collection, blood testing, making blood components, labeling, storage, and shipment;²⁴⁸ all of which would be relevant to stool, with the exception of “making

²⁴⁰ 21 C.F.R. § 601.12(a) (2020).

²⁴¹ FDA REGULATION OF BLOOD AND BLOOD COMPONENTS, *supra* note 238, at Slide 22. FDA has referred to the regulatory model for blood as the “Five layers of blood safety” and describes them as “overlapping, like layers of an onion.” *Id.* at Slide 14. The five layers are:

[1] selection of suitable donors by donor education and risk factor screening; [2] the use of deferral registries to identify unsuitable donations; [3] infectious disease testing on donated blood units. This testing involves both antibody and nucleic acid tests for HIV and HCV, tests for HBS Antigen, antibody testing for Human T-cell lymphotropic virus, tests for syphilis, and tests for West Nile virus[;] [4] quarantine of blood until all the test results are available and known to be negative[; and] [5] monitoring, investigating, and taking corrective actions to address any errors or accidents in the manufacturing process, and the investigation of an adverse reaction in product recipients.

Id.

²⁴² Final Regulations for Collection, Processing, and Storage, 40 Fed. Reg. 53,532 (Nov. 18, 1975) (stating “[b]lood is considered a tissue by the scientific community and is classified as such by most histology textbooks”).

²⁴³ Proposed Approach to Regulation of Cellular and Tissue-Based Products: Availability and Public Meeting, 62 Fed. Reg. 9,721, 9,721 (proposed Mar. 4, 1997).

²⁴⁴ *Blood Transfusion*, U. MICH. HEALTH (Sept. 23, 2020), <https://www.uofmhealth.org/health-library/tc4111#:~:text=Mismatches%20with%20the%20ABO%20and,at%20the%20most%2C%204%20times> [<https://perma.cc/DZP7-S9GZ>].

²⁴⁵ *Id.*

²⁴⁶ FDA REGULATION OF BLOOD AND BLOOD COMPONENTS, *supra* note 238, at slide 14.

²⁴⁷ See U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOLOGICS LICENSE APPLICATIONS FOR MINIMALLY MANIPULATED, UNRELATED ALLOGENEIC PLACENTAL/UMBILICAL CORD BLOOD INTENDED FOR HEMATOPOIETIC AND IMMUNOLOGIC RECONSTITUTION IN PATIENTS WITH DISORDERS AFFECTING THE HEMATOPOIETIC SYSTEM (Mar. 2014), <https://www.fda.gov/media/86387/download> [<https://perma.cc/J7VN-VKYU>].

²⁴⁸ 21 C.F.R. §§ 600–01, 606, 630, 640 (2020).

blood components.” Further, because of prior scandals with tainted blood and fear of HIV contamination in the blood supply, blood product testing regulations are very strict and strongly enforced.²⁴⁹ A single centralized stool bank, or one centralized bank and a handful of smaller regional stool banks across the country, supplying all the stool for FMTs, would also warrant strict product testing and enforcement of those same requirements.

The blood *banking* regulatory paradigm is highly relevant to stool banks. At the November 4, 2019 FDA hearing, OpenBiome’s representative described OpenBiome as operating “like a blood bank but for stool.”²⁵⁰ He went on to say that the nonprofit manufactures material in a “cGMP facility [and has] provided 50,000 treatments to over 1,200 hospitals and clinics in the U.S.”²⁵¹

While there are many similarities between the systems of sample collection, banking, and administration for blood and stool, there are also some differences that may be relevant to a regulatory framework for stool. For example, blood and its mechanism of action are well understood for the indications for which it is commonly used.²⁵² In contrast, researchers do not know the mechanism of action for stool used for rCDI (or any other indication). In addition, the volume of blood needed daily in the U.S. health care system is orders of magnitude greater than that needed for stool,²⁵³ making the need for a greater number of donors and banking establishments more important for blood than for stool. Also, blood banks must be highly regulated because blood is frequently used in emergency circumstances. If a blood transfusion is administered inappropriately by, for example, mismatching the blood type to the needs of the recipient, the result can be fatal.²⁵⁴ In contrast, the need for stool transplants is rarely urgent. Moreover, stool is not typed and does not need to be matched to a recipient.²⁵⁵ These distinctions may indicate that stool does not require as rigorous an oversight process as that required for blood products.

²⁴⁹ INST. OF MED., *supra* note 224, at 207.

²⁵⁰ PART 15 HEARING, *supra* note 121 (statement of Majdi Osman, CMO of OpenBiome).

²⁵¹ *Id.* See also Jørgensen et al., *supra* note 3, at 2777 (suggesting that blood banks and stool banks in Denmark might collaborate to distribute blood and stool and that the “regulatory framework and the principles of practice used by existing blood service organizations are readily applicable to FMT services”).

²⁵² See Sanjeev Sharma, Poonam Sharma & Lisa N. Tyler, *Transfusion of Blood and Blood Products: Indications and Complications*, 83 AM. FAM. PHYSICIAN 719 (Mar. 15, 2011) (“Indications for transfusion include symptomatic anemia . . . , acute sickle cell crisis, and acute blood loss of more than 30 percent of blood volume.”). *But see* Sandhya Yaddanapudi & L.N. Yaddanapudi, *Indications for Blood and Blood Product Transfusion*, 58 INDIAN J. ANAESTHESIA 538, 538 (2014) (noting that there is moderate evidence to support the use of plasma and platelets for massive blood transfusion but not enough evidence to support their use in any other clinical setting).

²⁵³ AM. RED CROSS, *Facts About Blood Needs* (Oct. 3, 2021), <https://www.redcrossblood.org/donate-blood/how-to-donate/how-blood-donations-help/blood-needs-blood-supply.html> [<https://perma.cc/5H5M-E4DL>].

²⁵⁴ *Blood Transfusion*, *supra* note 244.

²⁵⁵ While this is not the case for treatment of rCDI, matching could be possible for other indications. See, e.g., Koki Okahara, Dai Ishikawa, Kei Nomura, Shoko Ito, Keiichi Haga, Masahito Takahashi, Tomoyoshi Shibuya, Taro Osada & Akihito Nagahara, *Matching Between Donors and Ulcerative Colitis Patients is Important for Long-Term Maintenance after Fecal Microbiota Transplantation*, 9 J. CLINICAL MED. 1650 (2020).

B. *The Tissue Regulatory Framework and Its Application to Stool*

1. *Regulation of Human Tissue and Tissue Banks*

Tissue banking began to be practiced in the United States in the 1940s, but it was not regulated because it was considered the practice of medicine.²⁵⁶ Formal regulation of human tissues by FDA began in December 1993 with the urgent release of an interim rule.²⁵⁷ The rule was issued in response to reports of importation of potentially infectious tissue from other countries, including imported cadaveric tissue infected with hepatitis B virus²⁵⁸ and a report of transmission of HIV from a seronegative American organ and tissue donor.²⁵⁹ Despite this urgency, FDA decided not to require that banked human tissue go through premarket approval²⁶⁰ and instead issued the interim rule, and subsequent rules, under the authority of Section 361 of the PHS Act. The interim rule was effective immediately and required “all facilities engaged in procurement, processing, storage, or distribution of human tissues intended for transplant to ensure that minimum required infectious disease testing ha[d] been performed and that records documenting such testing for each tissue [were] available for inspection by FDA.”²⁶¹ The interim rule further gave the agency authority to inspect tissue facilities and to “detain, recall, or destroy tissue for which appropriate documentation [was] not available.”²⁶²

After a period of public comment on the interim rule, FDA issued its final rule on human tissue transplantation in July 1997.²⁶³ The final rule codified the interim rule with minimal modifications. As FDA’s 1997 final rule was limited in scope and only covered musculoskeletal tissue, ocular tissue, and skin, in that same year, FDA proposed a more comprehensive regulatory scheme in its “Proposed Approach to the Regulation of Cellular and Tissue-Based Products.”²⁶⁴ This proposal covered all human cells, tissues, and tissue-based products, which the agency referred to as HCT/Ps.²⁶⁵

²⁵⁶ Marc O. Williams, *The Regulation of Human Tissue in the United States: A Regulatory and Legislative Analysis*, 52 FOOD & DRUG L.J. 409, 410 (1997).

²⁵⁷ Human Tissue Intended for Transplantation: Interim Rule, 58 Fed. Reg. 65,514 (Dec. 14, 1993).

²⁵⁸ Michael J. Joyce, *Safety and FDA Regulations of Musculoskeletal Allografts*, 435 CLINICAL ORTHOPAEDICS & RELATED RSCH. 22, 23 (2005).

²⁵⁹ R.J. Simonds, Scott D. Holmberg, Richard L. Hurwitz, Theresa R. Coleman, Scott Bottenfield, Lois J. Conley, Sherry H. Kohlenberg, Kenneth G. Castro, Beverley A. Dahan, Charles A. Schable, Mark A. Rayfield & Martha F. Rogers, *Transmission of Human Immunodeficiency Virus Type 1 from a Seronegative Organ and Tissue Donor*, 326 NEW ENG. J. MED. 726, 726 (1992).

²⁶⁰ Williams, *supra* note 256, at 419.

²⁶¹ Human Tissue Intended for Transplantation: Interim Rule, 58 Fed. Reg. at 65,514.

²⁶² *Id.*

²⁶³ Human Tissue Intended for Transplantation: Final Rule, 62 Fed. Reg. 40,429 (July 29, 1997).

²⁶⁴ See U.S. FOOD & DRUG ADMIN., PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS (proposed Feb. 28, 1997), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/proposed-approach-regulation-cellular-and-tissue-based-products> [<https://perma.cc/WYQ8-FUGX>].

²⁶⁵ The proposal was the basis for three rules to implement the proposed framework: 1) the registration rule (requiring all establishments manufacturing HCT/Ps to register with FDA); 2) the donor suitability rule;

Although the 1997 rule for HCT/Ps went through some modifications, it is the basis for today's regulatory framework.²⁶⁶ It is a risk-based approach that is designed to be broad enough to cover a wide range of products.²⁶⁷

The regulation focuses on three general areas: 1) Preventing use of contaminated tissues with the potential for transmitting infectious diseases; 2) preventing improper handling or processing that might contaminate or damage tissues, or produce cellular or tissue-based products of inadequate quality; and 3) ensuring that clinical safety and effectiveness are demonstrated for most tissues that are highly processed, are used for other than their homologous use, are combined with non-tissue components, or have a systemic effect.²⁶⁸

There is no particularly helpful definition of human tissue in the controlling statutes or regulations. Rather, HCT/Ps are defined as articles “containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”²⁶⁹ HCT/Ps are derivatives of the human body and, thus, pose a potential risk of transmitting infectious disease.²⁷⁰ Since FDA's main regulatory concerns about HCT/Ps are prevention of communicable disease transmission and safe processing and handling, like the blood regulatory framework, the HCT/P framework has detailed regulations regarding donor screening and methods, facilities, and controls for manufacturing to prevent contamination and cross-contamination.²⁷¹

Consistent with its risk-based approach, FDA classifies HCT/Ps into two groups: Section 361 products and Section 351 products.²⁷² Products designated Section 361 products are considered less risky than Section 351 products and are less tightly regulated.²⁷³ Table 1 provides examples of Section 361 and 351 HCT/Ps.

and 3) the Good Tissue Practice Rule. Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5,447 (Jan. 19, 2001).

²⁶⁶ Subsequent to the 1997 proposal, FDA published the three proposed rules to implement the 1997 framework. Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products, 63 Fed. Reg. 26,744 (proposed May 14, 1998); Suitability Determination for Donors of Human Cellular and Tissue-Based Products, 64 Fed. Reg. 52,696 (proposed Sept. 30, 1999); and Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement, 66 Fed. Reg. 1,508 (proposed Jan. 8, 2001).

²⁶⁷ See 21 C.F.R. pt. 1271—Human Cells, Tissues, and Cellular and Tissue-Based Products [HCT/Ps] (2020).

²⁶⁸ Request for Proposed Standards for Unrelated Allogeneic Peripheral and Placental/Umbilical Cord Blood Hematopoietic Stem/Progenitor Cell Products; Request for Comments, 63 Fed. Reg. 2,985, 2,986 (Jan. 20, 1998).

²⁶⁹ 21 C.F.R. § 1271.3(d) (2020).

²⁷⁰ See *Testing Human Cells, Tissues, and Cellular and Tissue Based Product (HCT/P) Donors for Relevant Communicable Disease Agents and Diseases*, U.S. FOOD & DRUG ADMIN. (Feb. 10, 2021), <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-human-cells-tissues-and-cellular-and-tissue-based-product-hctp-donors-relevant-communicable> [https://perma.cc/4H7S-4R7U].

²⁷¹ See 21 C.F.R. § 1271.1–1271.440 (2020).

²⁷² Sections refer to the Public Health Service Act, which addresses prevention of the introduction, transmission, or spread of communicable disease. Pub. L. 78-410, 58 Stat. 682, 702–04 (1944).

²⁷³ See Mary Ann Chirba, *FDA Regulation of Stem Cell Therapies: Using a Stem Cell Fraud Strike Force to Separate Fact from Fiction*, 75 FOOD & DRUG L.J. 195, 201 (2020).

TABLE 1: Examples of HCT/Ps Regulated Under Sections 361 and 351 of the PHS Act

361 HCT/Ps ²⁷⁴	351 HCT/Ps (biologics) ²⁷⁵
<ul style="list-style-type: none"> • amniotic membrane (when used alone or without added cells) • bone • skin • tendon • heart valves • cartilage • cornea • fascia • ligament • reproductive cells (semen, oocytes, embryos) • bone marrow • cord blood for personal use or use in first- or second-degree relatives 	<ul style="list-style-type: none"> • all allogenic, unrelated hematopoietic stem cells from cord and peripheral blood (e.g., cord blood for use by a patient unrelated to the donor) • bone marrow that is more than minimally manipulated • bone marrow that is intended for non-homologous use • cultured cartilage cells • cultured nerve cells • gene therapy products • human cells used in therapy involving the transfer of genetic material

The regulatory scheme for both groups includes: 1) registration of facilities and submission of a list of all products to FDA; 2) donor screening and testing; 3) current good tissue practices; 4) labeling; 5) adverse event reporting; and 6) inspection and enforcement.²⁷⁶ For Section 361 *only* HCT/Ps, the governing regulations are set forth in 21 C.F.R. Part 1271.²⁷⁷ Section 351 HCT/Ps must comply with Part 1271 provisions for donor screening and testing and current good manufacturing practices, but they

²⁷⁴ U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: REGULATION OF HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/PS)—SMALL ENTITY COMPLIANCE GUIDE 4 (Aug. 2007), <https://www.fda.gov/media/70689/download> [<https://perma.cc/G6TD-746D>] [hereinafter FDA, GUIDANCE FOR INDUSTRY: REGULATION OF HUMAN CELLS]. Some products derived from column one substances are regulated as devices composed of human tissues as are some combination products, e.g., corneal lenticules, preserved umbilical cord vein grafts, and human collagen. *FDA Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/PS) Product List*, U.S. FOOD & DRUG ADMIN. (Feb. 1, 2018), <https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products/fda-regulation-human-cells-tissues-and-cellular-and-tissue-based-products-hctps-product-list> [<https://perma.cc/JNA5-YUUM>].

²⁷⁵ For list of Section 351 approved products, see Kazuo Yano, Alessandra T. Speidel & Masayuki Yamato, *Four Food and Drug Administration Draft Guidance Documents and the REGROW Act: A Litmus Test for Future Changes in Human Cell- and Tissue-Based Products Regulatory Policy in the United States?*, 12 J. TISSUE ENG'G & REGENERATIVE MED. 1579, 1588–89 (2018).

²⁷⁶ See FDA, GUIDANCE FOR INDUSTRY: REGULATION OF HUMAN CELLS, *supra* note 274.

²⁷⁷ 21 C.F.R. § 1271.1(b) (2020).

must also comply with separate regulations for registration,²⁷⁸ adverse event reporting,²⁷⁹ labeling,²⁸⁰ and inspections²⁸¹ as biologics.

Establishments that manufacture HCT/Ps must register and submit to FDA a list of every HCT/P that is manufactured in the establishment.²⁸² The registration provides FDA with a list of facilities that it may then inspect to ensure compliance with all regulations.²⁸³ The screening, testing, and good tissue practices requirements are arguably the most essential regulatory components. All cell or tissue donors must be screened for risk factors of relevant communicable disease.²⁸⁴ Such screening includes a medical history, physical exam, and medical record review of the donor.²⁸⁵ In addition to donor screening, the specimen to be donated must also be tested for specific diseases.²⁸⁶ Testing must be done in a CLIA²⁸⁷ approved laboratory or equivalent facility as determined by the Centers for Medicare and Medicaid Services, and the tests must be “FDA-licensed, approved, or cleared donor screening tests.”²⁸⁸

“Good Tissue Practice” refers to the recovery, processing, storage, labeling, packaging, and distribution of HCT/Ps.²⁸⁹ Each of these tasks must be done in a way that “prevents the introduction, transmission, or spread of communicable disease.”²⁹⁰ The focus is on ensuring not only that the cells or tissues do not contain communicable disease agents but also that they are not contaminated in the manufacturing process.²⁹¹ The regulations include requirements for facilities, environmental controls, processing equipment, supplies, and reagents as well as for each aspect of the manufacturing and

²⁷⁸ Section 351 manufacturers must “register and list their products in accordance with 21 C.F.R. pt. 207 or 807, as applicable, rather than 21 C.F.R. pt. 1271.” *Biologics Establishment Registration*, U.S. FOOD & DRUG ADMIN. (Jan. 27, 2021), <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-establishment-registration> [https://perma.cc/S6GC-H7UB].

²⁷⁹ See 21 C.F.R. § 312.32 (2020) (IND safety reporting); 21 C.F.R. § 312.64 (2020) (Investigator reports); 21 C.F.R. § 600.80 (2020) (Postmarketing reporting of adverse experiences).

²⁸⁰ 21 C.F.R. §§ 610.60–610.68 (2020).

²⁸¹ In order to reduce the burden on FDA for facility inspections, the agency revised its regulations requiring biennial inspection of biological product establishments and instead requires that FDA inspect such establishments in accordance with a risk-based schedule established by the agency. See *Removal of Certain Time of Inspection and Duties of Inspector Regulations for Biological Products*, 84 Fed. Reg. 12,505, 12,505 (Apr. 2, 2019).

²⁸² 21 C.F.R. § 1271.25(b) (2020).

²⁸³ 21 C.F.R. § 1271.400(a) (2020).

²⁸⁴ The specific diseases differ with the type of HCT/P being transplanted, but all donors must be screened for HIV; Hepatitis B and C; human transmissible spongiform encephalopathy, including Creutzfeldt-Jakob disease; *Treponema pallidum*; and communicable disease risks associated with xenotransplantation. 21 C.F.R. § 1271.75(a) (2020). Evidence of other diseases are specified for donors of viable, leukocyte-rich cells or of reproductive cells or tissues. See 21 C.F.R. § 1271.75(b)–(c) (2020).

²⁸⁵ 21 C.F.R. § 1271.75 (2020).

²⁸⁶ See 21 C.F.R. § 1271.85 (2020).

²⁸⁷ CLIA refers to the Clinical Laboratory Improvement Amendments of 1988, 42 U.S.C. § 263a. Laboratories must satisfy the statutory requirements under CLIA as well as the relevant FDA regulations, i.e., 42 C.F.R. pt. 493 (2020).

²⁸⁸ 21 C.F.R. § 1271.80(c) (2020).

²⁸⁹ 21 C.F.R. § 1271.150(a) (2020).

²⁹⁰ 21 C.F.R. § 1271.145 (2020).

²⁹¹ 21 C.F.R. § 1271.150(b) (2020).

distribution process.²⁹² Manufacturers must also track each HCT/P so that, in case of an adverse event, the root cause may be investigated.²⁹³ Finally, Part 1271 has provisions allowing FDA to inspect facilities engaged in manufacturing 361 HCT/Ps and authorizing orders of retention, recall, destruction, and cessation of manufacturing if FDA has reasonable grounds to believe that an HCT/P is in violation of any regulation.²⁹⁴

An HCT/P that meets the criteria for regulation *solely* under Section 361 of the PHS Act and the regulations in 21 C.F.R. Part 1271 is not subject to premarket clearance or approval.²⁹⁵ On the other hand, HCT/Ps that have characteristics of a biologic or drug product are subject to an additional layer of regulation under Section 351 of the PHS Act and under Section 505B of the Federal Food, Drug and Cosmetic Act (FDCA) governing biologics.²⁹⁶ These products must undergo extensive clinical trials to establish safety and effectiveness and to obtain FDA approval of a Biologics License Application (BLA).²⁹⁷ This difference is of major import to manufacturers of HCT/Ps given the significant cost and time of preparation and approval of a BLA.

²⁹² *Id.*

²⁹³ See 21 C.F.R. § 1271.290 (2020) for tracking requirements.

²⁹⁴ See 21 C.F.R. §§ 1271.400, 1271.440 (2020).

²⁹⁵ FDA, GUIDANCE FOR INDUSTRY: REGULATION OF HUMAN CELLS, *supra* note 274, at 3.

²⁹⁶ 21 U.S.C. § 355 note (2010) (Data Requirements for Drugs and Biologics).

²⁹⁷ *Id.*

Table 2 compares requirements for the alternative regulatory pathways for stool.

TABLE 2: Regulatory Requirements for Stool under Section 361 and 351 Products, Biologics, Blood, and Enforcement Discretion (ED)

Regulatory Requirements	Section 361 HCT/P	Section 351 HCT/P	Biologic (non HCTP)	Blood	ED
Registration and Submission of a list of all Products to FDA	21 C.F.R. Part 1271 Subpart B	21 C.F.R. § 207	21 C.F.R. § 207	21 C.F.R. Part 607	No
Donor Screening and Testing	21 C.F.R. Part 1271 Subpart C	21 C.F.R. Part 1271 Subpart C (as per 21 C.F.R. 210.1 (c))	No (specified as part of clinical trial)	21 C.F.R. § 640.5	No
Current Good Manufacturing Practices	21 C.F.R. § 1271 Subpart D *	21 C.F.R. § 210.1 (also applicable are 1271 Subpart D; and Parts 211, 225, & 226)	21 C.F.R. Part 210	21 C.F.R. Part 606	No
Clinical Trials to Determine Safety and Effectiveness as Part of BLA	No	21 C.F.R. § 601.2	21 C.F.R. § 601.2	No	No
Labeling and Adverse Event Reporting	Reporting: 21 C.F.R. § 1271.350; Labeling: 21 C.F.R. § 1271.370 **	Reporting: 21 C.F.R. § 314.80; Labeling: 21 C.F.R. Part 201	Reporting: 21 C.F.R. § 314.80; Labeling: 21 C.F.R. Part 201	Reporting: 21 C.F.R. § 606.170; Labeling: 21 C.F.R. § 606.121	No
Inspection and Enforcement	21 C.F.R. § 1271 Subpart F	21 C.F.R. § 601.20(d)	21 C.F.R. § 601.20(d)	21 C.F.R. Part 607	No

**Applies only to nonreproductive 361 HCT/Ps with the exception of 21 C.F.R. § 1271.150(c)²⁹⁸ and § 1271.155,²⁹⁹ which apply to all 361 HCT/Ps.*

***Do not apply to reproductive HCT/Ps.*

To be considered a Section 361 only HCT/P, the product must be: 1) minimally manipulated; 2) intended for homologous use as determined by labeling and advertising; 3) manufactured in such a way that it does not involve combination with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent (not raising new clinical safety concerns for the HCT/P); and 4) not have a systemic effect on the body nor be dependent upon the metabolic activity of living cells for its primary function.³⁰⁰ If the product has such an effect, it must be intended for autologous use or allogenic use in first- or second-degree relatives³⁰¹ or for reproductive use.³⁰²

The definitions of “minimal manipulation” and “homologous use” have been the subject of considerable confusion as well as the subject of more than one FDA Guidance document.³⁰³ For cells and nonstructural tissues, as stool would be, minimal manipulation is defined as “processing that does not alter the relevant biological characteristics of cells or tissues.”³⁰⁴ In Guidance, FDA has said that more than minimal processing is of concern as it raises the possibility of increased safety risks and reduced effectiveness “because there would be less basis on which to predict the product’s function after transplantation.”³⁰⁵ Thus, FDA considers whether an HCT/P is minimally manipulated by evaluating the effect of the manufacturing process “on the original relevant characteristics of the HCT/P as the HCT/P exists in the donor,” rather than on its intended use in the recipient.³⁰⁶

²⁹⁸ This section states, among other things:

If you are the establishment that determines that an HCT/P meets all release criteria and makes the HCT/P available for distribution, whether or not you are the actual distributor, you are responsible for reviewing manufacturing and tracking records to determine that the HCT/P has been manufactured and tracked in compliance with the requirements of this subpart and subpart C of this part and any other applicable requirements.

21 C.F.R. § 1271.150(c)(2) (2020).

²⁹⁹ This section permits approved exemptions or alternatives to any requirement in subpart C or D of 21 C.F.R. § 1271 (2020).

³⁰⁰ 21 C.F.R. § 1271.10(a) (2020).

³⁰¹ 21 C.F.R. § 1271.10(a)(4)(ii)(a)–(b) (2020). FDA defines first-degree blood relatives as parents, children, and siblings, and second-degree blood relatives as aunts, uncles, nieces, nephews, first cousins, grandparents, and grandchildren. Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5,447, 5,454 (Jan. 19, 2001). The policy is intended to reduce the regulatory burden of acquiring human leukocyte antigen (HLA)-matched HCT/P from related individuals, especially when “it is extremely difficult to find an appropriate unrelated donor” within certain ethnic groups. This policy justification, however, is not applicable to relatives by marriage or adoption and is “weaker for blood relatives beyond the second degree.” *Id.*

³⁰² 21 C.F.R. § 1271.10(a)(4)(ii)(c) (2020).

³⁰³ FDA published its most recent interpretation of the terms in Guidance dated July 2020. FDA, REGULATORY CONSIDERATIONS FOR HCT/PS, *supra* note 88.

³⁰⁴ 21 C.F.R. § 1271.3(f)(2) (2020).

³⁰⁵ FDA, REGULATORY CONSIDERATIONS FOR HCT/PS, *supra* note 88, at 7.

³⁰⁶ *Id.*

Homologous use means the “repair, reconstruction, replacement, or supplementation of a recipient’s cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.”³⁰⁷ Similar to its concerns about minimal manipulation, FDA believes there would be increased possibilities for lowered safety and effectiveness for HCT/Ps that are not intended for a homologous use because of the difficulty of predicting the product’s behavior in the recipient.³⁰⁸ In contrast, FDA believes that HCT/Ps for homologous use “can reasonably be expected to function appropriately (assuming all of the other criteria are also met).”³⁰⁹ FDA has also stated in Guidance that if an HCT/P is intended to treat a variety of diseases or conditions but has not been proven effective, it would not be considered as intended only for homologous use.³¹⁰

FDA finalized its regulatory approach to HCT/Ps in 2004.³¹¹ Until 2018 and the passage of the 21st Century Cures Act, the regulation of HCT/Ps remained largely unchanged.³¹² Some efforts at change, however, were brought forward by members of Congress who were concerned about slowing developments in stem cell treatment and regenerative medicine.³¹³ These policymakers proposed legislation that would loosen the regulatory reins on this emerging field. Specifically, the REGROW Act would have permitted stem cell treatments with demonstrated evidence of safety and “reasonable expectation of efficacy” to waive Phase III clinical testing.³¹⁴ These products would not receive a BLA but would be permitted to go on the market for conditional use for five years as long as the manufacturer submitted adverse event reports during that time.³¹⁵

The proposed legislation was widely criticized because it required FDA to disapprove the therapy once it had been put on the market if it received notice of adverse events indicating lack of safety rather than deny it a license prior to

³⁰⁷ *Id.* at 4.

³⁰⁸ U.S. FOOD & DRUG ADMIN., PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS 19 (Feb. 28, 1997), <https://www.fda.gov/media/70704/download> [<https://perma.cc/NWT3-BSV6>] [hereinafter FDA, PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS].

³⁰⁹ *Id.*

³¹⁰ FDA, REGULATORY CONSIDERATIONS FOR HCT/Ps, *supra* note 88, at 4 n.7 (citing “promotion of an HCT/P for an unproven therapeutic use, such as curing cancer, would clearly make it inappropriate to regulate the HCT/P solely under section 361 of the PHS Act and the regulations that will be in part 1271,” Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5,447, 5,458 (Jan. 19, 2001)).

³¹¹ *See* Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement, 69 Fed. Reg. 68,612, 68,612 (Nov. 24, 2004).

³¹² Barbara A. Binzak Blumenfeld, *FDA Sharpens its Focus on Regenerative Medicine Regulation*, FOOD & DRUG L. INST. (July/Aug. 2017), <https://www.fdi.org/2017/08/fda-sharpens-focus-regenerative-medicine-regulation/> [<https://perma.cc/49C4-DSMJ>].

³¹³ Andrew Joseph & Sheila Kaplan, *After Criticism from Scientists, Congress Eases its Pursuit of Faster Stem Cell Therapies*, STAT (Nov. 30, 2016), <https://www.statnews.com/2016/11/30/stem-cells-cures-act/> [<https://perma.cc/ZUU2-JRMF>].

³¹⁴ REGROW Act, S. 2689, 114th Cong. (2016).

³¹⁵ Margaret F. Riley, *A RAT by Another Name: 21st Century Cures Act and Stem Cell Therapies*, 44 AM. J.L. & MED. 291, 298 (2018). “Within 5 years of the safety and effectiveness determination described in this section, the sponsor of the conditionally approved new product prepares and submits an application for approval of a biological product under section 351(a), demonstrating potency, purity, safety, and efficacy of the use.” REGROW Act, *supra* note 314.

marketing.³¹⁶ Although the bill did not pass, the possibility of an “accelerated pathway” for regenerative medicine therapies was included in the 21st Century Cures Act.³¹⁷ One aspect of this accelerated route to approval is the use of “real world evidence” or observational data arising from clinical use rather than prospective randomized controlled trials.³¹⁸

i. Cord Blood—Regulation as a Section 351 and 361 HCT/P

Another option that has been suggested as a model for regulation of stool is the regulatory pathway for cord blood.³¹⁹ Umbilical cord blood (UCB) contains stem cells referred to as “hematopoietic progenitor cells (HPCs).”³²⁰ These cells are responsible for continually producing the blood cells in our bodies.³²¹ In the 1980s, researchers discovered that by transplanting HPC cord blood they could successfully regenerate blood and immune system cells.³²² The first transplant of UCB was performed in 1988, and the first public cord blood bank in the United States was established in 1992 with funding from NIH.³²³ Subsequently, NIH allocated \$30 million to establish a network of public cord blood banks that would operate under a “research protocol addressing optimal methods of cord blood collection and storage.”³²⁴ Between 1988 and 2019, approximately 40,000 cord blood transplants had been performed across the globe.³²⁵

The proliferation of these banks included both public and private facilities. Public banks are not-for-profit entities that do not charge for storage and maintenance of cord blood and that serve the needs of the general public.³²⁶ Private banks are for-profit

³¹⁶ Riley, *supra* note 315, at 154–55.

³¹⁷ *Id.* at 299.

³¹⁸ *Id.* at 299, 301.

³¹⁹ See Sachs & Edelstein, *supra* note 1, at 409.

³²⁰ *Hematopoietic Progenitor Cells, Cord Blood (Intravenous Route)*, MAYO CLINIC (Feb. 1, 2021), <https://www.mayoclinic.org/drugs-supplements/hematopoietic-progenitor-cells-cord-blood-intravenous-route/description/drg-20061187> [<https://perma.cc/D8GU-VZQ5>].

³²¹ *Id.*

³²² Jennifer L. Schenk, *Rethinking FDA’s Draft Document on Cord Blood Stem Cell Products*, 8 MD. J. CONTEMP. LEGAL ISSUES 151, 156 (1997). “The Wagner study legitimized the use of cord blood-derived stem cells as a viable alternative to bone marrow or peripheral blood stem cell transplantation. Indeed, the use of cord blood stem cells offers certain immediate advantages over its counterparts. For example, the use of cord blood eliminates the need for highly invasive and painful harvesting procedures associated with bone marrow transplantation.” *Id.*

³²³ Kulynych, *supra* note 166, at 408, 414.

[T]he immediate clinical utility of cord blood was such that in 1992, the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) decided to fund a pilot cord blood bank at the New York Blood Center. This study provided the initial evidence that cord blood could feasibly be harvested, stored and transplanted between unrelated child donors and recipients.

Id. at 414. See also Joan Stephenson, *Terms of Engraftment: Umbilical Cord Blood Transplants Arouse Enthusiasm*, 274 JAMA 1813, 1814 (1995).

³²⁴ Kulynych, *supra* note 166, at 414.

³²⁵ Ashish O. Gupta & John E. Wagner, *Umbilical Cord Blood Transplants: Current Status and Evolving Therapies*, 8 FRONTIERS PEDIATRICS 1, 1 (2020).

³²⁶ *Cord Blood Banking*, AM. COLL. OBSTETRICIANS & GYNECOLOGISTS, <https://www.acog.org/patient-resources/faqs/pregnancy/cord-blood-banking> (last updated Feb. 2021) [<https://perma.cc/7CHK-TQKP>].

companies and charge parents an annual fee to store and maintain their child's cord blood for possible future use by the child or other members of the patient's family.³²⁷ In the early days of their existence, private banks touted their advantages and attempted to persuade parents of the value of private cord blood banking. Some referred to these actions as "manipulative" marketing.³²⁸ In response, FDA received numerous complaints from parents and researchers, and, in 1996, the agency proposed a regulatory scheme for cord blood banks³²⁹ which called for regulating cord blood like new drugs requiring an IND and conduct of extensive clinical trials.³³⁰ Until such trials could be completed, the agency would permit cord blood banking in nonprofit banks under protocols that had been approved by FDA.³³¹ The proposal was highly controversial. A campaign of newspaper editorials and letters to Congress ensued with many written by panicked parents who were convinced that FDA regulation would destroy the seemingly magical potential of cord blood banking.³³² Public protest, lobbying on the part of industry,³³³ and congressional scrutiny led FDA to include cord blood transplantation in its efforts at regulatory reform.³³⁴

In 1997, FDA proposed a carve-out from the IND requirements for cord blood banking and transplantation intended for autologous use or use in a "first degree blood

³²⁷ *Id.*

³²⁸ Kulynych, *supra* note 166, at 409, 448 (observing that "[o]ne of the more controversial marketing practices in commercial cord blood banking [was] the mailing of unsolicited promotional videos to expectant parents. The content of such materials, which exhort[ed] parents to make the 'potentially lifesaving' decision to store their infant's cord blood, for fees typically amounting to more than \$1,000 plus additional yearly charges, exploit[ed] parents' most basic fears for the health of a newborn child.'").

³²⁹ *Id.* at 415–16 (citing U.S. FOOD & DRUG ADMIN., DRAFT DOCUMENT CONCERNING THE REGULATION OF PLACENTAL/UMBILICAL CORD BLOOD STEM CELL PRODUCTS INTENDED FOR TRANSPLANTATION OR FURTHER MANUFACTURE INTO INJECTABLE PRODUCTS (FDA Docket No. 96N-0002) (Feb. 26, 1996)).

³³⁰ This regulatory requirement was more stringent than that for peripheral blood-derived stem cells, which only required compliance with more onerous regulations if more than minimally manipulated. For cord blood-derived stem cells, the draft regulations required compliance with the full panoply of new drug regulations without regard to degree of manipulation. Kulynych, *supra* note 166, at 424–25.

³³¹ *Id.* at 416.

³³² *Parents Frightened by FDA Blood Rules*, TAMPA BAY TIMES (Sept. 16, 1996), <https://www.tampabay.com/archive/1996/06/16/parents-frightened-by-fda-blood-rules/> [<https://perma.cc/J7UT-XHHW>].

³³³ Industry commenters argued that the drug regulatory framework would stifle innovation and development of the new technology. Instead, they supported FDA oversight of the quality and safety of cord blood storage facilities. Many proposed the "use of establishment registration and inspectional oversight and advocated the use of industry standards." Schenk, *supra* note 322, at 168. Some went further "by advocating the use of Good Manufacturing Practices and the collection of follow-up data to better ensure the safety of cord blood products." *Id.* at 169.

Additionally, several private industry trade organizations . . . argued that only extensively manipulated cord blood stem cell products should be subject to the IND requirements. Minimally manipulated cord blood stem cell products [they argued], should not be regulated as a biological drug product at all but rather, should fall within the practice of medicine.

Id.

³³⁴ Kulynych, *supra* note 166, at 409. Those who supported the 1996 proposal argued that the use of UCB for transplantation was still relatively new, that the earliest recipients of the transplants had lived less than ten years after the transplant, and that "the risk of potential complications continues throughout a transplant recipient's lifetime." *Id.* at 430–31.

relative.”³³⁵ Cord blood for these purposes would need to comply with FDA requirements for cord blood storage and handling.³³⁶ Cord blood for all other uses would be regulated under the traditional new drug regulatory framework.³³⁷ This new regulatory proposal was part of FDA’s larger effort to regulate all human tissue.³³⁸ It allowed for ongoing clinical development but also allowed “significant commercialization of cord blood storage” despite many concerns about the “safety, efficacy, and ethics” of this new therapy.³³⁹

In 2001, when implementing the final rule for facility registration and listing under the regulations for HCT/Ps, FDA also broadened the permitted intended use for cord blood that would be regulated solely under Section 361 of the PHS Act to include cord blood for “second-degree blood relatives.”³⁴⁰ Thus, as part of the regulatory framework for HCT/Ps, cord blood hematopoietic stem cells for blood regeneration would be regulated differently depending on whether or not it met the four criteria³⁴¹ that determine whether a product is a Section 351 or Section 361 HCT/P. The two-track framework meant that public banks would be subject to licensure and private banks to the regulations for Section 361 *only* products under the PHS Act. In 2009, FDA put in place a two-year-phase-in period for public HPC Cord Blood manufacturers to submit a BLA or an IND to the agency.³⁴² The first license for HPC cord blood transplantation was granted in December 2011 to New York Blood Center for its product, “Hemacord.”³⁴³ The approval was based on safety and efficacy data that had been submitted to a public docket along with data submitted in the BLA.³⁴⁴

Although some public cord blood banks have received a license, many have not due to the significant regulatory burden associated with obtaining a biologics license³⁴⁵

³³⁵ FDA, PROPOSED APPROACH TO REGULATION OF CELLULAR AND TISSUE-BASED PRODUCTS, *supra* note 308.

³³⁶ *Id.*

³³⁷ *Id.*

³³⁸ *See supra* Section IV.B.1 (discussing the regulation of human cells and tissue).

³³⁹ Kulynych, *supra* note 166, at 416. Such ethical questions included those of privacy and informed consent because the donating mother must provide information about her sexual history as well as agree to genetic testing. *Id.* at 437. *See also* Jerry Sugarman, Emily G. Reisner & Joanne Kurtzberg, *Ethical Aspects of Banking Placental Blood for Transplantation*, 274 JAMA 1783 (1995).

³⁴⁰ Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5,447, 5,450 (Jan. 19, 2001).

³⁴¹ *See supra* notes 300–02 and accompanying text.

³⁴² *See* Guidance for Industry: Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution for Specified Indications; Availability, 74 Fed. Reg. 53,753, 53,753 (Oct. 20, 2009).

³⁴³ *FDA Approves New York Blood Center’s HEMACORD™ for Stem Cell Transplantation*, CISION (Nov. 10, 2011, 5:02 PM), <https://www.prnewswire.com/news-releases/fda-approves-new-york-blood-centers-hemacord-for-stem-cell-transplantation-133646483.html> [<https://perma.cc/T39E-84MQ>]. Cord blood has only been approved by FDA for “hematopoietic stem cell transplantation.” *Cord Blood Banking—Information for Consumers*, U.S. FOOD & DRUG ADMIN. (July 23, 2012), <https://www.fda.gov/vaccines-blood-biologics/consumers-biologics/cord-blood-banking-information-consumers>.

³⁴⁴ *Patient Overview*, HEMACORD, <http://hemacord.info/patients/> [<https://perma.cc/39QF-688Q>] (last visited July 2, 2021).

³⁴⁵ As of February 1, 2019, only eight public cord banks had received a license. *FDA BLA, PARENT’S GUIDE TO CORD BLOOD FOUND.*, <https://parentsguidecordblood.org/en/accreditation/fda-bla#:~:text=The%>

and, presumably, the lack of venture capitalists willing to provide funding to a public bank. These unlicensed banks have been permitted to continue operating as long as they do so under the auspices of an IND and are making progress towards licensure.³⁴⁶

2. *Application of the HCT/P Regulatory Framework to Stool*

Stool product used for FMT would likely be considered both minimally manipulated and intended for homologous use.³⁴⁷ In order to prepare the product, the stool is mixed with saline, and in some cases a preservative, and then frozen and thawed—all procedures that do not alter the relevant biological characteristics of its cells or tissues.³⁴⁸ Thus, it would be minimally manipulated. Stool product used for FMT would also be for homologous use because FMT aims to repair, reconstruct, or replace the dysfunctional and dysbiotic gut microbiome of the recipient with that of the donor.³⁴⁹ The stool product is obtained from the GI tract of the donor and transferred to the GI tract of the recipient with the goal of providing the beneficial function of the donor's gut microbiome to the recipient whose gut microbiome lacks the beneficial function.³⁵⁰ Stool donors are selected because their gut microbiome likely has some positive attribute, and it is this same attribute that one is trying to transfer to the recipient through FMT.³⁵¹ Examples of such attributes include resistance to rCDI or a propensity not to trigger the immune system.³⁵²

Stool for transplant (SFT) also meets the third criterion for an HCT/P, i.e., not combined with another substance that could raise safety concerns, because it is simply combined with saline, and glycerol when stored frozen, before insertion into the recipient.³⁵³ Since FMT will have a systemic effect on the body and will be dependent upon the metabolic activity of living cells for its primary function, whether or not SFT meets the fourth criterion³⁵⁴ depends on whether it is intended for use in a first- or second-degree blood relative. In some cases, FMT is performed using stool from a donor closely related to the recipient.³⁵⁵ However, in the large majority of cases in the United States, FMT performed by physicians has been done using stool product from OpenBiome or a hospital stool bank. In these cases, the donor is unlikely to be related to the patient.³⁵⁶

20FDA%20BLA%20license%20creates,blood%20inventory%20is%20not%20licensed_(last visited Nov. 24, 2021) [<https://perma.cc/C5DN-3DN7>].

³⁴⁶ *Id.*

³⁴⁷ *But see* Margaret F. Riley & Bernat Olle, *FDA's Pathway for Regulation of FMT: Not So Fraught*, 2 J.L. & BIOSCIENCES 742, 745 (2015) (stating that the definitions leave room for a good deal of subjective judgment).

³⁴⁸ *See supra* note 6 and accompanying text.

³⁴⁹ *See supra* note 33 and accompanying text.

³⁵⁰ *See supra* note 34 and accompanying text.

³⁵¹ Bakken et al., *supra* note 31, at 1046.

³⁵² *Id.*

³⁵³ *See supra* note 6 and accompanying text.

³⁵⁴ FDA has not yet promulgated regulatory definitions for the terms “systemic effect” and “metabolic activity,” thus the meanings are open to interpretation. 21 C.F.R. § 1271.3 (2020).

³⁵⁵ Ramai, *supra* note 8, at 31.

³⁵⁶ *Id.*

The criterion that the product be intended for use in a first- or second-degree relative was established primarily for the use of cord blood.³⁵⁷ Whether the requirement makes sense in the context of stool is highly questionable. In the case of cord blood, blood, or structural tissue transplant, there is a risk that the recipient will generate antibodies in response to the donor blood or tissue.³⁵⁸ All transplanted human tissues have human leukocyte antigen (HLA) proteins that, if unrecognized by the recipient, may result in an adverse immune response.³⁵⁹ First- or second-degree relatives often share many of the same HLA proteins and, hence, are better able to exchange blood and tissues without causing an immunological reaction.³⁶⁰ Stool, however, does not have the same properties, and stool from an unrelated donor is unlikely to result in an immune reaction by the recipient.³⁶¹ In addition, in some cases physicians have asserted that it does not make sense to use family members as donors for SFT because 1) family members may be less truthful when answering questions about risk factors for transmissible diseases, such as not disclosing intravenous drug use or high-risk sexual behaviors; and 2) they may share familial or household risk factors for the condition being treated with FMT.³⁶²

3. *Arguments for Regulating Stool for rCDI and Stool Banks Under the HCT/P Regulatory Framework*

Regulating stool as human tissue has been the most discussed alternative to regulating stool as a drug or biologic.³⁶³ Despite FDA's decision that stool is not human tissue, a number of persuasive arguments can be made as to why it could or should be treated as human tissue. For example, given that human stool is made up significantly of bacteria and other microorganisms from the human gut, Kelly and Khoruts have argued that it should be considered *human* tissue as it "has co-evolved with the human host" and is "distinguishable even from that of other primates." Further, they argue that "[f]undamentally, FMT is an approach to repair damaged

³⁵⁷ Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, 66 Fed. Reg. 5,447, 5,450 (Jan. 19, 2001).

³⁵⁸ Colin J. Brown & Cristina V. Navarrete, *Clinical Relevance of the HLA System in Blood Transfusion*, 101 VOX SANGUINIS 93, 95 (2011).

³⁵⁹ *Id.*

³⁶⁰ Jean-Marie Tiercy, *How to Select the Best Available Related or Unrelated Donor of Hematopoietic Stem Cells?*, 101 HAEMATOLOGICA 680, 680 (2016).

³⁶¹ Stool is composed of 75% water and 25% solid matter comprised of undigested food matter, chemicals, and cellular debris. *Feces Biology*, BRITANNICA (June 14, 2002), <https://www.britannica.com/science/feces> [<https://perma.cc/9ZML-MVY2>]. HLA molecules, in contrast, are transmembrane proteins expressed on the surface of nucleated (i.e., living) cells. Peter J. Delves, *Human Leukocyte Antigen (HLA) System*, MERCK MANUAL PROF. VERSION (Apr. 2020), <https://www.merckmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/human-leukocyte-antigen-hla-system> [<https://perma.cc/EVF6-XNUG>].

³⁶² At the November 4, 2019, Part 15 Hearing, Dr. Stacy Kahn, a pediatric gastroenterologist, testified that "As an IBD specialist . . . I do not want family members donating for my patients who have underlying IBD, family members may share familiar [sic] risk factors from FMT and in fact, may not be ideal donors in any circumstances." PART 15 HEARING, *supra* note 121 (statement of Stacy Kahn).

³⁶³ See Sachs & Edelstein, *supra* note 1; Riley & Olle, *supra* note 347; Summary Report, *Meeting of the Competent Authorities for Tissues and Cells*, EUR. COMM'N DIR.-GEN. HEALTH & FOOD SAFETY (Dec. 3-4, 2014), https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/ev_20141203_sr_en.pdf [<https://perma.cc/K6TZ-YB9X>] [hereinafter EUR. COMM'N, Summary Report].

tissue using healthy donor material.”³⁶⁴ Moreover, FDA has determined that, although secreted body fluids (e.g., amniotic fluid, milk, semen, collagen, and cell factors), with the exception of semen, are not considered HCT/Ps, *cells* from secreted body fluids are generally considered HCT/Ps.³⁶⁵

When asked to determine the regulatory status of feces, the European Union’s Commission Directorate-General for Health and Food Safety’s Competent Authorities for Tissues and Cells determined that feces are a combination product containing cells and other substances and are uncontestedly of human origin.³⁶⁶ For “combination products,” however, the cellular or tissue component must be the “active component” in any therapy and, because the human cells in feces are not the active substance in the recipient, feces “do not fall within the scope of the EU [Tissue and Cell] legislation.”³⁶⁷ As a result, EU member states have been free to determine what type of regulatory framework they will apply. This can include creating a unique regulatory framework for stool or “applying one of the existing legislative frameworks, including the tissues and cells quality and safety requirements.”³⁶⁸ Recently, researchers in Europe have called for regulation under the EU Tissue and Cells Directive (2004/23/EC) asserting it “best suited to guide FMT.”³⁶⁹ Regulation of feces is still evolving in Europe, but, as of early 2020, at least three European countries and Australia regulated stool for FMT as a tissue.³⁷⁰

V. IS THE DEATH OF THE INDEPENDENT NONPROFIT STOOL BANK INEVITABLE OR IS THERE A LIFE-SUSTAINING OPTION?

OpenBiome, one could say, was destined for a short life when FDA announced its intent to require independent non-hospital-based stool banks to operate under an IND. Although it allowed the INSB to operate under enforcement discretion for almost a decade, its stated plan in 2016 was to eliminate enforcement discretion for all but hospital-based stool banks.³⁷¹ Such a requirement would have made it virtually impossible for a nonprofit entity to survive. As stated *supra*, numerous obstacles stand in the way of stool, as prepared by OpenBiome, from going through the IND process

³⁶⁴ Letter from Colleen Kelly and Alexander Khoruts, co-signed by FMT listserv, to Scott Gottlieb, M.D., Commissioner U.S. Food and Drug Admin. (Jan. 14, 2019).

³⁶⁵ FOOD & DRUG ADMIN., *supra* note 88, at 15.

³⁶⁶ EUR. COMM’N, Summary Report, *supra* note 363, at 3.

³⁶⁷ *Id.* See also Merrick et al., *supra* note 15, at 4.

³⁶⁸ EUR. COMM’N, Summary Report, *supra* note 363, at 4.

³⁶⁹ Keller et al., *supra* note 174, at 1409.

³⁷⁰ The European countries include the Netherlands, Belgium, and Italy. See Merrick et al., *supra* note 15. See also Alyce Maksoud, *The Regulation of Faecal Microbiota Transplantation (FMT)*, AUSTL. GOV’T DEP’T OF HEALTH THERAPEUTIC GOODS ADMIN. (Nov. 2019), <https://www.tga.gov.au/sites/default/files/presentation-the-regulation-of-faecal-microbiota-transplantation.pdf> [<https://perma.cc/JJA4-HJ2N>]. In these countries, there is a risk-based regulatory framework where the low risk tier “covers tissues and cells that are not ‘substantially manipulated’” and the high risk tier covers products “subject to additional processes and manipulation.” Merrick et al., *supra* note 15, at 3. See also Alexandra Scheeler, *Where Stool is a Drug: International Approaches to Regulating the use of Fecal Microbiota for Transplantation*, 47 J.L., MED. & ETHICS 524 (2019).

³⁷¹ FDA, ENFORCEMENT POLICY (Mar. 2016), *supra* note 14, at 1.

without “additional characterization and release specifications and greater control of the manufacturing process.”³⁷² Moreover, a nonprofit company will not have the resources to support the significant expense of the application process and the required clinical trials.

Without significant modification to the IND requirements, a nonprofit stool bank such as OpenBiome could not survive. While OpenBiome never got to the point where FDA required it to obtain an IND, it was instead forced to stop distributing new stool for FMT due to the COVID-19 pandemic and the discovery that the virus could be detected in the stool of infected individuals.³⁷³ The nonprofit decided to halt provision of stool collected after December 1, 2019 until a test for the SARS-CoV-2 virus in stool could be developed and approved to test its backlog of stool product.³⁷⁴ During this time, OpenBiome made stool for FMT to treat rCDI available only for emergency use from inventory collected prior to December 1, 2019.³⁷⁵

As a result of its decreased revenue and increased operating costs during the pandemic, OpenBiome was unable to cover its fixed costs.³⁷⁶ Moreover, the company believed that FDA would soon approve a drug product that would be an alternative to FMT and demand for its product would significantly decline.³⁷⁷ As a result, in spring 2021, OpenBiome decided to phase out its “production of additional stool product” and sell its “equipment and other manufacturing assets.”³⁷⁸

When new stool-derived microbiota-based drugs are approved by FDA, stool product from stool banks for FMT to treat rCDI may no longer be necessary. It is possible, however, that the natural (raw) stool product may be more effective, or more effective for some populations, than the FDA-approved alternatives. In addition, researchers may find that the natural stool product is effective for other indications for which we currently have no cure or effective treatment and for which the newly approved drugs/biologics are not effective. Stool and an FMT will likely be less expensive than the newly approved biologics as biologics are among the most expensive therapeutics on the market. Based on these assumptions, we argue that there is good reason to continue not only to allow stool banks, specifically INSBs, to operate but also to support their doing so in a way that provides assurances that their product will be safe and effective.

A. Potential Paths Forward

While there are likely numerous ways in which stool and stool banks could be regulated in the future, we explore several regulatory possibilities: 1) a path that is similar to that for blood and tissue; 2) a system of decentralized hospital stool banks regulated under FDA’s enforcement discretion; and 3) alternatives under an IND.

³⁷² See *supra* note 190 and accompanying text.

³⁷³ OpenBiome Press Release, *supra* note 13.

³⁷⁴ *Id.*

³⁷⁵ *Id.*

³⁷⁶ *Id.*

³⁷⁷ *Id.*

³⁷⁸ *Id.*

1. Regulating Stool Product and Stool Banks for FMT Like Blood or HCT/Ps

Because blood is regulated as a biologic, it has all the safety benefits of that regulatory paradigm, but because it was grandfathered out of the requirements of an IND, it did not have the regulatory burden of the IND clinical trials process. Under the Biologics Efficacy Review, blood and blood components were determined to be safe and effective because of a long history of safe and effective use (with appropriate screening and good manufacturing practices).³⁷⁹ The primary focus of regulation is on preventing transmissible diseases from contaminating the blood supply and being transmitted to recipients. The blood regulatory framework specifies factors that determine donor eligibility, including when and how a facility must establish the eligibility of the donor, how the donor's medical history is to be assessed, and how a physical assessment of a donor must be performed.³⁸⁰ The regulations further require that each unit of blood is marked or identified in a way that allows it to be traced back to the individual donor³⁸¹ and that extensive records are kept detailing how samples are obtained and tracked. Each of these requirements would also be important for stool product and most would be required under the biologics framework but were not required under enforcement discretion.

The regulations for blood and blood components further specify what tests must be done on donor blood. In addition to specified tests for relevant transfusion-related infections,³⁸² the regulations specify that blood establishments must test for evidence of infection when there is an FDA-licensed and approved or cleared test available for the infection and the testing is necessary to reduce the risk of transmission of the infection.³⁸³

The blood regulations provide flexibility in that the Director of the Center for Biologics Evaluation and Research (CBER) may approve an exception or alternative procedures to any requirement in the regulations regarding blood, blood components, or blood products.³⁸⁴ This type of flexibility would also be valuable to stool product as researchers and clinicians continue to learn more about transmissible diseases/infections; the best way to prepare, administer, and store stool product for FMT; and what makes a "good" donor.

The exception granted by the Biologics Efficacy Review committee to the IND application process for blood could also be a model for stool and stool banks, i.e., stool for FMT to treat rCDI could be subject to the BLA requirements with the exception of the conduct of clinical trials. In FDA's 2016 FMT Draft Guidance, the agency permitted sponsors to request waivers of "certain IND regulations" but did not clarify what could be waived.³⁸⁵ FDA will grant waivers if it finds that the waiver "would not

³⁷⁹ Biological Products; Blood and Blood Derivatives; Implementation of Efficacy Review, 50 Fed. Reg. 52,602, 52,604 (proposed Dec. 24, 1985).

³⁸⁰ 21 C.F.R. § 630.10 (2020).

³⁸¹ 21 C.F.R. § 640.4(e) (2020).

³⁸² See *supra* note 243.

³⁸³ 21 C.F.R. § 610.40(a)(3)(i) (2020).

³⁸⁴ 21 C.F.R. § 640.120(a) (2020).

³⁸⁵ FDA, ENFORCEMENT POLICY (Mar. 2016), *supra* note 14, at 2.

pose a significant and unreasonable risk to human subjects of the investigation.”³⁸⁶ In addition, one of the following must be met: “(1) [t]he sponsor’s compliance with the requirement is unnecessary for the agency to evaluate the application, or compliance cannot be achieved; (2) [t]he sponsor’s proposed alternative satisfies the requirement; or (3) [t]he applicant’s submission otherwise justifies a waiver.”³⁸⁷

In a comment response to the proposed Industry Guidance, FDA stated that “[t]he waiver provision was intended to give applicants flexibility to seek alternative ways of complying with the regulatory requirements governing the conduct of clinical studies.”³⁸⁸ At the same time, FDA stated that it would not waive regulatory requirements, especially those concerning safety of human subjects, unless sponsors comply fully with the stated conditions justifying waivers.³⁸⁹ The takeaway seems to be that FDA will consider alternatives to certain IND requirements but will impose a high bar that a sponsor must satisfy to successfully waive requirements that might affect safety.

The use by FDA of its enforcement discretion policy arguably leads to under-regulation of stool as it does not specify any requirements for donor selection or screening, specimen testing, storage, labeling, or shipping. In contrast, hospital, laboratory, and independent blood banks that do not participate in interstate commerce are subject to accreditation by multiple organizations, including the Joint Commission, College of American Pathologists, and the American Association of Blood Banks.³⁹⁰ Many are also licensed by state health departments.³⁹¹

FDA could alternatively regulate stool similarly to how it regulates HCT/Ps under Section 361 of the PHS Act. If FDA had decided in 2012 that stool should be regulated as a human tissue, patients would likely have had similar access to FMT as they have had under FDA’s enforcement discretion policy, but greater access than under the drug/biologic framework. Certainly, that would have been the case in the short term as stool would not have been required to go through the IND process. However, it would also likely be the case going forward. As stated above, assuming new stool-derived microbiota-based drugs and biologics are licensed by FDA for treatment of rCDI in the near future, their cost would be significantly greater than that of stool for FMT regulated as a tissue, making it out of reach for some patients.

Regulating stool as a tissue might have made its cost higher than its cost under the enforcement discretion policy. Under Section 361 of the PHS Act, stool banks would have been required to meet tissue regulations for screening of donors and donor stool and required to comply with Good Tissue Manufacturing requirements.³⁹² While this was not a requirement under the enforcement discretion policy, stool banks, in

³⁸⁶ 21 C.F.R. § 312.10(b) (2020).

³⁸⁷ *Id.*

³⁸⁸ New Drug, Antibiotic, and Biologic Drug Product Regulations, 52 Fed. Reg. 8,798, 8,805 (Mar. 19, 1987).

³⁸⁹ *Id.*

³⁹⁰ Salwa Hindawi, *Systems for Accreditation in Blood Transfusion Services*, 4 ISBT SCI. SERIES 14 (2009).

³⁹¹ See, e.g., N.J. REV. STAT. § 26:2A-4 (2016); MD. CODE REGS. 10.50.01 (2021); 28 PA. CODE § 30.10 (1998).

³⁹² The HCT/P (Section 361) framework requires screening of donors and testing of the transplanted material for relevant communicable diseases. See *supra* note 284 and accompanying text.

particular OpenBiome, have engaged in self-regulation and likely in the type of screening and testing that FDA regulations would have required. As a result, the cost of stool for FMT under the enforcement discretion policy and regulation as a tissue would probably have been, or be, comparable.

The major difference between the HCT/P and biologics pathways is that the former does not require the IND process and lengthy and costly clinical trials that offer additional evidence of efficacy. This process can be viewed as a benefit as well as a cost to relevant stakeholders, but, from a policy perspective, it depends on the magnitude of the incremental benefit and cost. We argue that, based on the current data of efficacy of FMT for rCDI, the potential incremental benefit of the IND process does not outweigh the additional costs. Further, we argue that a benefit of the HCT/P framework over the biologic framework is that the latter does not allow for certain changes to the donor screening and testing regimen after premarket approval without additional clinical trials. The only exception is if the manufacturer can prove that the changes do not affect safety, identity, purity, or potency of the product.³⁹³ In contrast, the HCT/P process is nimbler and can more easily accommodate changes to the screening and testing regime.³⁹⁴

The HCT/P regulatory framework, like that for biologics, requires adverse event reporting for any communicable disease related to a transplanted product.³⁹⁵ Additionally, the HCT/P regulations require tracking of all samples and recordkeeping of donor and recipient so that investigations can be easily performed to find out the cause of any reported adverse events.³⁹⁶ This is not done for biologics.

If stool had been regulated under Section 361 only, innovation and research may also have been affected, although research on FMT would likely have continued, similar to research conducted under FDA's enforcement discretion policy.³⁹⁷ The research conducted under enforcement discretion led to new discoveries and improvements in stool product preparation and delivery and selection of donors.³⁹⁸ The research was able to continue as a result of funding by NIH, other government agencies, and foundations interested in a cure/treatment for microbiome-based diseases.³⁹⁹ On the other hand, it is possible that pharmaceutical companies would be less inclined to invest in research involving minimally manipulated stool regulated under an HCT/P (Section 361) framework. There is little incentive under the HCT/P framework for rigorous, placebo, randomized controlled trials to assess efficacy or safety issues because there is no mechanism to obtain data or market exclusivity for

³⁹³ 21 C.F.R. § 601.2(a) (2020); *see also* U.S. FOOD & DRUG ADMIN., DEMONSTRATION OF COMPARABILITY OF HUMAN BIOLOGICAL PRODUCTS, INCLUDING THERAPEUTIC BIOTECHNOLOGY-DERIVED PRODUCTS (Mar. 21, 2018), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstration-comparability-human-biological-products-including-therapeutic-biotechnology-derived> [<https://perma.cc/N8WS-LER5>]. *See also* Khoruts et al., *supra* note 3, at 488–89.

³⁹⁴ Khoruts et al., *supra* note 3.

³⁹⁵ *See supra* note 276 and accompanying text.

³⁹⁶ 21 C.F.R. § 1271.290.

³⁹⁷ *See* Khoruts et al., *supra* note 3, at 493; *supra* note 145 and accompanying text.

³⁹⁸ *Id.* at 492–93.

³⁹⁹ *Id.*

this type of product.⁴⁰⁰ Moreover, it may not be possible to obtain a patent on stool and thus achieve supra-competitive prices for a monopoly on the banked product.⁴⁰¹ In general, efforts to determine cell and tissue transplant efficacy under the HCT/P framework would likely be through small-scale clinical trials by practicing physicians or researchers (subject to IRB approval).

There is perhaps more uncertainty about whether pharmaceutical companies would have been, or would be, willing to invest in development of drugs/biologics (i.e., stool-derived microbiota-based products) to treat rCDI if stool were to have been regulated as a tissue. However, they have done so under the enforcement discretion policy even with the uncertainty of how FDA would regulate stool banks and FMT going forward.⁴⁰²

Although FDA's Tissue Reference Group rejected the idea of regulating stool for FMT as a tissue,⁴⁰³ this is at odds with the arguments of a number of researchers and physicians in both the United States and Europe who have urged regulators to consider the tissue/cell regulatory framework.⁴⁰⁴ These commenters also consider the drugs/biologics pathway to be inappropriate both because of its inability to accommodate the variability of donor-based therapies and its cost.⁴⁰⁵

Sachs and Edelstein have suggested that the regulatory framework for cord blood (an HCT/P) and cord blood banks could be a model for stool and stool banks because of its bifurcated regulatory path.⁴⁰⁶ While the line that FDA has drawn between cord blood regulated solely as an HCT/P and cord blood regulated as an HCT/P and biologic makes sense because of the immunological match necessary between the blood of the donor and recipient, regulating stool transferred from a donor to a close relative less stringently than stool from a stool bank may not be prudent. FDA seemed to be moving in that direction, however, when it issued its 2014 Draft Industry Guidance stating that it would continue to exercise its enforcement discretion for stool donated from someone known or closely related to the recipient⁴⁰⁷ while terminating its enforcement discretion for stool product from stool banks.

Sachs and Edelstein's recommendation was not based on the distinction between regulatory treatment of closely related donor and recipient and that of unrelated individuals, but rather on the precedent for regulating the same entity under two different regulatory frameworks.⁴⁰⁸ For stool, they suggest, the Section 361 regulatory

⁴⁰⁰ Sachs & Edelstein, *supra* note 1, at 402 (asserting that licensing FMT "will have the effect of granting market exclusivity to a single provider for the provision of ubiquitous human stool").

⁴⁰¹ See FitzGerald & Spek, *supra* note 204 (stating that manufacturers of FMT-based therapeutics face numerous challenges to obtaining a patent but distinguish composition and method patents).

⁴⁰² See Khoruts et al., *supra* note 3, at 486–87 (discussing the range of microbiome-based products to treat rCDI currently in clinical trials).

⁴⁰³ See *supra* note 89 and accompanying text.

⁴⁰⁴ Riley & Olle, *supra* note 347, at 744–45.

⁴⁰⁵ *Id.*

⁴⁰⁶ Sachs & Edelstein, *supra* note 1, at 410.

⁴⁰⁷ It is possible that this exception for stool from a relative or close friend of the patient was based on FDA's legitimate concern that it not regulate the practice of medicine.

⁴⁰⁸ Sachs & Edelstein, *supra* note 1, at 409.

pathway could be applied to stool used to treat rCDI and the Section 351 pathway applied to stool used for other indications.⁴⁰⁹

2. *A System of Decentralized Hospital Stool Banks*

With its 2014 and 2016 Draft Industry Guidances, FDA seemed to be laying the groundwork for a decentralized stool supply system wherein a small number of hospital-based stool banks around the country would provide a relatively small number of units of stool for the hospital with which it is affiliated and perhaps a few nearby hospitals and physicians. The Guidance would allow physicians to perform FMT for a patient with stool provided from hospital banks or from a friend or relative but not from an independent stool bank.⁴¹⁰ The Guidance does this by exempting from the definition of stool bank 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).”⁴¹¹

This proposed regulatory strategy seems to be based on at least two assumptions: 1) stool provided by a friend or relative of a patient will be adequately screened and tested; and 2) a number of smaller stool banks operating under the supervision of one or more health care providers will be safer than a single, independent, larger stool bank sending stool product to health care providers across the country. This latter assumption is explicit in the Draft Guidance, which states that “[c]entralized manufacturing in stool banks presents safety concerns related to the use of FMT from a limited number of donors administered to multiple patients. These safety concerns include transmission of infectious agents and potentially other unidentified risks related to changes in the microbiome.”⁴¹² Clearly, FDA was concerned with the number of people put at risk if stool comes from a universal donor at a stool bank who has an infectious disease for which he is not tested. However, there is reason to challenge the assumption that stool from family members or friends or from a handful of smaller stool banks will be safer than stool from one or a few large, independent banks. Comments from physicians and researchers on the 2014 proposed guidance indicated that stool from a friend or relative of the patient was not likely to be screened as thoroughly as stool from a large, independent stool bank with the resources to recruit and stringently screen potential donors and test their stool.⁴¹³ Nor could they afford the application of cGMPs that OpenBiome has applied.

By exercising its enforcement discretion over the smaller, hospital- and laboratory-based stool banks, as it does now, FDA does not have a list of the number of such banks, where they are located, or how they are screening and testing donors and their stool. The banks are virtually unregulated, other than possibly by state law and threat of malpractice. Although there is a significant difference in terms of scale and numbers, the proposed system for stool banks resembles the U.S. system of decentralized blood banks. There are over 2,000 blood banks in the country that are

⁴⁰⁹ *Id.* at 410.

⁴¹⁰ FDA, ENFORCEMENT POLICY (Mar. 2016), *supra* note 14, at 1.

⁴¹¹ *Id.* at 1–2. 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.” *Id.* at 1.

⁴¹² *Id.* at 3.

⁴¹³ *See supra* notes 101–02 and accompanying text.

not licensed, but, at a minimum, they must register with FDA so that the agency knows where they are operating and what products they are storing and selling.⁴¹⁴ If FDA allows hospital stool banks to continue to operate, at a minimum, such registration should be required.

An additional factor to consider is whether physicians who do not have access to a hospital stool bank will be willing to perform FMTs if they are responsible for screening the donor, testing the stool, and preparing the stool for administration. Finally, patients may not be able to find a relative or friend willing to donate their stool, but, if they do, they may decide to perform the procedure themselves rather than pay the additional cost of having the screening and procedure done at a hospital.

3. *Alternatives Under an IND*

The requirement of an IND for INSBs only allows such stool banks to remain viable if the cost of the IND process is significantly reduced. Several authors have suggested alternatives to the traditional IND path that are worth considering. Khoruts and colleagues proposed that FDA allow INSBs to operate under an “ongoing observational” research IND requiring them to submit regular reports on adverse events and efficacy.⁴¹⁵ This option, like other research (non-commercial) INDs, would not require that the stool bank proceed to drug development and approval.⁴¹⁶ It would differ from a typical research IND, however, in that it would be continuous and have broad enrollment criteria, including patients who could likely benefit from the “treatment.”⁴¹⁷ The pathway would also capture safety and efficacy data that is not currently collected under the enforcement discretion policy.⁴¹⁸ The stool bank could charge for its stool under human subject research regulations, which allow cost recovery for “experimental” products.⁴¹⁹ This might cover or partially cover a stool bank’s fixed costs.

This option incorporates the idea of “real world” data as a basis for new drug/biologic approval set forth in the 21st Century Cures Act. Although the ongoing research IND proposal does not contemplate that an INSB would seek a BLA, it is based on the idea of collecting real world data on a continuing basis. The 21st Century Cures Act lists the use of “observational data from routine clinical use or ‘real world evidence’” as a way to facilitate more rapid drug and device approval.⁴²⁰ “Real world evidence” (RWE) is defined as data based on use of a drug or its potential benefits or risks “derived from sources other than randomized clinical trials.”⁴²¹ Although the 21st Century Cures Act states that RWE may be used for new indications of already approved drugs, it also states that nothing prohibits the Secretary of HHS from using the evidence for other purposes if there is a “sufficient basis” for doing so.⁴²² This

⁴¹⁴ See *supra* note 224 and accompanying text.

⁴¹⁵ Khoruts et al., *supra* note 3, at 498.

⁴¹⁶ *Id.* at 499.

⁴¹⁷ *Id.* at 498.

⁴¹⁸ *Id.*

⁴¹⁹ *Id.* at 499.

⁴²⁰ Michael Gabay, *21st Century Cures Act*, 52 HOSP. PHARMACY 264, 264 (2017).

⁴²¹ 21st Century Cures Act, H.R. 34, 114th Cong. (2016).

⁴²² *Id.*

provision of the law presents an opportunity for FDA to consider real world data for granting a biologics license for stool. Such data could come from an INSB.⁴²³

A second non-traditional approach has been proposed by Ossorio and Zhou.⁴²⁴ They suggest a limitation on, but not total elimination of, the enforcement discretion policy for independent stool banks.⁴²⁵ Under their proposal, enforcement discretion would only apply to use of stool for FMT by health care providers who are not at large academic medical centers, but rather at “smaller, non-academic, less-well-resourced” facilities.⁴²⁶ Others who are at research institutions or have an IND (for any clinical research) would have to obtain an IND to perform an FMT “for any reason” and for any stool, whether obtained from a stool bank or procured “in-house.”⁴²⁷ In this scenario, the health care providers would be investigators, not “sponsor-investigators.”⁴²⁸ In addition, when possible, the authors propose that FDA approve expanded access to stool bank product for “intermediate-size patient populations with rCDI”⁴²⁹ as long as it does not interfere with clinical trials that are underway. This proposal, they argue, would allow stool banks to operate and would not put them at a competitive disadvantage with hospital facilities, as they would not bear the brunt of the cost of the IND. Just as OpenBiome does now, stool banks would share their master file with the sponsors/investigators submitting INDs.⁴³⁰

A third option, not mentioned in the literature, is similar to that proposed by sponsors of the REGROW Act for stem cell products. The bill was introduced in order to diminish the cost and time required to commercialize stem cell-based treatments derived from the patient’s own cells.⁴³¹ Although the bill did not pass, it would have allowed such products to bypass Phase III clinical trials if researchers could show they were safe and had a “reasonable expectation of efficacy.”⁴³² These products would be permitted to go on the market without a BLA.⁴³³ This type of expedited pathway could allow INSBs to remain operational with funding from outside sources to conduct Phase I and Phase II clinical trials. This would entail more oversight than they received under FDA’s enforcement discretion policy. In addition to adverse event reporting, the stool banks might also be required to collect data on effectiveness.

⁴²³ To some extent, the American Gastroenterological Association attempted to fill the gap of unacquired data by establishing its NIH-funded Registry for physicians performing FMT. *See AGA Releases Largest Real-World Report on Safety and Effectiveness of Fecal Microbiota Transplantation (FMT)*, AM. GASTROENTEROLOGICAL ASSOC. (Oct. 1, 2020), <https://gastro.org/press-releases/aga-releases-largest-real-world-report-on-safety-and-effectiveness-of-fecal-microbiota-transplantation-fmt-2/> [<https://perma.cc/39RM-NBZK>]. *See also* Kelly et al., *The AGA’s FMT National Registry*, *supra* note 49.

⁴²⁴ Ossorio & Zhou, *supra* note 122.

⁴²⁵ *Id.* at 514.

⁴²⁶ *Id.*

⁴²⁷ *Id.*

⁴²⁸ *Id.*

⁴²⁹ *Id.* at 513.

⁴³⁰ *Id.* at 514.

⁴³¹ *See supra* notes 314–315 and accompanying text.

⁴³² REGROW Act, S. 2689, 114th Cong. (2016).

⁴³³ Riley, *supra* note 315, at 298.

B. Subsidies for Nonprofit Stool Banks

Whether or not some type of regulatory carve-out or less costly regulatory path should be considered for INSBs merits the attention of policymakers and Congress. The prior section suggested three such pathways; however, even with those options, nonprofits may still require subsidies to remain viable if required to obtain an IND. Nonprofits are generally precluded from going through the BLA/IND process because of its immense costs. Cost is especially problematic for not-for-profit entities such as public cord blood banks⁴³⁴ and stool banks, which are unlikely able to raise the capital required for the drug/biologic approval process for reasons specified above.⁴³⁵ These banks perform a public service by providing a necessary therapeutic product at an affordable price.

In contrast, for-profit storage banks have been known to take advantage of consumers by making unsubstantiated claims. For example, early cord blood banks that adopted a for-profit business model came under scrutiny as they tried to convince new parents of the necessity of banking cord blood for future needs of their newborn.⁴³⁶ Such a need is highly unlikely for most families unless they already have a child with a blood disorder. In addition, these banks tout the potential for stem cells derived from cord blood to treat or cure multiple diseases, although there is limited, if any, data supporting such claims.⁴³⁷ Critics argue that the industry uses “inflated arguments, aggressive marketing and misleading information to convince parents to buy in.”⁴³⁸

In addition to cord blood banks, for-profit blood transfusion clinics⁴³⁹ have “popped up” that claim to rejuvenate aging individuals through infusions with the blood plasma of young people.⁴⁴⁰ The clinics state that the product/procedure can protect against

⁴³⁴ Approximately “90% of public [cord blood] banks are unable to self-sustain” and must be subsidized to operate. Carla Dessels, Marco Alessandrini & Michael Sean Pepper, *Factors Influencing the Umbilical Cord Blood Stem Cell Industry: An Evolving Treatment Landscape*, 7 STEM CELLS TRANSLATIONAL MED. 643, 648 (2018).

⁴³⁵ See *supra* Section V.A.3.

⁴³⁶ Kulynych attributed the cord blood banking controversy in the U.S. to “a growing phenomenon in American science: the entry of venture capital at an early phase in the development of a scientific field, through profit-oriented collaborations between academic scientists and biotechnology entrepreneurs.” Early researchers patented their technique, obtained venture capital, and founded a for-profit company. Kulynych, *supra* note 166, at 415.

⁴³⁷ Carly Weeks, *Why Banking on Cord Blood isn't Necessarily a Good Idea*, GLOBE & MAIL (May 26, 2012), <https://www.theglobeandmail.com/life/health-and-fitness/why-banking-on-cord-blood-isnt-necessarily-a-good-idea/article4209835/> [<https://perma.cc/G4DM-PM6Y>].

⁴³⁸ *Id.*

⁴³⁹ *FDA Warns Against For-Profit Plasma Infusions*, YOUNG BLOOD INST., (Feb. 27, 2019), <http://youngbloodinstitute.org/blog.html> [<https://perma.cc/66DB-X8V9>]. See also U.S. FOOD & DRUG ADMIN., STATEMENT FROM FDA COMMISSIONER SCOTT GOTTLIEB, M.D., AND DIRECTOR OF FDA'S CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, PETER MARKS, M.D., PH.D., CAUTIONING CONSUMERS AGAINST RECEIVING YOUNG DONOR PLASMA INFUSIONS THAT ARE PROMOTED AS UNPROVEN TREATMENT FOR VARYING CONDITIONS (Feb. 19, 2019), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-director-fdas-center-biologics-evaluation-and-0> [<https://perma.cc/F58G-B9CL>] [hereinafter FDA, STATEMENT FROM FDA COMMISSIONER].

⁴⁴⁰ A startup company called Ambrosia offered “young blood” transfusions to older individuals “at a cost of \$8,000 for 1 liter of young blood, or \$12,000 for 2 liters.” The company caught the attention of FDA, and the agency issued a statement that blood plasma from young people offers “no proven clinical benefit”

“normal aging, Alzheimer’s disease, or a host of other diseases.”⁴⁴¹ These claims are considered “misbranding” under the FDCA⁴⁴² and false claims under the Federal Trade Commission Act.⁴⁴³ Similarly, hundreds of stem cell clinics now operate around the country promoting the administration of stem cell transplants for a variety of unapproved conditions.⁴⁴⁴ These clinics not only cause financial harm but have also caused severe adverse events such as blindness and the growth of a spinal tumor.⁴⁴⁵ These differences in behavior further support different regulatory approaches to for-profit and not-for-profit storage banks for human-sourced products for transplant.

Although the financial challenges confronted by OpenBiome were caused by a sudden and unexpected pandemic, the public health crisis arguably brought into stark relief the likely future the company would have faced if demand for its product was significantly cut by the availability of an alternative FDA-approved drug. The company’s predicament also raises the question of whether there is any business model under which an INSB could continue to operate. The answer would appear to be one with significantly reduced costs and/or additional revenue.⁴⁴⁶

Congress and FDA have created financial incentives and benefits for drug manufacturers to fill gaps in the availability of essential medicines for rare diseases. For example, the Orphan Drug Act provides drug companies that manufacture treatments for a rare disease a 25% federal tax credit for certain clinical trials, a rebate on FDA application fees, and seven years of market exclusivity once the drug is approved.⁴⁴⁷ While these sorts of financial benefits are attractive to for-profit pharmaceutical companies, they are not helpful to nonprofit companies, which may not benefit from tax credits due to their “comparatively lower revenues and limited tax liabilities.”⁴⁴⁸ Also, market exclusivity, which benefits for-profit companies by

as a therapy for aging. Rebecca Robbins, *FDA Issues Warning about Young-Blood Transfusions*, STAT (Feb. 20, 2019), <https://www.scientificamerican.com/article/fda-issues-warning-about-young-blood-transfusions/> [<https://perma.cc/UC8L-7LTK>].

⁴⁴¹ Rebecca Robbins, *FDA: Young-Blood Transfusions Provide ‘No Proven Clinical Benefit’ for Aging, Alzheimer’s*, STAT (Feb. 19, 2019), <https://www.statnews.com/2019/02/19/fda-young-blood-transfusions-provide-no-proven-clinical-benefit-for-aging-alzheimers/> [<https://perma.cc/C5GW-FXEY>].

⁴⁴² See FDA, STATEMENT FROM FDA COMMISSIONER, *supra* note 439. “[T]reatments using plasma from young donors have not gone through the rigorous testing that FDA normally requires in order to confirm the therapeutic benefit of a product and to ensure its safety. As a result, the reported uses of these products should not be assumed to be safe or effective. We strongly discourage consumers from pursuing this therapy outside of clinical trials under appropriate institutional review board and regulatory oversight. . . . There are reports of bad actors charging thousands of dollars for infusions that are unproven and not guided by evidence from adequate and well-controlled trials.” *Id.*

⁴⁴³ Federal Trade Commission Act, 15 U.S.C. §§ 41–58 (as amended by Pub. L. No. 109-455) (Dec. 22, 2006).

⁴⁴⁴ *FDA Warns about Stem Cell Therapies*, U.S. FOOD & DRUG ADMIN. (Sept. 3, 2019), <https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies> [<https://perma.cc/DBE3-8QUE>].

⁴⁴⁵ *Id.*

⁴⁴⁶ The Biologics Efficacy Review expert panel for blood and blood products spoke to the need for such support for blood “manufacturers” attempting to perform clinical trials on blood. See *supra* notes 229–30 and accompanying text.

⁴⁴⁷ Orphan Drug Act of 1983, Pub. L. 97-414, 96 Stat. 2049 (codified at 21 U.S.C. § 360aa-ee (1983)).

⁴⁴⁸ *Nonprofit Pharmaceutical Companies: Background, Challenges, and Policy Options*, WAXMAN STRATEGIES 5 (Dec. 2019), <https://waxmanstrategies.com/wp-content/uploads/2020/01/Nonprofit-Pharmaceutical-Companies-White-Paper.pdf> [<https://perma.cc/7DCX-DTSB>].

allowing them to charge supra-competitive prices,⁴⁴⁹ does not fit the mission of the not-for-profit entity, which often is to provide goods and services at an affordable price to increase access.

Over the last two years, some attention has been paid to newly established not-for-profit drug companies as one way to reduce the cost of drugs in the United States and to fill needed areas of drug development that have been ignored by the for-profit industry, e.g., antibiotic development.⁴⁵⁰ In December 2019, Waxman Strategies, a public interest consulting firm, published a white paper advocating the potential of nonprofit pharmaceutical companies,⁴⁵¹ a handful of which had been formed,⁴⁵² to address skyrocketing drug prices. The paper's key finding was that, despite the promise these companies hold for greater drug affordability, they are thwarted by a host of federal policies and market structures geared toward incentivizing for-profit companies to invest in new drug development.⁴⁵³ These policies and market practices include tax code issues and tax credits, financing of drug research and development, FDA extraction of large user fees, "access to pharmaceutical supply chains and distribution channels," and insurance reimbursement policies.⁴⁵⁴ The white paper recommends a range of solutions, some of which are relevant to INSBs, including the establishment of a new tax-exempt status designation for nonprofit drug companies that would allow the income of such companies to be considered non-taxable revenue.⁴⁵⁵ Companies meeting the criteria for this designation would be eligible for new and existing "tax-advantaged programs" to support their research and drug development.⁴⁵⁶

The report further suggests establishment of programs to provide upfront financial support such as grants or no/low interest loans to develop therapies in areas where for-profit companies have not been inclined to invest.⁴⁵⁷ The paper highlights public health needs and references the Biomedical Advanced Research and Development Authority (BARDA) within the U.S. Department of Health and Human Services as a potential model.⁴⁵⁸ BARDA provides funding for research and development of "countermeasures" for biological, chemical, or nuclear threats as well as pandemics

⁴⁴⁹ Sachs & Edelstein, *supra* note 1, at 402.

⁴⁵⁰ See, e.g., Travis B. Nielsen, Eric P. Brass, David N. Gilbert, John G. Bartlett & Brad Spellberg, *Sustainable Discovery and Development of Antibiotics – Is a Nonprofit Approach the Future?*, 381 NEW ENG. J. MED. 503 (2019).

⁴⁵¹ *Nonprofit Pharmaceutical Companies*, *supra* note 448.

⁴⁵² HARM REDUCTION THERAPEUTICS, <https://www.harmreductiontherapeutics.org/> [<https://perma.cc/U78M-8HBJ>] (last visited July 3, 2021); CIVICA RX, <https://civicarx.org/> [<https://perma.cc/WC9B-FQSE>] (last visited July 3, 2021); FAIR ACCESS MEDS., <https://www.fairaccessmedicines.org/> [<https://perma.cc/97TK-6ZW9>] (last visited July 3, 2021).

⁴⁵³ *Nonprofit Pharmaceutical Companies*, *supra* note 448, at 2.

⁴⁵⁴ *Id.*

⁴⁵⁵ *Id.* at 4.

⁴⁵⁶ *Id.* at 7.

⁴⁵⁷ *Id.* at 8.

⁴⁵⁸ *Id.*

and emerging infectious diseases.⁴⁵⁹ In this area of financial support, the white paper also recommends the use of rewards for companies that successfully bring a product to market, including opportunities to receive “priority review vouchers” or “monetary prizes.”⁴⁶⁰ In addition, INSBs requiring an IND would benefit from FDA waiver or reduction of user fees.

The European Commission, recognizing that small- and medium-sized drug companies are often stymied in marketing their products by virtue of the costs associated with premarket approval requirements, has adopted some of these suggestions. The Commission, for example, provides these companies with financial breaks in the fees associated with “scientific advice, inspections, and other scientific services” and “defer[s] marketing authorization application fees until the end of the evaluation procedure.”⁴⁶¹ These special incentives target “Advanced Therapies,” which include “gene therapy, somatic cell therapy, and tissue-engineered products,” but address the need for assistance of small- and medium-sized nonprofit companies more generally.⁴⁶²

VI. RECOMMENDATION AND CONCLUSION

The “enforcement discretion” approach that FDA has taken for stool used for FMT has enabled the almost decade-long life of the INSB, OpenBiome, and the related treatment of thousands of patients for unrelenting and life-threatening rCDI. However, that life may be prematurely cut short by the COVID-19 pandemic and the pending approval of a stool-derived microbiota-based new biologic for the same indication. We argue that the death of such a stool bank is premature because INSBs may continue to provide societal benefit after a new drug/biologic is on the market by virtue of being superior to the FDA-approved product in terms of safety, effectiveness, or cost for rCDI or other possible indications.

The lessons from OpenBiome’s short life include that a nonprofit storage bank for a human-sourced therapeutic seeking to (or required to) obtain a new drug approval or biologic license does not really stand a chance—the odds are stacked against it. In this paper, we discuss reasons why this is the case, from the poor “fit” of the drug and biologics regulatory pathway for a “raw,” i.e., minimally manipulated human-sourced material, to the fact that our drug approval process relies heavily, or exclusively, on a for-profit model of drug development that makes it virtually impossible for a not-for-profit entity to succeed.

To address this overlooked opportunity for additional societal benefit in the form of higher quality, lower cost drugs, we argue that for this product class, i.e., nonprofit storage banks for human-sourced products, FDA consider alternative regulatory frameworks such as those for transfusion medicine or HCT/Ps. Alternatively, if FDA

⁴⁵⁹ Biomedical Advanced Research and Development Authority, U.S. DEP’T HEALTH & HUM. SERVS. (Aug. 13, 2021), <https://aspr.hhs.gov/AboutASPR/ProgramOffices/BARDA/Pages/default.aspx> [<https://perma.cc/T7KG-CC9A>].

⁴⁶⁰ *Nonprofit Pharmaceutical Companies*, *supra* note 448, at 8.

⁴⁶¹ Mary Anne Chirba & Stephanie M. Garfield, *FDA Oversight of Autologous Stem Cell Therapies: Legitimate Regulation of Drugs and Devices or Groundless Interference with the Practice of Medicine*, 7 J. HEALTH & BIOMEDICAL L. 233, 271 (2011).

⁴⁶² Eve Hanna, Cécile Rémuzat, Pascal Auquier & Mondher Toumi, *Advanced Therapy Medicinal Products: Current and Future Perspectives*, 4 J. MKT. ACCESS & HEALTH POL’Y 31036, 31036 (2016).

believes that the drug/biologic pathway is superior, it should consider modifications to that pathway that reduce costs to the product sponsor. Such alternatives could include: 1) an ongoing, observational research IND as proposed by Khoruts, Hoffmann, and Palumbo; 2) a requirement for INDs only for physicians/researchers at large, well-resourced academic medical institutions as proposed by Ossorio and Zhou; 3) the use of “real world” observational data, as defined in the 21st Century Cures Act, to support a BLA; or 4) a waiver of Phase III clinical trials as proposed in the REGROW Act.

While these modifications to the new drug approval process would perhaps be sufficient for a few nonprofit storage banks, most would need additional support, including financial benefits such as tax credits, grants, loans, and/or reduced fees. We suggest such benefits specifically target nonprofit drug manufacturers, including storage banks for human-sourced products, so that their products can compete in the marketplace with for-profit drugs and biologics.