The Current Regulatory Framework for Fecal Microbiota Transplantation

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Overview

• The FDA’s Position to Date
• Understanding the IND Framework
• An Uneasy Fit as Applied to FMT
• Current Progress Through IND Review

1. The FDA’s Position to Date

• Choice to regulate FMT as a drug and biological product requiring an Investigational New Drug (IND) application

• Use of enforcement discretion for particular cases of treatment of recurrent C. diff infection
FMT as a Drug and Biological Product


- 42 U.S.C. § 262(i)(1): “The term ‘biological product’ means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product … applicable to the prevention, treatment, or cure of a disease or condition of human beings.”

FMT as Falling Outside of the HCT/P Paradigm

- 21 C.F.R. § 1271.3(d): “Human cells, tissues, or cellular or tissue-based products (HCT/Ps) means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient.”

- Tissue Reference Group, FY 2012 Update: “Microbiota isolated from fecal matter of a donor is not an HCT/P”

Use of Enforcement Discretion (1)

- July 2013 Federal Register guidance: “The Agency intends to exercise enforcement discretion regarding the IND requirements for the use of FMT to treat C. difficile infection not responding to standard therapies, provided that the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products.”

- Importantly:
  - “FDA intends to exercise this discretion on an interim basis while the Agency further considers the matter.”
  - “This policy does not extend to other uses of FMT.”
Use of Enforcement Discretion (2)

- March 2014 draft guidance: "we intend to exercise enforcement discretion regarding the [IND] requirements for the use of [FMT] to treat refractory C. diff. FDA intends to exercise this discretion provided that: (1) the licensed health care provider treating the patient obtains adequate informed consent from the patient; (2) the FMT product is obtained from a donor known to either the patient or to the licensed health care provider treating the patient; and (3) the stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product to treat his or her patient."

2. Understanding the IND Framework

- Appreciating the review process and clinical trial requirements of the IND, 21 CFR 312
- Considering elements of the IND process that are particularly important in the FMT context
**IND Requirements**

- 21 CFR 312 specifies in great detail all required components of an IND, including:
  - General investigational plan
  - Investigator’s brochure (in some cases)
  - Clinical protocols (and investigator information)
  - Chemistry, manufacturing, and control information
  - Pharmacology and toxicology data to support that it is safe to initiate studies in humans
  - Summary of previous human experience with the drug
  - Additional/relevant information

**Chemistry, Manufacturing, and Control**

- 21 CFR 312.23(a)(7): “a section describing the composition, manufacture, and control of the drug substance and the drug product... the submission is required to contain the following:”
  - “Drug substance. A description of the drug substance, including its physical, chemical, or biological characteristics;... the general method of preparation of the drug substance, the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance;”
  - “Drug product. ... where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage;”
3. An Uneasy Fit as Applied to FMT

- Challenges in applying IND to FMT
  - Difficulty of characterizing active ingredients
  - Exclusivity may lead to unsafe DIY treatments
  - Adequacy of addressing safety concerns
  - Availability of off-label prescribing discourages investment

Difficulty of Characterizing Active Ingredients

- Stool’s complexity and consistency vary across individuals and across samples from the same individual

- Unless the active components are identified, purified, and tested, it will not be possible to guarantee that the product is consistent across batches

- Possibility of characterizing the product by the process used to prepare it for transplantation, rather than the variable contents of the product

Exclusivity May Lead to Unsafe DIY Treatments

- Under the drug regulatory paradigm, the FDA must award periods of exclusivity to newly approved drugs
  - Orphan Drug Act of 1983: 7 years of market exclusivity
  - Biologics Price Competition and Innovation Act of 2010: 12 years of data exclusivity

- Social bargain not fulfilled when treatment is already available (colchicine, Makena)

- FMT offers possibility of unsafe DIY treatments, not present for most other drugs or biologics
Adequacy of Addressing Safety Concerns

• Ongoing monitoring for the presence of possible pathogens is necessary for maintaining a safe product

• Pathogen testing not necessarily part of drug manufacturing process as overseen by FDA

• Importance of including pathogen testing as part of approval process or condition of manufacture

Availability of Off-Label Prescribing

• Generally, physicians may prescribe any FDA-approved drug for any use

• Result: pharmaceutical companies’ incentives to study new uses for old drugs are diminished

• FDA approval of FMT for C. diff may decrease incentives to study its efficacy for IBD, Crohn’s, etc.


• Orphan designations received by two companies

• Breakthrough designation granted to one company
Orphan Designations Made by FDA (1)

Orphan Designations Made by FDA (2)

Breakthrough Designations Awarded

PRESS RELEASES
Seres Therapeutics Receives FDA Breakthrough Therapy Designation for its Lead Product Candidate, SER-109

Seres Therapeutics, Inc., a leading microbiome therapeutics company, today announced that SER-109 (Probactrium Fermentis), its lead product candidate under investigation for the prevention of recurrent Clostridium difficile infection (CDI), was granted breakthrough therapy designation by the U.S. Food and Drug Administration (FDA). Breakthrough Therapy designation is intended to expedite the development and review of therapies for serious or life-threatening conditions when preliminary evidence indicates that the product may demonstrate a substantial improvement over existing therapies or one or more important unmet medical needs. This designation enables more frequent FDA interactions, an accelerated drug development program, an organizational commitment involving senior managers, and eligibility for rolling review and priority review (if supported by clinical data at the time of submission).