Fecal Microbiota for Transplantation

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Outline

• Why does FDA regulate fecal microbiota for transplantation?
• When is an IND application required?
• What is included in an IND application?
• FMT research needs, and how FDA can help achieve them
Why does FDA regulate fecal microbiota for transplantation?
Drugs and Biologics: Statutory Definitions

Drug: “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease” and “articles (other than food) intended to affect the structure and function of the body of man or other animals…”

FD&C Act Sec. 201

Biological Product: “. . . 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.”

PHS Act Sec. 351
Fecal Microbiota

- When used to cure, treat, mitigate or prevent a disease fecal microbiota for transplantation meets the legal definition of a drug and biological product.
When is an IND required?
When is an IND required?

• If the fecal microbiota are being used to cure, treat, mitigate or prevent a disease or condition it is considered an unapproved new drug for which an Investigational New Drug application (IND) is required.
What is an IND?

• **Investigational New Drug Application**
  – 21 CFR 312

• If an IND is “in effect” for an investigational new drug, it...
  – exempts an investigational new drug from premarketing approval requirements
  – allows an investigational new drug to be lawfully shipped across state lines for the purpose of conducting a clinical study¹ of that investigational new drug

¹IND not needed to conduct non-clinical studies
Phases of Product Development under IND

- **Preclinical**
  - Safety
  - Dose Ranging
  - 10s of subjects

- **Phase 1**
  - Safety
  - Early evidence of effectiveness
  - Several hundred subjects

- **Phase 2**
  - Safety
  - Effectiveness
  - Several thousand subjects

- **Phase 3**
  - Safety
  - Effectiveness
  - Several thousand subjects

**FMT**

Earlier Stages

Later Stages
Primary Objectives of IND Review

21 CFR 312.22(a)

• In all phases of the investigation, to assure the safety and rights of subjects
• In Phase 2 and 3, to help assure that the quality of the scientific evaluation is adequate to permit an evaluation of effectiveness and safety
What is included in an IND?
IND Content

21 CFR 312

• Content of an IND application:
  – General investigational plan
  – Investigator’s brochure (not necessary if sponsor is the investigator)
  – Manufacturing and product information
  – Available non-clinical pharmacology and toxicology data to support that it is safe to initiate studies in humans
  – Summary of previous human experience
  – Clinical protocols (and investigator information)
21 CFR 312.22

• The amount of information that must be submitted in an IND depends on such factors as the novelty of the drug, the extent to which it has been studied previously, the known and suspected risks and the developmental phase of the drug.

• The central focus of the initial submission should be on the general investigational plan and the protocols for specific human studies.
Phase 1 protocols

21 CFR 312.23(a)(6)

• In general, protocols for phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation – an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan. And should specify in detail only those elements of the study that are critical to safety…
IND Protocol - Content

21 CFR 312.23(a)(6)

• Objectives and purpose of study
• Name address and qualifications (CV) of investigator, name of sub-investigator(s), name and address of research facilities; name and address of IRB
• Patient inclusion/exclusion criteria
• Description of study design
• Dose/duration of exposure
• Description of observations and measurements
• Description of clinical procedures to monitor effects of the drug and to minimize risk
• Individual and study stopping rules
Phase 1 CMC

21 CFR 312.23(a)(7)

• “…[A] section describing the composition, manufacture, and control of the drug substance and the drug product….The emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance”
Phase 2 Clinical Studies

21 CFR 312.21(b)

• Controlled clinical studies conducted to provide preliminary evidence of effectiveness
• Typically *randomized, well-controlled, closely monitored*
• Up to several hundred subjects
• Entry criteria less restrictive, reflect target population
Fecal Microbiota for Transplantation: IND Review

• Clinical:
  – Study design, procedures to minimize bias and risks
  – Patient inclusion/exclusion criteria
  – Number of patients
  – Procedures to limit transfer of pathogens
    • Donor screening procedures
    • Product testing
  – Procedure for administration
  – Quantity of product to be administered (dose) and frequency of administration
  – Monitoring and reporting of adverse events
  – Patient outcomes (monitor for treatment effects)
Fecal Microbiota for Transplantation: IND Review (continued)

• CMC:
  – Manufacturing process:
    • Process for donation and storage (e.g. fresh/frozen)
    • Method of preparation (e.g. addition of saline/stabilizer), quality of the ingredients used
    • Tests to characterize the material
    • Storage conditions
Fecal Microbiota: Product Characterization Challenges

• Defining the “product”
  – Active ingredient?
  – Potency?
  – Stability?

• Defining the manufacturing process
  – Consistency of manufacture

• Complex product characterization challenges have been overcome in the past (whole blood or human cells, tissues, or cellular- or tissue-based products)
Expanded Access to Investigational Drugs for Treatment Use (21 CFR 312 Subpart I)

• Aim: Facilitate the availability of investigational new drugs\(^1\) to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy

• *Aim is not to obtain safety and effectiveness data from adequate and well-controlled studies to support approval*

\(^1\)And approved drugs where availability is limited by a REMS
Criteria for Expanded Access Use (21 CFR 312.305(a)):

FDA must determine that:

- Patients have a serious or immediately life threatening disease or condition, for which there is no comparable or satisfactory alternative therapy [e.g., recurrent C. difficile colitis]
- Potential benefit justifies potential risks in the context of the disease or condition to be treated
- Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded use or otherwise compromise the potential development of the expanded access use

Additional criteria for use in intermediate size (10s to 100s) populations [21 CFR 312.315(b)]:

- Evidence for safety
- Preliminary evidence of effectiveness
FMT research needs, and how FDA can help achieve them
FMT for treatment of disease

• Where we are now
  – Published data and studies encouraging for treatment of refractory *C. difficile* colitis

• What is needed
  – Adequate and well-controlled clinical trials to evaluate therapeutic potential of FMT for treatment of *C. difficile* colitis and other diseases

• What would be ideal
  – Identify the key microbes in fecal material responsible for beneficial effects leading to efficacious, defined products targeted for specific diseases
FMT Research Needs

• Understanding of the human gut microbiota in health and disease state(s)

• Assessment of risks of manipulation of microbiota to the recipient
  – early pre-clinical and clinical studies suggest that perturbations in the gut microbiome can have profound effects in health and disease
    • these effects may be beneficial or harmful, may appear short-term or long-term, and may extend far beyond the gut

• Investigate which components of stool are responsible for therapeutic effect

• What are the potential longer term effects of the transferred microbiota on the recipient?
Potential long-term effects of alterations in the gut microbiome

- immune status
- nutritional status
  - body weight
  - nutrient absorption
  - diabetes risk
  - cardiovascular risk
- autoimmune status
- wound repair/fibrosis
- cognition/mood
- cancer risk
- other?
Today's topic is fecal microbiota transplantation (FMT). A new Current Procedural Terminology (CPT) code [44705, "Preparation of fecal microbiota for instillation, including assessment of donor specimen"] has been assigned to FMT. Biotransplantation has recently come on the scene as a gastrointestinal procedure that can make a meaningful difference in patients with chronic *Clostridium difficile* infection (CDI).

**Bottom line:** *FMT is a very low-tech procedure with a CPT code*
Controlled Clinical Studies of FMT

Can enhance progress in FMT research by assuring:

– appropriate entry and exclusion criteria
– clearly defined endpoints
– subject safety
– good records of treatment protocols, patient demographics, medical histories
– oversight/input on the design and conduct of trials by fellow HCPs, scientists, ethicists
– appropriate and consistent product characterization
– good, analyzable, interpretable data regarding outcomes and adverse events
Why the scientific and medical community should support FDA’s continued involvement in FMT

• FDA will continue to work with the medical and scientific communities to assure patient safety and medical progress
Summary

• FMT used to treat, prevent or cure a disease meets the regulatory definition of a drug and biological product
• An IND is required when FMT is an unapproved new drug
• Early-phase IND review is focused on safety
• Evaluation of FMT presents some unique challenges (e.g. product characterization)
• Future clinical and laboratory research is important to further develop this therapy
• Controlled clinical studies will help advance the science and assure patient safety