Regulation of Microbiota-Based Products

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My presentation is an informal communication and represents my own best judgment. These comments do not bind or obligate FDA.
Overview

• Background
• Investigational New Drug Applications
• Biologics Licensure
• Conclusion
Background
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…”

**Biologic**: “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.”
Live Microorganisms at the FDA

• **Biologics (OVRR)**
  – *Vaccines*, biologic intended for prevention of a specific disease e.g. BCG, Salmonella Ty21a typhoid vaccine
  – *Live Biotherapeutic Products*, e.g. probiotics when used as a drug, defined bacterial consortia
  – *Research Challenge Agents*, e.g. influenza, malaria sporozoites
  – *Microbiota*, e.g. fecal microbiota transplantation (FMT)

• **Others**
  – *Dietary supplements*, a product intended for ingestion that contains a "dietary ingredient" intended to add further nutritional value to (supplement) the diet e.g. Lactobacillus acidophilus, Saccharomyces cerevisiae
    • Can make ‘Health” and “Structure/function” claims
  – *Foods*, e.g. yogurt
FMT at the FDA

• Being used for many different indications
  – Based on published data

• FMT used to treat or prevent a disease or condition is considered an unapproved new drug
Regulatory History

• 2010: First INDs for FMT submitted to the FDA
  – OVRR Responsible for oversight of FMT
  – Joint FDA-NIH Workshop held in 2013 to engage with stakeholders

• Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies (July 2013)
  – Draft March 2014 Guidance has been superseded by the March 2016 draft. Neither is in effect.
  – March 2016 document is out of the public comment.
Investigational New Drug Applications
What is an IND?

- **Investigational New Drug Application (21 CFR 312)**

- If an IND is in effect
  - 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 study of that investigational new drug
Purposes of the IND process

- Phase 1,2,3: to assure the safety and rights of subjects
- Phase 2 and 3: to help assure that the quality of the scientific study is adequate to permit an evaluation of the drug’s safety and effectiveness
Drug Development

**Pre-clinical**

- Safety (~20-80)

**Phase 1**

- Safety

**Phase 2**

- Safety
- Dose-Ranging, Efficacy (100’s)

**Phase 3**

- Safety
- Efficacy (100-1,000’s)
- Powered for hypothesis-testing

**Post-Marketing**

- Safety
- Effectiveness (»1,000’s)

**IND, Pre-marketing Phase**

**SAFETY**

- Effectiveness

**Manufacturing Consistency**
General IND Considerations
IND content (21 CFR 312.23)

• FDA Forms 1571 (cover sheet), 1572 (signed investigator statement), 3674 (compliance with clinical trials.gov data bank)
• Introductory statement and general investigational plan
• Investigator’s brochure (if needed)
• Protocol for each planned study
• Chemistry, manufacturing and controls information
• Pharmacology and toxicology information
• Previous human experience
Important Points, Clinical Studies

• Ensure an adequate Safety Monitoring Plan
  – Major review focus for Phase 1
  – Stopping Rules
  – Adverse event adjudication criteria
  – Long-Term Follow up
• Target Population (Inclusion/Exclusion Criteria)
  – Typically need safety data in adults before pediatric populations can be studied
• Phase 2/3, ensure adequate design
  – Statistical Analysis Plan (SAP), clearly defined indication
  – Pre-specified endpoints and success criteria (Esp. P3)
Important Points, CMC

• Need sufficient information to assure proper identification, quality, purity and strength
  – information needed to make assurance will vary with the phase of the investigation

• Justification of dose

• Clear testing and release criteria

• Sufficient data to assure stability during the planned study

• For FMT, should include donor screening/testing
  – May vary depending on target population
INDs- Additional Information

• Pre-IND nonclinical toxicology study review
  – Known toxicity concerns
  – New molecular entities
  – Animal studies designed to support initial administration in people

• Pre-IND meetings (Formal PDUFA type-B) to discuss early product development
Biologics Licensure
Drug Development

Pre-clinical → **Phase 1** → **Phase 2** → **Phase 3** → Approval

Pre-clinical Safety (≈20-80)

**Phase 1** Safety

**Phase 2** Safety

**Phase 3** Safety

Dose Ranging, Efficacy (100’s)

Efficacy (100-1,000’s) Powered for hypothesis-testing

SAFETY

Effectiveness

Manufacturing Consistency

Post-Marketing Safety

Effective-ness (≈1,000’s)
Biologics Licensure

• Must demonstrate
  
  – A particular product is safe, pure and potent; and
  
  – the facility in which the biologic product is manufactured, processed, packed, or held meets standards designed to assure that the biologic product continues to be safe, pure and potent…

• Only those biologics that are demonstrated to be safe and effective, and that can be manufactured in a consistent manner will be licensed by the FDA.
Scientific and Regulatory Considerations for FMT

• Potency: How can this be measured/quantitated? — How to relate structure/function of microbiota to therapeutic effect
• Purity: Ensuring no detectable known pathogens
• Identity: The presence of certain organisms
• Stool is a complex biologic, does not require “manufacture” and is readily available
• Ingredient(s) responsible for therapeutic effect unknown
• Broad range of indications, each with separate considerations
FMT Summary Remarks

• Should be considered experimental, safety and effectiveness to be demonstrated
• Many unresolved scientific issues
• Think carefully about every item in an IND
• Build in time for FDA interactions
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Extra Slides
Human cells, tissues, or cellular or tissue-based products

• 21 CFR 1271.1
• \textit{HCT/Ps} means articles containing or consisting of \textit{human} cells or tissues…
• Secreted or extracted human products are not considered HCT/Ps
IND Expedited Pathways

• Fast Track:
  – A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need
  – More meetings, eligible for expedited BLA

• Breakthrough:
  – A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies
  – More meetings, intensive management involvement, accelerated communication timelines
Accelerated Approval

- A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)
Priority Review

• An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness

• Or certain pediatric submissions, priority review vouchers

• Shorter Review Timeframe