Regulatory Aspects of Microbiome-Related Biologic Products

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Paul Carlson, PhD
(paul.carlson@fda.hhs.gov)
Laboratory of Mucosal Pathogens and Cellular Immunology
DBPAP/OVRR/CBER/FDA
The views expressed in this talk represent the views of the speaker and do not necessarily represent the views of FDA.
Outline

• Basic primer on regulation of Biologics
  – INDs and BLAs

• Considerations for microbiome based therapeutics:
  – Including:
    • Live Biotherapeutic Products
    • Fecal Microbiota for Transplantation
  – Some history
  – Some challenges
Definition of Biologic

“...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, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound),] applicable to the prevention, treatment, or cure of a disease or condition of human beings.”

Public Health Service Act, sec. 351 (i)
Who at the FDA reviews microbiome-based biological product INDs?

**Office of Vaccines Research and Review**
Director
Marion F. Gruber, Ph.D.
(DKKBF)

- **DBPAP**
  Division of Bacterial, Parasitic, and Allergenic Products
  • Product review
  • Laboratory Research

- **DVRPA**
  Division of Vaccine and Related Product Applications
  • Primary review and project management
  • Clinical review
  • Toxicological review

- **DVP**
  Division of Viral Products

Statistical review – **OBE** (Office of Biostatistics and Epidemiology)
Who sponsors biologics INDs?

<table>
<thead>
<tr>
<th>Big Companies</th>
<th>Individual Bench Researchers</th>
<th>Individual Clinical Investigators</th>
<th>Other Government Agencies (NIH, Defense Dept.)</th>
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- Sponsor regulatory expertise and support available varies greatly.
- At critical points in development the opportunity exists (and it is **highly recommended**) to meet with FDA prior to submission (pre-IND, pre-pivotal studies, pre-license application).
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When in biologic product development does FDA get involved?

• First in human use

• Human studies are done under IND (Investigational New Drug application)

• Allows the use of a non-licensed product in clinical trials (interstate commerce)

• Not all INDs are for product development (e.g. research only human studies)
FDA’s Objectives in Reviewing an IND

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

**SAFETY**
- Safety (≈20-80)
- Safety, Dose-Ranging, Effectiveness (100’s)
- Safety Effectiveness (100-1,000’s) Powered for hypothesis-testing
- Safety, Effectiveness (≥1,000’s)

**Effectiveness**
- Manufacturing Consistency

**Assay Development**
cGMP represents manufacturing practices and controls to assure that a drug is safe and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

For Phase 1 some GMP controls and their extent will differ from later phases of clinical studies.
Phase I cGMP

Guidance for Industry
CGMP for Phase 1
Investigational Drugs

- “Because certain requirements in part 211, which implement § 501(a)(2)(B) of the FD&C Act, were directed at the commercial manufacture of products typically characterized by large, repetitive, commercial batch production (e.g., those regulations that address validation of manufacturing processes (§ 211.110(a)), and warehousing (§ 211.142)), they may not be appropriate to the manufacture of most investigational drugs used for phase 1 clinical trials.”

- “The approach described in this guidance reflects the fact that some manufacturing controls and the extent of manufacturing controls needed to achieve appropriate product quality differ not only between investigational and commercial manufacture, but also among the various phases of clinical trials.”
Ultimate goal: FDA license

*Safety database considerations include intended population and condition being treated.

**Demonstration of effectiveness is expected to be based on adequate and well-controlled clinical studies.
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Live biotherapeutic products (LBPs)
Brief overview of “probiotics” regulation at CBER

CFSAN
- When intended for use as a food or dietary supplement

CBER
- When intended for use as a drug/biologic
- Reviewed many IND applications for Live Biotherapeutic Products over the last ten or more years.

Published a guidance document early 2012 on CMC issues for Live Biotherapeutic Products; revised June 2016
A LBP, for the purposes of this guidance document, is a biological product that: 1) contains live organisms, such as bacteria; 2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and 3) is not a vaccine. For the purposes of this document, LBPs are not filterable viruses, oncolytic bacteria, or products intended as gene therapy agents and, as a general matter, are not administered by injection. An example of an LBP, for the purposes of this document, would be one or more strains of lactobacilli administered orally to treat patients with ulcerative colitis, or administered vaginally to prevent bacterial vaginosis.
LBP-Relevant Guidance documents – CMC

- Strain information
  - Name
  - Source
  - Passage history
  - If from clinical specimen, context information
  - Relevant genotype and phenotype

- Information on cell-banking system

- MICs/resistance phenotype for relevant antibiotics
  - May need to assess transferability
  - If antibiotic resistance introduced intentionally, discuss need and possible alternatives.

- Documentation of methods of attenuation if otherwise pathogenic
  - If mechanism of action known, provide information and approaches for assessment of this as a stability indicating parameter.

- Potency testing
  - Need to be able to enumerate all strains.

- Purity testing
  - Need to demonstrate absence of extraneous undesirable organism.
  - Depending on other organisms manipulated in the same facility, may need to add specific tests for organisms of concern.
Challenges in Regulating LBPs

- Typically sponsor is not the manufacturer
  - Can use the Master File mechanism to provide manufacturing information directly to FDA – treated confidentially

- Typically manufacturer has been producing as a dietary supplement or food ingredient
  - Testing to ensure safety in high risk populations may not have been performed.

→ It is inherently difficult to assess microbial purity of a live biotherapeutic product (non-sterile, large number of product bacteria can obscure testing)
Why all this testing?

While probiotics are generally considered safe in healthy adults

\(\Rightarrow\) Safety issues may be critical due to clinical trial populations compromised by specific health concerns (e.g. inflammatory disease) or immature immune system/immunocompromised (elderly, very young).

Past incidents highlight this fact:

- Dutch Propatria Trial - 2008
- Mucormycosis and infant death - 2014.

\(\Rightarrow\) FDA revised the LBP guidance when proposed trial is in generally healthy subjects.
Relevant Guidance documents – II new guidance (June 2016)

- for LBPs that are available OTC as dietary supplements
- Applies to foods and dietary supplements in early clinical trials
- Published in Federal Register July 1, 2016

FDA anticipates that the label on the commercially available product(s) would be considered adequate to satisfy the requirement for CMC information under § 312.23 (a)(7)(iv)(a)-(b) and intends to grant a waiver provided that the following conditions are met:

- the LBP product that is proposed for investigational use is lawfully marketed as a conventional food or dietary supplement
- the investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of risk) associated with the use of the food or dietary supplement
- the investigation is not intended to support a marketing application of the LBP as a drug for human use or a biological product for human use
- the investigation is conducted in compliance with the requirements for INDs (part 312), the requirements for review by an institutional review board (21 CFR part 56), and with the requirements for informed consent (21 CFR part 50)

FDA recommends that the sponsor submit the information to the IND to meet the requirements of a waiver request under 21CFR 321.10 (a): (1) information showing the above; (2) a copy of the label of the commercially available food or dietary supplement; and (3) a commitment to record the lot(s) number and date of expiry in the case report form.
Fecal Microbiota for Transplantation (FMT)
FMT at the FDA – a brief history

- May 2-3, 2013 – FDA held a public workshop on Fecal Microbiota for Transplantation
  - Attended by clinicians, bench researchers, members of the public, and government employees
  - FDA announced publicly its position that FMT is a drug/biologic and experimental and therefore needs to be used under IND
  - “After the workshop, FDA received numerous inquiries about the application of the IND regulations to the administration of FMT products, and many expressed concern about the use of these products under IND”
FMT and the FDA – a brief history

- May 1-2, 2013 – CBER public workshop on FMT
- July 18, 2013 – New guidance published for immediate implementation
  - “FDA acknowledges these concerns and intends to exercise enforcement discretion regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies.”
- February 26, 2014 – Draft guidance published in Federal Register and open for comment
  - Proposed an added requirement that the donor be known to the doctor or the patient.
  - Many comments were received.
  - This guidance was not put into effect.
- March, 2016 – Draft guidance published in Federal Register and open for comment
  - Enforcement discretion does not extend to stool banks*
  - INDs required for Stool Banks (doctors using FMT from Stool Banks may be sub-investigators)
  - Sponsors may request a waiver of some IND for requirements for investigators and sub-investigators

* “A stool bank is defined, for the purpose of this guidance, 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. 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) is not considered to be a stool bank under this guidance.”
Challenges in regulation of FMT

How do we ensure safety?

Extrinsic safety

- Screening of donors
  - How frequently should donors be tested?
  - Should off-site donations be allowed?
- Testing of stool
  - How much do we test for?
  - How good are our tests?

Intrinsic safety

- What are the long-term health effects of changes to the gut microbiome?
  - Metabolic syndrome/diabetes?
  - Weight loss/weight gain?
  - Inflammatory disease?
  - Behavioral changes?

How do we characterize the product to maximize effectiveness?

- Are there specific organisms that mediate effectiveness?
- Are there specific consortia of organisms that mediate effectiveness?
- What is a good potency assay?
Final Thoughts

Interest in microbiome-related biological products has increased greatly in recent years.

CBER’s regulatory approach has been flexible and science-based.

This has allowed these novel approaches to be safely tested in the clinic.
Questions?