Regulatory Considerations for Microbiome Based Therapeutics

Paul E. Carlson Jr., Ph.D.
Division of Bacterial, Parasitic and Allergenic Products
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Paul.Carlson@fda.hhs.gov

ISCTM
Washington DC
February 20, 2020

Disclaimer

My comments are an informal communication and represent my own best judgment. My comments do not bind or obligate FDA.

Outline

- **Investigational New Drug Applications (INDs)**

- Additional Chemistry, Manufacturing and Controls (CMC) considerations for INDs with:
  1. Live Biotherapeutic Products (LBPs)
  2. Fecal Microbiota Transplantation (FMT)

IND Regulations [21 CFR 312]

IND: Investigational New Drug Application

- 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[1] of that investigational new drug

[1]IND not needed to conduct non-clinical studies

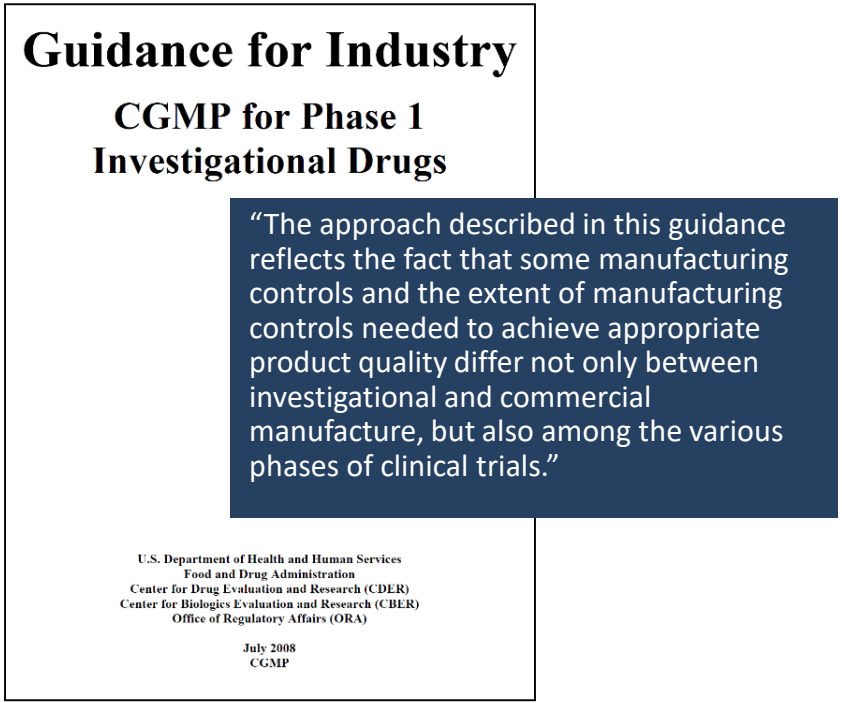
Stages of Review and Regulation

FDA's primary objectives in reviewing an IND (21 CFR 312.22):

1. To assure the safety and rights of subjects in all phases of an investigation, and,

2. In phases 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety.

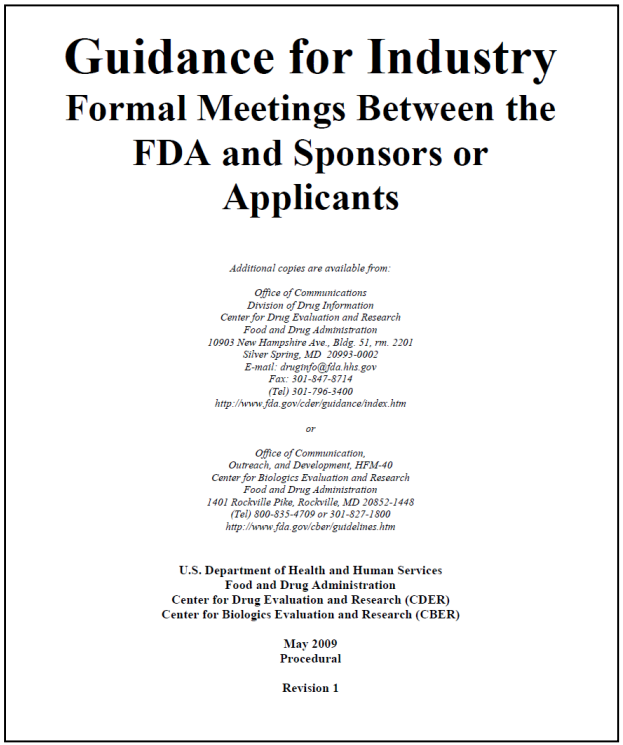
CMC: Current Good Manufacturing Practices (CGMP)



- CGMP: Current Good Manufacturing Practices
- Assures 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." (21 CFR 210)
- For Phase I, CGMP is not expected to be as extensive as for later phases or for an approved product

https://www.fda.gov/downloads/drugs/guidances/ucm070273.pdf

Meeting with the FDA



Guidance for Industry

Formal Meetings Between the FDA and Sponsors or Applicants

Additional copies are available from:

Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
E-mail: druginfo@fda.hhs.gov
Fax: 301-847-8714
(Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication,
Outreach, and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
http://www.fda.gov/cber/guidelines.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2009
Procedural

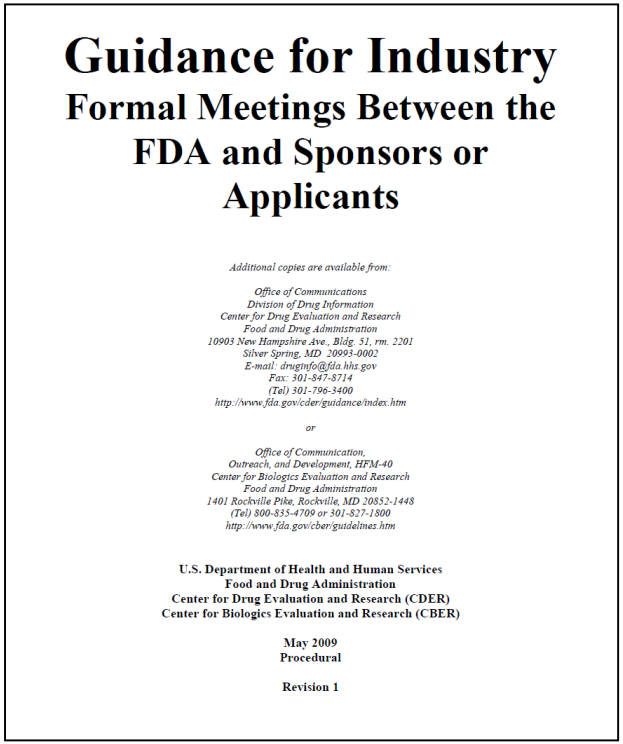
Revision 1

Pre-IND / Type B Meeting

- Highly recommended
- Sponsor provides briefing package and specific questions for CBER 30 days prior to scheduled meeting
- CBER assembles review team and provides responses
- Meeting is held to discuss further clarification of CBER responses
- May touch on CMC, Preclinical, and Clinical topics

(http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf)

Meeting with the FDA



Guidance for Industry

Formal Meetings Between the FDA and Sponsors or Applicants

Additional copies are available from:

Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
E-mail: druginfo@fda.hhs.gov
Fax: 301-847-8714
(Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication,
Outreach, and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
http://www.fda.gov/cber/guidelines.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2009
Procedural

Revision 1

Pre-IND / Type B Meeting

- Information to be submitted should include (not limited to):
  - ❑ Rationale for use of product
  - ❑ Purpose, objectives of planned investigations
  - ❑ Product description (available CMC; product release testing)
  - ❑ Proposed indication
  - ❑ Protocol (Summary or draft)
  - ❑ **Specific questions for CBER**

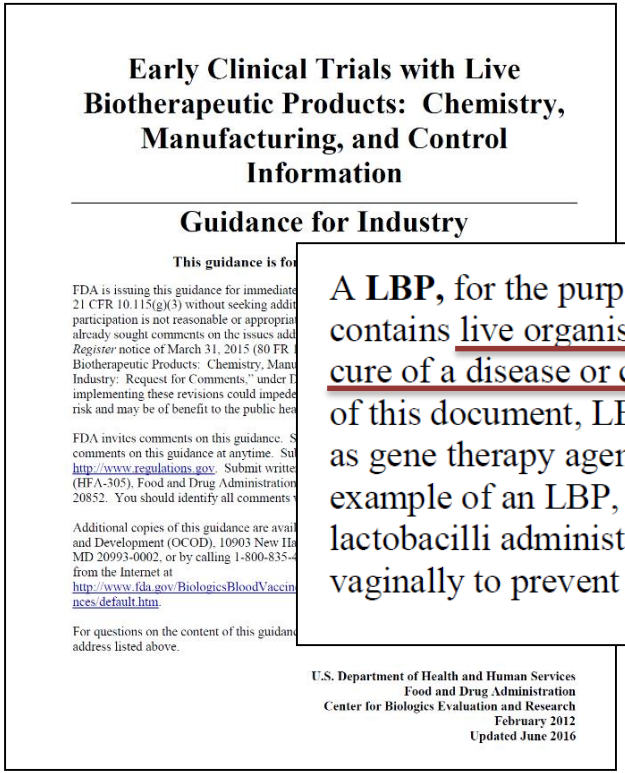
(http://www.fda.gov/downloads/Drugs/Guidances/ucm153222.pdf)

Outline

- Investigational New Drug Applications (INDs)

- Additional Chemistry, Manufacturing and Controls (CMC) considerations for INDs with:
  1. **Live Biotherapeutic Products (LBPs)**
  2. Fecal Microbiota Transplantation (FMT)

Chemistry, Manufacturing and Controls (CMC) for LBPs: Guidance Document



Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information

Guidance for Industry

This guidance is for

FDA is issuing this guidance for immediate
21 CFR 10.115(g)(3) without seeking addit
participation is not reasonable or appropriat
already sought comments on the issues add
Register notice of March 31, 2015 (80 FR
Biotherapeutic Products: Chemistry, Manu
Industry: Request for Comments," under
implementing these revisions could impede
risk and may be of benefit to the public hea

FDA invites comments on this guidance. S
comments on this guidance at anytime. Su
http://www.regulations.gov. Submit writte
(HFA-305), Food and Drug Administration
20852. You should identify all comments

Additional copies of this guidance are avai
and Development (OCOD), 10903 New Ha
MD 20993-0002, or by calling 1-800-835-
from the Internet at
http://www.fda.gov/BiologicsBloodVaccin
nces/default.htm.

For questions on the content of this guidan
address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 2012
Updated 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[3]; 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.

https://www.fda.gov/downloads/Biologi.../UCM292704.pdf

CMC for LBP INDs Should Include:

- ❑ Strain information (as available)
  - Name
  - Source
  - Strain and passage history
  - Relevant genotype and phenotype; full genomic sequence
- ❑ Antibiotic resistance profiles for clinically relevant antibiotics
- ❑ Information on cell banking system
- ❑ Description of Drug Substance/Drug Product manufacturing process
- ❑ Stability data (duration of treatment phase of the study)

- ❑ Manufacturing controls and release testing
  - Potency testing
    - Typically a measure of viable cells (CFU)
      - For multi-strain products: enumerate all strains
    - Additional biochemical or physicochemical measurements thought to predict potency, as applicable
  - Bioburden testing
    - Demonstrate absence of extraneous undesirable bacteria (USP<61> ,<62>)
    - Additional testing may be required depending on:
      - Intended population
      - Other organisms manipulated in the same facility

https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM292704.pdf

CMC for INDs Using Commercially Available Products: 2016 LBP Guidance Update

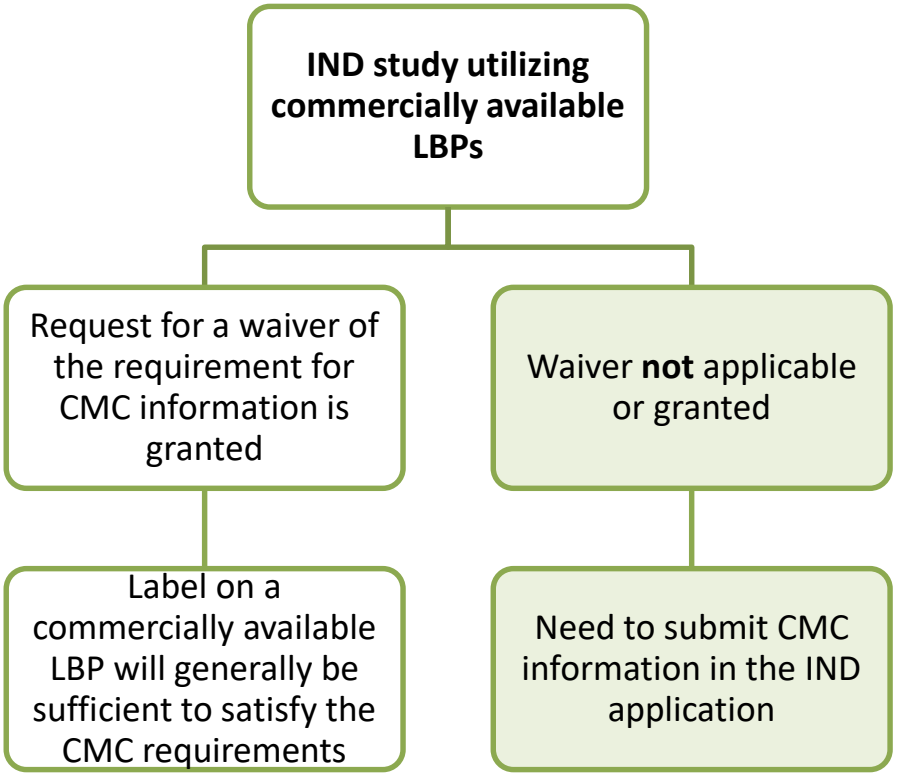
- Commercially available probiotics may fit the definition of an LBP depending on the intended use.

While commercially available probiotics are generally considered safe in healthy adults:

→ Safety issues may be critical in clinical trial populations compromised by specific health concerns or conditions.

→ Recognizing the difficulty that sponsors had providing the CMC information required under 312.23, FDA revised the LBP guidance in 2016 for proposed trials in generally healthy subjects.

CMC for LBP INDs

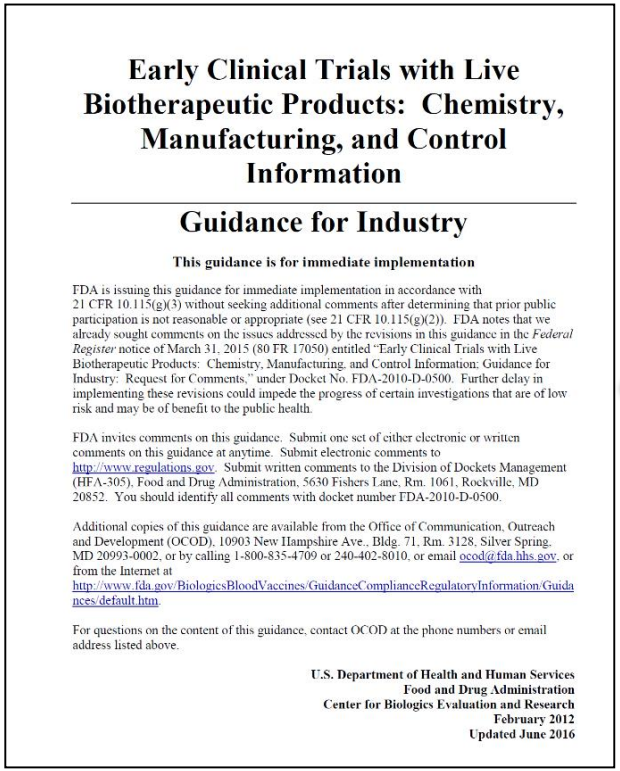


❖ IND sponsor may not be the manufacturer

→ Can use the Master File mechanism to provide confidential manufacturing information directly to FDA

https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/UCM292704.pdf

CMC for INDs Using Commercially Available Products: Waiver of the Requirement for CMC Information



Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information

Guidance for Industry

This guidance is for immediate implementation

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(3) without seeking additional comments after determining that prior public participation is not reasonable or appropriate (see 21 CFR 10.115(g)(2)). FDA notes that we already sought comments on the issues addressed by the revisions in this guidance in the *Federal Register* notice of March 31, 2015 (80 FR 17050) entitled "Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information: Guidance for Industry: Request for Comments," under Docket No. FDA-2010-D-0500. Further delay in implementing these revisions could impede the progress of certain investigations that are of low risk and may be of benefit to the public health.

FDA invites comments on this guidance. Submit one set of either electronic or written comments on this guidance at anytime. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with docket number FDA-2010-D-0500.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 2012
Updated June 2016

Section D. IND Studies Utilizing Commercially available Live Biotherapeutic Products.

A waiver may be granted if <u>all 4</u> of the following conditions are met:

1. The LBP proposed for investigational use is lawfully marketed as a conventional food or dietary supplement.
2. 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.
3. 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.
4. The investigation is otherwise conducted in compliance with the requirements for INDs (21 CFR Part 312).

→ Submit a waiver request documenting the above, a copy of the label, and a commitment to record the lot number(s) and date of expiry.

U.S. Regulatory Considerations for Development of Live Biotherapeutic Products as Drugs

SHEILA M. DREHER-LESNICK, SCOTT STIBITZ, and PAUL E. CARLSON, JR.

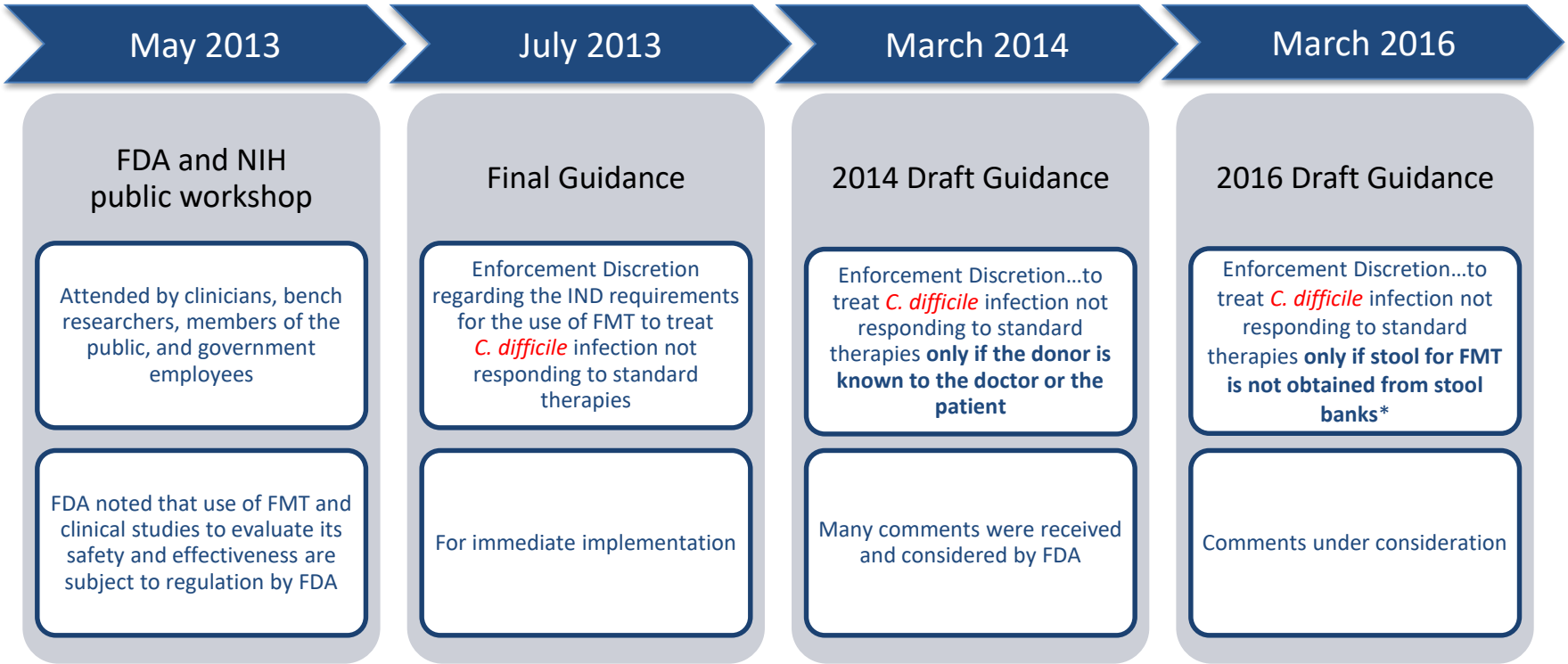
Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD 20993

Outline

- Investigational New Drug Applications (INDs)

- Additional Chemistry, Manufacturing and Controls (CMC) considerations for INDs with:
  1. Live Biotherapeutic Products (LBPs)
  2. **Fecal Microbiota Transplantation (FMT)**

FMT Guidance: A Brief History



* "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.

Multi-Drug Resistant Organisms

Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms

https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse

Multi-Drug Resistant Organisms

Summary of the Issue:

- Two immunocompromised adults who received investigational FMT developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli (E.coli)*. One of the individuals died.

- FMT used in these two individuals were prepared from stool obtained from the same donor.

- The donor stool and resulting FMT used in these two individuals were not tested for ESBL-producing gram-negative organisms prior to use. After these adverse events occurred, stored preparations of FMT from this stool donor were tested and found to be positive for ESBL-producing *E. coli* identical to the organisms isolated from the two patients.

Multi-Drug Resistant Organisms

1. Donor screening must include questions that specifically address risk factors for colonization with MDROs, and individuals at higher risk of colonization with MDROs must be excluded from donation.

2. FMT donor stool testing must include MDRO testing to exclude use of stool that tests positive for MDRO.

3. All FMT products currently in storage for which the donor has not undergone screening and stool testing for MDROs as described above must be placed in quarantine until such time as the donor is confirmed to be not at increased risk of MDRO carriage and the FMT products have been tested and found negative.

4. The informed consent process for subjects being treated with FMT product under your IND going forward should describe the risks of MDRO transmission and invasive infection as well as the measures implemented for donor screening and stool testing.

https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation

Donor screening recommendations

Stool testing:

- *Clostridium difficile*
- *Salmonella* spp.
- *E. coli* 0157
- *Shigella* spp.
- *Vibrio* spp.
- *Yersinia* spp.
- *Campylobacter* spp.
- *Plesiomonas* spp.
- Giardia
- Cryptosporidium
- Cyclospora
- Isospora
- Microsporidia
- Entamoeba histolytica
- Ova and parasites
- Rotavirus
- Norovirus
- Adenovirus
- Enterovirus
- Multi-drug resistant organisms (MDROs)
  - Extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*
  - Vancomycin-resistant enterococci (VRE)
  - Carbapenem-resistant *Enterobacteriaceae* (CRE)
  - Methicillin-resistant Staphylococcus aureus (MRSA)[1]

Serological testing:

- Hepatitis A
- Hepatitis B
- Hepatitis C
- HIV 1/2
- HTLV 1/2
- Syphilis
- Strongyloides
- EBV
- CMV

Cell Host & Microbe
Forum

Regulatory Considerations for Fecal Microbiota Transplantation Products

Paul E. Carlson, Jr.[1,*]
[1]Laboratory of Mucosal Pathogens and Cellular Immunology, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA
*Correspondence: paul.carlson@fda.hhs.gov
https://doi.org/10.1016/j.chom.2020.01.018

Final Thoughts

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

CBER's regulatory approach is science-based.

This allows novel approaches to be safely tested in the clinic.

Additional resources and contacts

Guidance documents:

- Early Clinical Trials with Live Biotherapeutic Products: Chemistry, Manufacturing and Control Information
- CGMP for Phase 1 Investigational Drugs
- Formal Meetings Between the FDA and Sponsors or Applicants
- Investigational New Drug Applications (INDs)- Determining Whether human Research Studies Can Be Conducted Without an IND

Contacts: CBER Office of Communication, Outreach and Development

- **Phone 800-835-4709; 240-402-8010 or email ocod@fda.hhs.gov**
- Manufacturers Assistance: Industry.Biologics@fda.hhs.gov

FDA Websites:

- FDA-IND application website: https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm
- FDA-IND forms and instructions: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071073.htm
- FDA-Drug Master Files for CBER-Regulated Products: https://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/NewDrugApplicationNDAProcess/ucm211604.htm


FDA
U.S. FOOD & DRUG
ADMINISTRATION