



Regulatory Considerations for Microbiome Based Therapeutics

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Drug Development Considerations for the Prevention of HealthCare-Associated Infections

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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. Fecal Microbiota Transplantation (FMT)
 2. Live Biotherapeutic Products (LBPs)

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 study¹ of that investigational new drug

¹IND 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)

Guidance for Industry

CGMP for Phase 1 Investigational Drugs

“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.”

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)
Office of Regulatory Affairs (ORA)

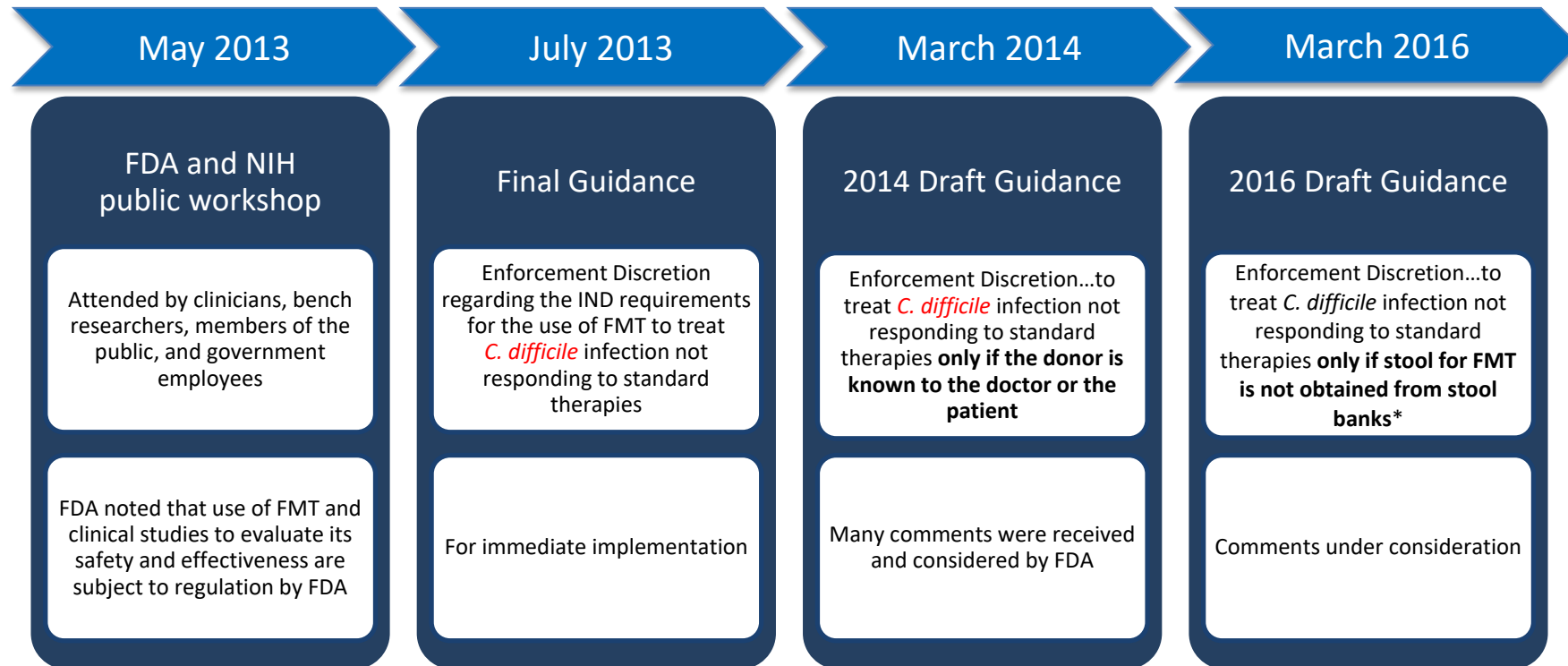
July 2008
CGMP

- 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

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 1. **Fecal Microbiota for Transplantation (FMT)**
 2. Live Biotherapeutic Products (LBPs)

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.

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
 - What organisms should 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 ensure consistency of effectiveness?

- Are there specific organisms/consortia that mediate effectiveness?
- Are there specific functions provided by these organisms that mediate effectiveness?
- What is a good potency assay?

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Recent FDA Safety Alerts related to FMT

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>

Information Pertaining to Additional Safety Protections Regarding Use of Fecal Microbiota for Transplantation - Screening Donors for COVID-19 and Exposure to SARS-CoV-2 and Testing for SARS-CoV-2

<https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation-1>

Information Pertaining to Additional Safety Protections Regarding Use of Fecal Microbiota for Transplantation -- Testing of Stool Donors for Enteropathogenic Escherichia coli and Shigatoxin-Producing Escherichia coli

<https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation-0>

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

- CMV

- **STEC by NAAT**
- **EPEC**
- **SARS-CoV-2**



Cell Host & Microbe

Forum

Regulatory Considerations for Fecal Microbiota Transplantation Products

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Outline

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



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 additional participation is not reasonable or appropriate already sought comments on the issues add Register notice of March 31, 2015 (80 FR Biotherapeutic Products: Chemistry, Manufacturing, and Control Information) under Implementing these revisions could impede risk and may be of benefit to the public health.

FDA invites comments on this guidance. Submit comments on this guidance at any time. Submit written comments (HFA-305), Food and Drug Administration 20852. You should identify all comments to:

Additional copies of this guidance are available from the Internet at <http://www.fda.gov/BiologicsBloodVaccines/default.htm>.

For questions on the content of this guidance, contact the address listed above.

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 beings³; 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.

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

CMC for LBP INDs

- Sufficient information to assure the proper identification, quality, purity and strength of the investigational drug
- As drug development proceeds, the sponsor should submit amendments to the IND to supplement the initial CMC information.

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

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



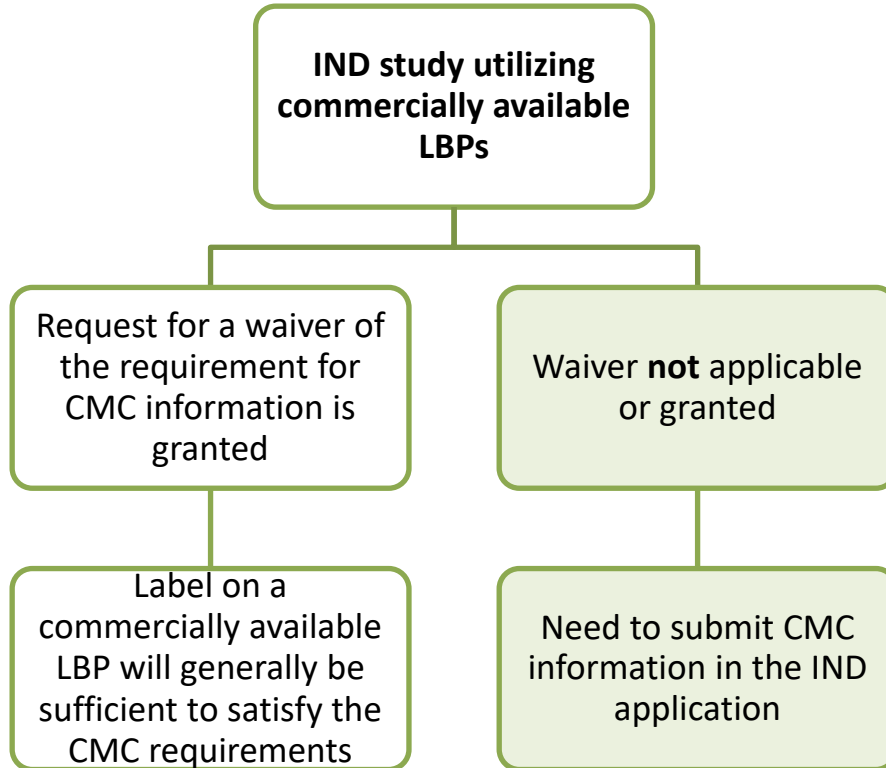
- Commercially available probiotics may fit the definition of an LBP depending on the intended use.

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

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 all 4 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

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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>



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