

Regulatory Considerations - Product Development, Preclinical Testing and Toxicity Issues

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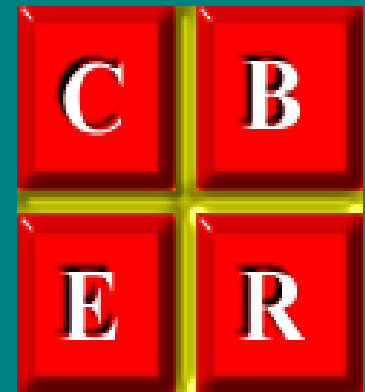
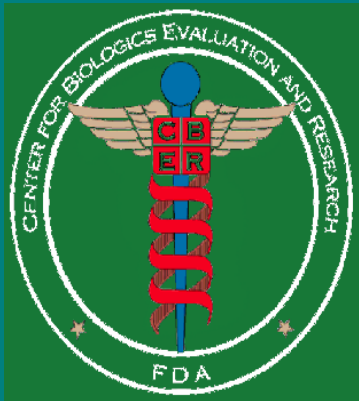
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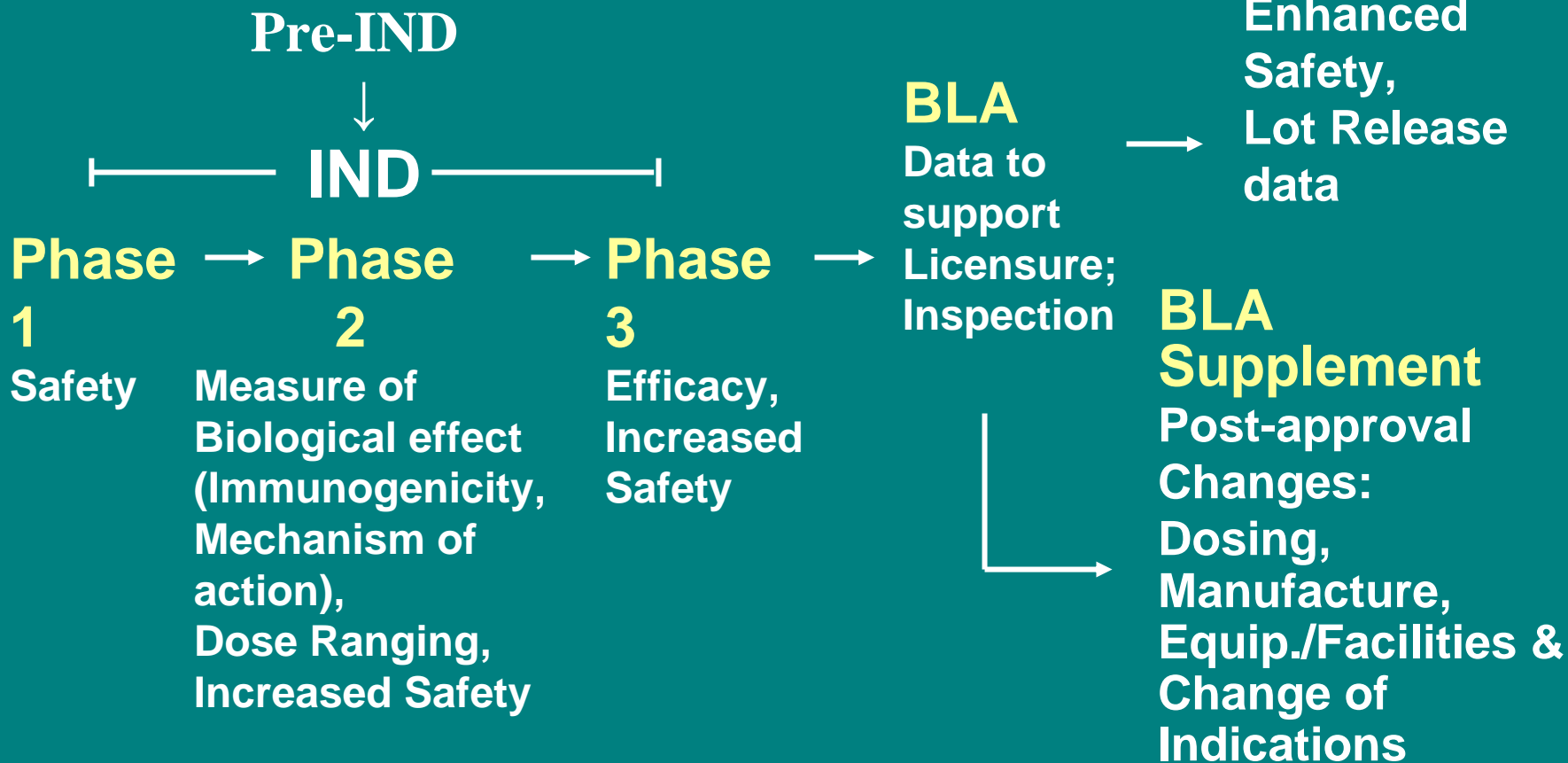


Regulatory Definitions

- **Drug** – article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (Food, Drug & Cosmetic Act of 1938). CDER
- **Biological product** – any virus, therapeutic serum, toxin, anti-toxin or analogous product, applicable to the prevention, treatment or cure of diseases or injuries of man (21 CFR600.3). CBER
- **Dietary supplement** - a product taken by mouth that contains a “dietary ingredient” intended to supplement the diet (DSHEA of 1994, amendment to the Food, Drug & Cosmetic Act). CFSAN

Stages of Review and Regulation

Clinical Investigational Plan



IND =Investigational New Drug Application; BLA=Biologics License Application

PRE-IND MEETING-1

A. Purpose of Meeting- (Sponsor provides formulated questions)

B. Meeting Request, Information Package, and Format-

See section II of SOPP 8101.1 for general aspects regarding the meeting request, information package, and format for the meeting.

C. Focus of Meeting

The pre-IND meeting should focus on any specific questions related to the planned clinical trials. The meeting should also include a discussion of various scientific and regulatory aspects of the product as they relate to safety and/or potential clinical hold issues. Basically, sponsor may ask any question related to IND submission.

PRE-IND MEETING-2

The CMC issues that can be discussed in pre-IND meetings include, but are not limited to:

1. Physical, chemical, and/or biological characteristics of product
2. Manufacture – site
3. Source and method of preparation
4. Removal of toxic reagents
5. Quality controls (e.g., identity assay, purity)
6. Formulation
7. Sterility/Bioburden (e.g., sterilization process, release sterility and endotoxin testing, if applicable)
8. Linkage of preclinical pharmacological activity to clinical trial batches
9. Product Stability information (different temperatures over time)
10. Safety

Regulatory Definitions - (21 CFR 600.3)

- **Safety**

- Relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered...

- **Purity**

- Relative freedom from extraneous matter in the finished product...

- **Potency**

- Specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

General information about meetings can be found in the following documents:

- **Section 119 of the Food and Drug Administration Modernization Act (Pub. L. 105- 115).**
- **Regulations applicable to meetings on investigational products in 21 CFR 312.47**
- **FDA guidance for industry on Formal Meetings with Sponsors and Applicants for PDUFA Products (Feb,2000)**
- **FDA guidance for industry on Fast Track Drug Development Programs Designation, Development and Application Review (November 1998)**
- **FDA policies and procedures for formal meetings with external constituents described in CDER's Manual of Policy and Procedures (MAPP 4512.1) and CBER Standard Operating Procedures and Policies (SOPP) 8101 .1**

What are Probiotics or Prebiotics versus Live Biotherapeutics?

- **Probiotics** – No single standard definition

- “Live microorganisms which when administered in adequate amounts confer a health benefit on the host” (joint FAO/WHO working group, 2002)

- “Microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being”. (Marteau et. al, 2002)

- **Prebiotics**

- “A non-digestible food ingredients that beneficially affects the host by selectively stimulating the growth and or activity of one or a limited number of bacteria in the colon, that can improve the host health”

- **Live Biotherapeutics (LBP)**

- CBER/OVRR working definition

- Live microorganisms with an intended therapeutic effect in humans (may include bacteria or yeast, may be used in disease prevention or treatment, intended for local or regional action, and include probiotics for clinical use)

Microorganisms Reported Having Health Benefits Include

- *Lactobacillus acidophilus*
- *Lactobacilolus rhamnosus*
- *Lactobacillus plantarum*
- *Lactobacillus casei*
- *Lactobacillus bulgarius*
- *Bifidobacterium infantis*
- *Bifidobacterium longum*
- *Streptococcus thermophilus*
- *Escherichia coli* Strains
- *Saccharomyces boulardii*

Biological Nature of the Component Organisms in LBP

- 1. Source and history of the organisms**
 - a. Strain passage from the original isolate to the current form
 - b. It is insufficient to merely cite intermediate sources such as procurement through ATCC or other commercial providers
 - c. Details of the health status of the host from which the organism was derived (e.g. HIV, Hep B status)
 - d. Method and media used in the propagation of original strain-Critical regulatory consideration

Biological Nature of the Component Organisms in LBP

2. Safety

- a. Phenotypic and genotypic characterization.
- b. Biological activity or genetic loci that may be potency or toxicity indicating.
- c. Genetic attenuation: Details of the genetic construction.
- d. Product organisms **should not** be more ecologically fit than their natural, wild type counterpart.

Biochemical Characterization Should Include:

- 1. Methods for identification of LBP.**
- 2. Antibiotic sensitivity/resistance profile (antibiogram of the actual drug product organisms). Rule out the presence of transposable/transmissible genetic elements**
- 3. Analysis of residual virulence.**
- 4. Ability to produce microbial substances such as bacteriocins, hydrogen peroxide or lactic acid**
- 5. Proposed mechanism of action. Information is useful in establishing safety & potency assays, which are integral to product development.**

Non-clinical Assessment of LBP-1

- 1. Data from pharmacologic or toxicology studies (in lab animals and /or in vitro)- for safety prior to clinical studies.**

- 2. The type, duration and scope of animals and other tests required vary with the duration and nature of the proposed clinical studies. The information on animals should include, but is not limited to :**
 - a. the species and age of the animals**
 - b. the health status of the animals, e.g., specific pathogen free**
 - c. the results of adventitious agent screening**
 - d. the animal husbandry practices, e.g. quarantine procedure, used to ensure the suitability of the animals**
 - e. veterinary and laboratory monitoring are used to ensure the suitability of the animals**
 - f. a description of the inoculation of the animals**
 - g. a description of the tissues harvested and the method of harvest.**

Non-clinical Assessment of LBP-2

- 3. Safety assessment of LBP includes the following evaluation of the microorganisms:**
 - a. Antibiotic sensitivity**
 - b. Ability to adhere, colonize and inhibit pathogen binding**
 - c. Duration of fecal shedding**
 - d. Potential translocation across the gut lumen under certain circumstances**
 - e. Adequate attenuation/inactivation/control for reversion to toxicity/virulence**
 - f. Reproductive toxicology studies, if necessary**

Toxicity studies should address-1

- 1. Local inflammatory reactions**
- 2. Systemic toxicities**
- 3. Immune-mediated toxicities**
- 4. Liver and renal function tests (e.g., ALT, AST, creatine kinase & BUN)**
- 5. Hematologic analyses (CBC & differential)**
- 6. Data should be collected at specific intervals during treatment and following recovery periods (e.g. 1 to 3 days and two weeks or more following the last dose) to evaluate the reversibility of any potential adverse effect**

Toxicity studies should address -2

- 7. At study termination, a complete gross necropsy (including gross lesions and organ weights) and full tissue collection and preservation should be conducted.**
- 8. Potential toxic effects of the products should be evaluated via histopathology with regard to selected organs and potential reversibility of observed toxic effects.**
- 9. Ideally, the toxicity studies, and generally all animal studies are conducted in compliance with the GLP regulations with the exact formulation proposed for use clinically.**
- 10. As product and clinical development proceeds, additional toxicity studies may be necessary to further assess potential safety concerns that have been identified in the literature or that may arise during Phase 1 and 2 clinical trials.**

Manufacture

- 1. Identification of the Manufacturer.**
- 2. Facility diagrams (HVAC, heating, ventilation and air conditioning systems, water systems, computer systems)**
- 3. Contamination precautions (Cleaning procedures and Validation)**
- 4. Manufacture of other products.**

Methods of Manufacture

1. **Raw materials** (list of all materials used in the manufacture of the drug substance, their tests and specifications and certificate of analysis of purchased materials)
2. **Flow Charts for manufacturing facilities and processes**
3. **Detailed Description** (master and working cell banks, cell growth and harvesting, tests for purity, identity and biological activity, a list of final acceptance criteria for the purified drug substance, description of storage conditions and time limits, verification of the stability of the drug substance, batch records)
4. **Process Validation** (Validation studies of each critical process or factor that affects drug substance manufacture should be provided)
5. **Manufacturing consistency**
6. **No bovine or ovine-derived products from unapproved sources at any stage in isolation, passage or manufacture.**

cGMPs For INDs

- As of May 2, 2006 FDA is withdrawing the direct final rule published in the Federal Register of January 17, 2006 to amend the current good manufacturing practice (cGMP) regulations for human drugs, including biological products to exempt most investigational “Phase1” drugs from complying with the requirements in FDA’s regulations. FDA is withdrawing the rule because significant adverse comments were received.

Drug Product Characterization/Specifications

1. **Composition** (Drug Substances, Excipients, Adjuvant, Preservative)
2. **Analytical Methods for Drug Product Characterization and Specifications** (Description, Identity, Purity, Potency, Residual moisture, Pyrogenicity, pH, Particle count, Chemical analysis - to show Lot to Lot Consistency)
3. **Sterility** (oral product-low bioburden allowed- USP Microbial Limits Test)
4. **General Safety Test-** Unexpected Toxicity (exemption can be requested)

Drug Product

Characterization/Specifications

4. **Drug Product Stability** (Dating period and recommended storage conditions, for lyophilized products stability after reconstitution).
 - A. **Stability Protocol** (potency, physiochemical measurements which are potency indicating, moisture if lyophilized, pH if appropriate, sterility, viable cells and pyrogenicity).
 - B. **Stability Data and Ongoing Stability Program**
5. **Environmental Assessment** (21 CFR Part 25 or a request for a categorical exclusion with rational basis for exclusion).
6. **Assess Potential Adverse Effects** (e.g. Guillain Barre Syndrome, Reiter's syndrome).

Summary

- Probiotics for clinical use are regulated as biological products by FDA's Center for Biologics Evaluation and Research (CBER)
- Currently CBER refers to probiotics for clinical uses as live biotherapeutic products.
- Based on experience to date, CBER has identified some issues for consideration in the development of live biotherapeutics(e.g. colonization/length of shedding, antibiotic sensitivity/resistance)
- Sponsors are encouraged to take advantage of pre-IND and other formal meetings with FDA to expedite product review.
- IND review process is a data driven scientific review and requires submission of all supporting data

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