Regulating Pre- and Pro-biotics: a US FDA Perspective

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Objectives

• Review the terms probiotic, prebiotic, and biotherapeutic.

• Review the regulatory definition of drug, biologic, dietary supplement and GRAS.

• Discuss the regulatory difference between a dietary supplement and a drug/biologic.

• Focus on the regulation of probiotics as biologics.

• Discuss regulatory considerations in the development of probiotics for clinical indications.
Non-regulatory Terms

• Probiotic
• Prebiotic
• Live Biotherapeutic
“Probiotic”

- Broad use of the term.

- 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 ....” (Salminen et al., 1999)
“Prebiotic”

• “A non-digestible food ingredient 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.” (Gibson & Roberfroid, 1995)

• Non-digestible substance
  – enhances probiotic growth
  – serves as fermentation media for probiotics

• Oligosaccharides
“Live Biotherapeutic”

• 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 local or regional action
    • Includes “probiotics for clinical use”

• “Biotherapeutic Agent”
  – Defined by Elmer, McFarland and Surawicz in *Biotherapeutic Agents and Infectious Diseases*:
    • “Microorganisms having therapeutic effects in humans.”
    • Excludes “probiotics,” defined as “microorganisms having general beneficial effects on the health of animals or humans.”
How are probiotics and prebiotics regulated in the US?
Intended use determines how a substance is regulated.
Regulatory Definitions

- **Drug** – article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (Food, Drug & Cosmetic Act of 1938).

- **Biological product** – a “virus,” (i.e., bacteria, fungi, etc.) “…etc….applicable to the prevention, treatment, or cure of a disease or condition of human beings (Public Health Service Act of 1944, 42 USC §262).

- **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).
GRAS

- “Generally Recognized As Safe”
- 21 CFR 170.3 and 170.30
- A food ingredient classification that distinguishes a substance from a food additive on the basis of common knowledge about safety for its intended use.
- Pertains to the use of a food substance, rather than the substance itself.
Dietary Supplement vs. Biological Product

• A probiotic may be marketed and regulated as a dietary supplement and/or a biological product. It all depends on how it is intended to be used.

• Biological products require premarket review and approval by FDA. Dietary supplements do not.

• The safety, purity and potency, as well as efficacy, of a biological product must be demonstrated for approval. Dietary supplements need not demonstrate any of these to be marketed.
FDA’s Center for Food Safety and Applied Nutrition (CFSAN) regulates probiotics and prebiotics marketed as dietary supplements or food ingredients.
When is a probiotic a drug/biological product?
A probiotic used to diagnosis, cure, mitigate, treat, or prevent disease is a drug and a biological product.

FDA’s Center for Biologics Evaluation and Research (CBER) regulates probiotic products when used for clinical indications.

CBER’s Office of Vaccines Research and Review has regulatory jurisdiction over most probiotic products for clinical use.
Unapproved Drug

A probiotic product marketed or promoted as a treatment, prevention or cure for a specific disease or condition without an approved indication for such is considered an unapproved and thus, illegal drug.
A probiotic manufacturer who intends to market a probiotic product based on a drug claim must seek approval for that claim.
Currently, CBER/OVRR views probiotics for clinical use as live biotherapeutics.

- CBER/OVRR has vast experience in regulating products that contain microorganisms and/or their components.
- Focus & experience to date has been on the safety and activity of ‘live’ agents.
Biological Product Development

• Data to support approval of a biological product are provided to CBER in a Biologics License Application (BLA) for review.

• Clinical data for inclusion in a BLA are generated during the investigational phase of drug development.
Stages of Premarket Review & Regulation for Live Biotherapeutics

Pre-IND

Phase 1
Safety
Colonization? Other?

Phase 2
Safety
Dose-Ranging
Colonization? Other?

Phase 3
Safety
Efficacy
Colonization? Other?

BLA
Data to support approval; Inspection

IND = Investigational New Drug Application; BLA = Biologics License Application
Conducting clinical studies of probiotics under US IND

• A probiotic intended for study of an unapproved indication is an investigational new drug.

• An investigational new drug application (IND) is submitted to FDA/CBER for review.
  – Protocol for the proposed study of the probiotic product in humans
  – Data (product, nonclinical, previous human, etc.) to support study in the intended population

• IND regulations are found in chapter 21 Section 312 of the U.S. Code of Federal Regulations (21 CFR 312).
The IND as a Mechanism & Process for Collecting Data

• Clinical
  – Safety and efficacy
  – To support a BLA
  – Other (e.g., colonization)

• Data to support study of the product in humans
  – Chemistry, manufacturing & controls (CMC)
  – Stability
  – Pharmacology/toxicology
A CBER-approved biological product must be...

• Safe (21 CFR 600.3)
  – Relative freedom from harmful effect when prudently administered...

• Pure (21 CFR 600.3)
  – Relative freedom from extraneous matter in the finished product...

• Potent (21 CFR 600.3)
  – Specific ability…to effect a given result.

• Manufactured consistently according to current Good Manufacturing Practices (21 CFR 210-211).
Some issues to consider in the development of live biotherapeutic products

1) Inconsistent use of term “probiotic” and lack of a standard definition for this product area.

2) Misuse of the term “GRAS.”
3) Inadequate chemistry, manufacturing and controls (CMC) data to support use of a live biotherapeutic product in clinical trials.

a) When the IND sponsor is an investigator and not the manufacturer of the product, the manufacturer may submit such proprietary data directly to CBER for review in a Master File.

b) Probiotic manufacturers may not be familiar with biological product manufacturing requirements, which greatly exceed those for manufacture of dietary supplements.
Issues (cont.)

4) Need for education among probiotics investigators and sponsors on:
   – How to prepare and submit an IND
   – Drug and biologic regulations in general.

5) Product development should focus on demonstrating a clinical benefit that has to be reflected by a meaningful treatment effect.
Issues (cont.)

6) Consensus on the importance of colonization, how it should be defined, and how and when it should be evaluated in clinical development.

7) How potency should be defined and evaluated for these products.

8) Concerning safety, the potential pathogenicity of product strains.
Conclusions

• Probiotics for clinical uses 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.
References


References (cont.)


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• For food and drug related laws: [http://www.fda.gov/opacom/laws/](http://www.fda.gov/opacom/laws/)
References (cont.)

• Online CFR:

• CBER weblink on submitting an IND:
References (cont.)

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