

Development of Probiotics as Biologic Drugs

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In the United States, probiotics that are intended to be used to diagnose, cure, mitigate, treat, or prevent disease in humans or other animals and that affect the structure or the function of the body are considered to be drugs. This article provides a brief overview of the historical basis of US regulation of drugs and biologics and explores the legal, regulatory, and policy considerations for probiotics as biologic drugs for humans.

Probiotics are ingredients. They are live microbes and are regulated in the United States as both foods and biologic drugs. The US Food and Drug Administration (FDA) is the key federal regulatory agency whose authority has an impact on both the clinical research and the development of probiotics as biologic drugs. The FDA regulates ~25% of the US gross national product, with jurisdiction over products in interstate commerce, the manufacturing and labeling of products, and, for prescription products, advertising and promotion [1]. As products, probiotics may be regulated by several FDA centers, depending on which regulatory category is being used. These centers include the Center for Food Safety and Applied Nutrition, which is responsible for foods, dietary supplements, and “foods for special dietary uses”; the Center for Veterinary Medicine, which is responsible for animal feed products and animal drugs; and the Center for Biologics Evaluation and Research (CBER), which regulates human biologics.

As live microbial products, probiotics have several potential sources of risk: (1) intrinsic toxicity (e.g., a dangerous bacterium), (2) intrinsic variation (e.g., virulent variants of the same bacterial species), (3) product misidentification, (4) product mislabeling, (5) contamination, and (6) adulteration. In 1901, 13 children who were given diphtheria antitoxin died of tetanus due to the use of contaminated horse serum. This tragedy resulted in the passage of the Biologics Control Act of

1902 [2]. This act authorized, for the first time, the federal government to inspect manufacturing facilities, to monitor manufacturing processes, and to require standards for product quality and proper product labeling. Other federal statutes followed. The Pure Food and Drug Act of 1906 required the declaration of ingredients on product labels [3]. In 1938, Congress passed the most comprehensive food and drug legislation the world had yet seen: the Federal Food, Drug, and Cosmetic Act [4]. As currently amended, the Food, Drug, and Cosmetic Act defines the terms “drug” and “new drug” and authorizes the FDA to ensure that drugs are both safe and effective before marketing. “Drugs” are defined as “articles...intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, and articles (other than food) intended to affect the structure or function of the body” [5]. If a drug is “not generally recognized as safe and effective under the conditions prescribed, recommended, or suggested in the labeling (and marketed after 1938),” it is a “new” drug [6]. Prior to US marketing, new drugs must demonstrate both safety and efficacy. Efficacy is defined as “evidence consisting of adequate and well controlled investigations, including clinical investigations, by qualified scientific experts, that proves the drug will have the effect claimed by its labeling” [7].

In 1944, the Public Health Services Act revised and incorporated the original Biologics Control Act (Section 351), and, under Section 352, it permits the federal government to manufacture biologic products if the need arises [8]. Under the Public Health Services Act, a “biologic product” is defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or anal-

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ogous product... (or any...trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings” [9]. The CBER has regulatory responsibility for human vaccines, microbial and animal cell products, allergenic extracts and patch tests, cell and gene therapies, xenotransplantation, tissue, blood and its derivatives, and blood-related medical devices (e.g., hepatitis tests and HIV test kits) [1].

Regardless of how a probiotic is currently marketed, when it is intended to prevent or treat a disease or abnormal condition, it becomes a “drug.” According to an FDA working definition, probiotics are classified as “live biotherapeutics”: “live microorganisms with an intended therapeutic effect in humans, including bacteria and yeast used in disease prevention or treatment, intended local or regional action.” It includes “probiotics for clinical use” [10].

The development pathway for a “biologic new drug” is similar to that of any new drug. Following discovery, nonclinical safety testing precedes clinical safety testing and then efficacy testing. This approach is based on the “new” drug provisions of the Food, Drug, and Cosmetic Act, which is further defined by federal regulation [11]. The Investigational New Drug (IND) application exempts an unapproved new drug from the requirements of a marketed drug (i.e., safety and efficacy).

An IND application must be filed when a clinical investigation is to be conducted on an article when the article is an “unapproved” drug (i.e., not marketed as a drug in the United States) or when the article is an “approved” drug and the clinical investigation is intended to significantly “change labeling and/or current use, route, advertising, promotion, etc.” “Clinical investigation” means any experiment in which a drug is administered to one or more human subjects [12]. An “unapproved” drug is a product not generally recognized as safe and effective when used as labeled (also called a “new” drug), as defined in Section 201(p) of the Food, Drug, and Cosmetic Act (Section 321(p)) (standard language from sample FDA Warning Letters) [13]. Because there are currently no probiotics approved as “drugs” in the United States, a probiotic sponsor is required to file an IND application with the FDA before the initiation of clinical trials for a “drug” indication.

The conditions for filing an IND application exclude the use of the product under the “practice of medicine.” Practice of medicine is the use of any product legally available in the United States to a licensed health practitioner for the management of his or her patients, as long as the practitioner is not manufacturing, marketing, advertising, or promoting the product for an “unapproved” use, if premarketing approval for that indication is required. This scenario includes the “off-label” use of approved drugs.

Biologics must demonstrate safety, purity, and potency. Safety is defined as “relative freedom from harmful effect to persons

affected, directly or indirectly, by a product when prudently administered....” Purity is the “relative freedom from extraneous matter in the finished product....” Potency is the “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” [14].

Safety information may include documented human experience—for example, historical, traditional, anecdotal, and postmarketing surveillance from other (food) uses, and so forth. However, the prior human use must be applicable to the intended use of the product as a drug—for instance, oral use of a probiotic as a food does not directly support its topical administration as a drug. Nonclinical assessment of safety consists of toxicology studies in animals, testing for systemic toxicity (e.g., clinical, gross and histological pathology, and blood chemistries). This assessment should include examination for local inflammatory reactions and immune-mediated toxicities (e.g., allergy). In the selection of animals for study, it is important to consider species specificity and to identify appropriate dosing, route of administration, and treatment schedules to support those planned for the clinical protocols. The CBER recommends that safety studies also assess the antibiotic susceptibility of the strain, adherence, colonization, pathogen-binding inhibition, duration of fecal shedding, potential translocation across the gut lumen under certain circumstances, and adequate attenuation, inactivation, and/or control for reversion to toxicity or virulence [15]. Classic pharmacologic assessments, such as absorption, distribution, metabolism, and excretion (“ADME”) studies, are not particularly useful or feasible for probiotics. Bioassays, however, may be very helpful in establishing potency.

Biologics differ from other drugs in that they are required to have an approved Biologic License Application (BLA), rather than a New Drug Application (NDA) for marketing. The Food, Drug, and Cosmetic Act applies to “a biological product..., except that a product for which a license has been approved...shall not be required to have an approved [New Drug (NDA)] application under Section 505 of such Act” [16]. BLAs are approved on the basis that the biologic product is “...safe, pure, and potent, that the manufacturing facility...meets standards” designed to assure that the biological product continues to be safe, pure, and potent; and the facility passes FDA’s inspection [9].

Examples of FDA requirements for a licensed bacterial biologic are demonstrated in the following excerpts from an approval letter for a bacille Calmette-Guérin (BCG) product: “You are requested to submit to...CBER samples of each future lot of product in final containers together with protocols showing the results of all applicable tests; No lots of product shall be distributed until notification of release is received from the

Director, CBER; ...Any changes in the manufacturing, testing, packaging, or labeling of BCG Live, the accompanying diluent, or in the manufacturing facilities may require submission of a Supplement to your license application for our review and written approval prior to implementation; ...It is requested that adverse experience reports for BCG Live be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that the distribution reports be submitted as described (21 CFR 600.81); ...Please submit three copies of the final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information; ...In addition, please submit three copies of the introductory advertising and promotional labeling" [17].

How probiotics are regulated in the United States has a major impact both on product development and on their clinical research. Because probiotics are derived from nature, they are unpurified heterogeneous mixtures with multiple and undefined "active" principles. Changes to the product manufacturing process can result in a different product; the process is the product! To address the natural heterogeneity of this product class, lot-release protocols are required, defined by manufacturing process controls.

Prior human use alone of a probiotic may be insufficient to support initial clinical studies under an IND application if this use does not match the intended use as a drug. Probiotics marketed as foods in the United States are usually not manufactured to pharmaceutical-grade requirements; therefore, additional manufacturing controls may be necessary, in particular to reduce lot-to-lot variability of the product. More importantly, until December 2006, supplement manufacturers were not required to submit serious adverse events to the FDA [18]. A lack of reported adverse events does not imply safety for a particular patient population. Finally, very few large-scale, long-term clinical trials of probiotics have been conducted, and published journal articles often omit details necessary to support drug development.

Reasons for filing IND applications or BLAs include oversight of the manufacturing process and consistency of the manufacturing process, leading to reproducible clinical results. Data collected under an IND application can usually support the BLA (marketing application). An approved BLA permits the product sponsor to make claims based on adequate and well-controlled trials. Such claims can be used in advertising and promotion and are usually exclusive to the product. Approval also increases acceptance by the medical community and makes

reimbursement more likely for those products sold under prescription.

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