

Business Considerations in the Development of Probiotics

Freddie Ann Hoffman

HeteroGeneity, Washington, D.C.

Many opportunities exist for probiotics in the marketplace. Over the course of a 2-day workshop on probiotics, current and potential uses for probiotics were examined. This article discusses many of the elements that should be considered in the decision to market probiotics as foods, dietary supplements, or drugs.

Industry stakeholders for probiotics include businesses involved in conventional and specialty foods, dietary supplements, consumer health care, biopharmaceuticals, veterinary health care, and agriculture. Although the workshop was focused mainly on the use of probiotics in humans, agricultural and veterinary uses should not be overlooked.

Marketing decisions usually reflect a company's core business and competencies. Internal corporate strategy should take into account the market niche (e.g., consumers or patients); access to distribution channels; pricing, profit margins, and proprietary insulation in the marketplace; and so forth. With this said, many companies underestimate the full impact of regulatory requirements on both business objectives and plans for product development.

Probiotics are natural products. Historically, many probiotic strains have been dietary components. In the United States, probiotics can be regulated as foods, including conventional foods, dietary supplements, and "foods for special dietary uses" (including "medical foods"); as drugs, both prescription and nonprescription; as cosmetics; and as medical devices.

Categorization of most products in the United States can be determined on the basis of 4 underlying regulatory elements: (1) administration route, (2) formulation, (3) safety, and (4) intended use. Topically ad-

ministered products can be marketed as cosmetics, drugs, and medical devices but not as foods. Foods, including dietary supplements, must be ingested and must exert their effects systemically. Probiotics sold as sauces, dips, desserts, or beverages are considered to be in "conventional" food formats. Acceptable formulations for dietary supplements are specified by law and include tablets, capsules, drops, and sachets. Foods in conventional food formats (e.g., beverages) cannot be labeled as dietary supplements [1].

Whether a product can be marketed directly to consumers or can qualify as a food or dietary ingredient depends on how safe it is. "Safety," however, is a relative term. Because foods are marketed to the general public, they must be intrinsically safe, and little if any risk is acceptable. Ingredients found in conventional foods or dietary supplements must either be "generally recognized as safe" (GRAS) [2] or have "the history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe" [3], or they must be approved food additives [4]. Active ingredients for drugs either are GRAS and "generally recognized as effective" ("GRAE") [5] or must be approved "new" drugs. A "new" drug is defined as a drug that is "not generally recognized as safe and effective under the conditions prescribed, recommended, or suggested in the labeling" [6]. Although a drug may not be safe for everyone, it may be safe for a particular use in a target population for whom the clinical benefit outweighs the risk. The sponsor of a "new" drug must develop data to support the drug's safety and efficacy for a specific indication, which eventually will be

Reprints or correspondence: Dr. Freddie Ann Hoffman, HeteroGeneity, LLC, 5611 16th St. NW, Washington, DC 20011 (fhoffman@heterogeneity-LLC.com).

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submitted to the US Food and Drug Administration (FDA) for premarket approval in a marketing application (for probiotics, this is the Biologics License Application or “BLA”). The first step in this process is usually the filing of an Investigational New Drug (IND) application.

Arguably, the most important factor in determining a product’s regulatory category is the manufacturer’s “intended use.” Intended use is established through the claims made on the product label (i.e., indication), the package, the package insert, and all aspects of advertising and promotion of the product (i.e., “labeling”). The Food, Drug, and Cosmetic Act legally defines products on the basis of their intended use. Foods are defined as articles used for food or drink. This category includes chewing gum and components of any such articles [7]. Drugs are defined as articles “intended for use” in the “diagnosis, mitigation, treatment, cure, or prevention of disease” and to “affect the structure or function of the body” [8]. The definition of a drug also pertains to biologics, where a biologic “means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product... (or any...trivalent organic arsenic compound), *applicable to the prevention, treatment, or cure of a disease or condition of human beings*” [9, italics added].

The types of claims that a product may bear are also based on the product’s regulatory category. Food claims reference taste, flavor, energy, growth, weight, body composition, nutrient content (e.g., “low fat” or “a good source of ____”), and disease-risk reduction. Similar claims can be made for dietary supplements, but they may also include claims of “well-being,” health promotion, or health maintenance, as well as claims about nutrient and nonnutrient effects on the body’s structure or function. However, the drug category allows the broadest range of claims. Drugs can bear not only “structure or function” claims but also direct claims to diagnose, treat, prevent, mitigate, or cure disease (also called “disease” claims). The level of evidence needed to support the claims made for drugs, however, is substantially greater than that for other categories and requires “adequate and well-controlled clinical studies” [10].

Selecting the “right” product is the initial challenge in developing a probiotic. A history of prior human use can often be used to support certain claims and indications for probiotics, particularly if they are marketed as foods. However, changes in the manufacturing process and/or genetic modification result in a different product from the original, for which new data must be generated to document safety.

Clinical use of probiotics, particularly for disease states, necessitates a highly reproducible product. For complex drugs and biologics, validation of each step of the manufacturing process is a fundamental means of controlling intrinsic product variability. Lot-to-lot consistency is achieved through tight lot-release specifications and through the potency and stability test-

ing that is required for drug-grade products. Requirements for drug manufacturing, also called “good manufacturing practices” (GMPs), differ significantly from the GMPs for foods. Source materials for foods can be changed without prior notification of the FDA. For complex drugs and biologics, sourcing is not interchangeable. This is also true for changes in the manufacturing process. For these reasons, it is essentially impossible to develop a probiotic as a drug unless the product manufacturer is willing to provide sufficient details to the FDA about the manufacturing process and controls. This information can be supplied confidentially, either in an IND application or in a separate document called a “drug master file” (“DMF”) that the FDA may reference in support of a specific IND application.

Decisions about which probiotic strain to pursue and the desired regulatory pathway should be made as early as possible in the development process. Choosing a product that is “overmanufactured” or “undermanufactured” will translate into longer time lines and unnecessary costs. For example, the initiation of testing of a food-grade product for a drug indication will eventually lead to required manufacturing upgrades and may result in the need to repeat clinical studies with pharmaceutical-grade product. Using a drug-grade product to produce a food will add needlessly to the cost of goods, which cannot easily be recovered in the marketplace.

How does the development of probiotics compare with that of other classes of drugs? Before clinical studies can begin, development of a single “new chemical entity” as a drug usually starts at the “discovery” stage, followed by in vitro and in vivo screening, modeling, formulation, and safety testing in animals. In contrast, most probiotics are already in use in humans. From a product standpoint, however, probiotics are more complicated than are single chemical entities. Unlike synthetic molecules, live microbial products require consistent sourcing, may pose more-complicated issues regarding chemistry, manufacturing, and controls (“CMC”), and usually require a scale-up of the manufacturing process for marketing. Formulation and packaging may also pose significant challenges to maintain stability and to ensure live, active cultures. With this said, prior human use and recognized biological activity make probiotics particularly good candidates for drug development. What is known regarding the safety and potential biological activity of the probiotic can replace nonclinical testing by providing direction to the design and implementation of the clinical trials needed for drug approval. This may allow the initiation of clinical trials very early in the development process, thereby streamlining and shortening the time to market.

As products of nature, probiotics may not always be patentable. Even so, such products may have protection by other means. US law maintains strict confidentiality for drugs developed under the “new” drug provisions in the Food, Drug

and Cosmetic Act. In addition, the complexity of the product, along with marketing exclusivity, can provide protection against competition for probiotics as drugs [11]. Although parts of the Food, Drug and Cosmetic Act apply to biologics, biologics are not “required to have an approved application under of such Act (21 U.S.C. 355)” [12]. As a result of this legal point, generic biologic drugs do not currently exist.

In summary, opportunities for the use of probiotics will continue to include foods and dietary supplements. However, as more scientific evidence accrues, there also may be opportunities to develop these products as drugs. If a probiotic were to be licensed by the FDA as a biologic drug, it would not be the first live biotherapeutic to traverse the FDA process. Several bacille Calmette-Guérin products already have been licensed [13].

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