The US Food and Drug Administration and Probiotics: Regulatory Categorization

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Probiotics are living microorganisms that, when consumed, have the potential to confer a beneficial health effect. Unfortunately for purveyors of probiotic products, the system of regulation delineated in the Food, Drug, and Cosmetic Act is anything but “one size fits all.” How a probiotic product is used or is intended to be used will govern the regulatory category or categories that the US Food and Drug Administration (FDA) will assign to the product. The extent and nature of the restraints and data-collection requirements that may be imposed on the marketing of a product hinge on how a product is categorized under the Act. More specifically, the categorization of a product governs the respective regulatory burdens of an industry sponsor and the FDA. Premarket systems, such as those for new drugs and biologics, place a heavy evidentiary burden on the sponsor of a product. Postmarket systems, such as those for dietary supplements, place, at least initially, a higher regulatory evidentiary burden on the FDA than on the product sponsor. This article explains regulatory categorizations under the Food, Drug, and Cosmetic Act and their effects regarding the federal regulation of probiotic products.

The Food, Drug, and Cosmetic (FDC) Act [1] lays out a highly varied legal framework that governs a wide array of products. The system of regulation delineated in the FDC Act is anything but “one size fits all.” When one stands back and, employing a scientific and public health perspective, thinks about how best to regulate foods, drugs, biological products, medical devices, and the array of other products that the US Food and Drug Administration (FDA) oversees, the diversity of requirements and sanctions found in the FDC Act makes sense. Simply put, some products, by virtue of the claims made on their behalf or of the risks they present, merit more concern, attention, substantiation, and vetting than do others. Under the regulatory system laid out in the FDC Act, the nature of the restraint that can be imposed on a given product (and on its purveyor) hinges, in large part, on how the product is categorized.

Accordingly, the notion of “categorization” is key to understanding the type and scope of regulation under the FDC Act and why the regulatory status of products containing probiotics—components that are widely viewed as safe and potentially beneficial—is far from cut-and-dried.

Specifically, how a product is categorized under the FDC Act governs the regulatory and evidentiary burdens that the sponsors and the FDA have with respect to demonstration of the lawfulness of a given product. For example, if a product falls within the definition of “food additive,” “new drug,” or “biological product,” an evidentiary burden is placed on the sponsor to demonstrate the propriety of its product before the product may be marketed lawfully. Conversely, other product categorizations under the FDC Act result in regulation under “postmarket” systems, which permit a manufacturer to place a product on the market without first seeking clearance from the FDA. This, in turn, places an evidentiary burden on the FDA to take action against that product. Understandably, if the FDA has a regulatory concern about a marketed product, the FDA may look for ways to categorize that product so that it is subject to premarket, as opposed to postmarket, controls, which thereby reduces the regulatory and evi-
dentistry burden on the FDA with regard to restricting the marketing of that product.

One final general point needs to be made about categorization: regarding matters deemed by the FDA to present meaningful public health benefits, there has been, on occasion, a certain tension about how the FDA opts to administer and apply the FDC Act. This tension regards whether the FDA should opt to foster restraint or to foster innovation. The FDA’s regulation of plant biotechnology provides a relatively recent and clear example of the agency’s conscious decision to choose the latter. In doing so, the FDA considered the promising potential of the technology to yield a safe and abundant food supply and, in light of that potential, opted to pursue regulatory pathways and categorizations that are tailored, in part, to encourage innovation, not restrict it. Of course, it must be kept in mind that, as a matter of routine, the FDA, as a public health protector, is naturally inclined to favor restraint in its efforts to ensure the public health. Nevertheless, history reveals that, on occasion, the FDA is open to innovative regulatory approaches when doing so is in the interest of public health.

Thus, in the context of probiotics, a scientific and policy-based issue arises: Do probiotics and the potential advantages they offer in the context of potentially healthier and more beneficimer consumer products provide a basis for the FDA to consider flexible regulatory pathways to encourage the development of such products?

PROBIOTICS: WHAT REGULATORY CATEGORIES APPLY?

The use of probiotics in products can result in several regulatory categories, 4 of which are fundamental: “food” or food ingredient, “medical food,” “dietary supplement,” and “drug” or “biological product.” The categorization of a product is determined in large part by its intended use, as in the following examples.

1. An article is a medical food if it is intended for enteral use in the “dietary management of a disease or condition for which distinctive nutritional requirements have been established by medical evaluation” and is formulated to be administered “under the supervision of a physician” [2].

2. An article is a dietary supplement if it is intended to “supplement the diet,” is or contains a “dietary ingredient,” is “intended for ingestion,” and is not in “conventional” food form [3].

3. An article is a drug if it is intended for the cure, mitigation, treatment, diagnosis, or prevention of disease [4].

4. An article is a biological product if it contains a virus, serum, or toxin “applicable” to the prevention, treatment, or cure of a disease or condition [5].

Foods are the only FDA-regulated product categorized not by “intended use” but rather simply by “use”; a “food” is circularly defined as “an article used for food” [6].

REGULATORY CONSEQUENCES FOR PROBIOTICS THAT DEPEND ON CATEGORIZATION

Drug, biological product, or new drug. The FDA’s current (and defensible) position is that a probiotic product intended for use as a “drug” is also a “biological product.” If the product meets the definition of “new drug” found in section 201(p) of the FDC Act [7], the FDA will require an approved Biologics License Application for any intended clinical use and will apply the pertinent drug regulations, including the requirements of an Investigational New Drug application for clinical inquiry into the safety and efficacy of the product.

The foregoing proposition raises the fundamental question, What is a new drug? “New drug” is a statutory term of art [8]. A drug is a new drug if it is not “generally recognized as safe” (GRAS) and not “generally recognized as effective” (GRAE) for its intended use. GRAS and GRAE are demanding standards that call for expert agreement on whether publicly available data, of the same quantity and quality as required for the approval of a new drug application, exist and provide a basis for the conclusion that the drug is safe and effective for its intended use.

If a probiotic falls within the definition of a “drug” and is not GRAS and GRAE, then the probiotic also falls within the definition of a “new drug” and, accordingly, is subject not only to rigid premarket clearance requirements but also to the testing requirements of the Investigational New Drug application, with regard to clinical studies. These requirements include the following steps:

1. Formal notification of the FDA about the intent to conduct clinical studies
2. Submission to the FDA of comprehensive test protocols
3. Development of an investigation plan
4. Institutional review board oversight [9] (As a practical matter, whenever a company sponsors clinical research involving any product, regardless of the regulatory categorization[s] attending the product, it is sensible to take the necessary steps to ensure that an institutional review board is used and that the fundamental commitment to the agency’s regulations [9] are met.)

Dietary supplement. The regulatory consequences that accompany a probiotic product that is categorized as a dietary supplement differ dramatically from those that accompany a probiotic categorized as a drug. For example, if a probiotic product meets the definition of a dietary supplement, no premarket approval is required for the dietary ingredients; however, notification requirements apply for “new dietary ingre-
enforcement action. It might disagree with the manufacturer’s assessment and bring approval. The risk in this situation, of course, is that the FDA will consider the propriety of the claim. If a manufacturer of a dietary supplement makes claims that fall within the statutory definition of a “health claim” (i.e., claims that characterize a relationship between a food [or a nutrient in the food] and a disease or health-related condition) [11], the manufacturer must secure either premarket clearance from the FDA for the claim or acquiescence from the FDA that, as a matter of its enforcement discretion, the agency will not take action against a “qualified” version of the claim.

**Food or food ingredient.** If a probiotic is categorized as a food or food ingredient, the FDA will regulate the probiotic component either as a food additive [12], subject to premarket clearance, or simply as a GRAS food ingredient, subject to regulation under the FDA’s postmarket controls that govern the adulteration of food. As with “new drugs,” GRAS is a gatekeeping concept. Similar to the concept in the context of new drugs, a food ingredient can be GRAS only if there is no genuine dispute among qualified experts as to whether the available scientific information provides a basis for the conclusion that the probiotic component is safe for its intended use in food. If a food ingredient is not GRAS, it is, by definition, a food additive and, as noted above, must go through a rigorous premarket clearance process before it may be marketed lawfully [13]. To facilitate regulatory decision making for industry and the FDA alike, the agency has implemented a premarket “notification” process, whereby it will consider, on the request of a sponsor, whether the question of GRAS status is presented by the use of a food ingredient. If the FDA concludes that it has no questions about the GRAS status of such use, a manufacturer may proceed to market without further premarket considerations. A manufacturer or user of an ingredient is free to make its own determination of whether an ingredient is GRAS for a given use and, thus, is not subject to premarket approval. The risk in this situation, of course, is that the FDA might disagree with the manufacturer’s assessment and bring enforcement action.

**Medical food.** If a probiotic product is categorized as a medical food, no premarket clearance requirements apply other than food-additive and GRAS considerations with respect to ingredients. Any claim made about a medical food must be limited to a focus on the dietary management of disease, must be conditioned on appropriate medical supervision, and must address a distinctive nutritional need.

In summary, as a practical matter, the intended use of a probiotic product will determine its regulatory categorization under the FDC Act. This categorization, in turn, will determine the regulatory status of the product. For example, depending on its intended use, a probiotic product can be categorized as a drug or biological product, as a dietary supplement, or as a food or food ingredient (including medical food). Depending on which of these regulatory categories applies, a probiotic product is subject to different requirements with respect to the conduct of medical tests, premarket versus postmarket authorization requirements, and evidentiary burdens to establish safety and to substantiate claims.

The spectrum of regulatory categorizations in the FDC Act is by no means perfect. It does reflect, however, a deliberate attempt on the part of Congress to avoid a one-size-fits-all approach to the regulation of products. Because probiotics may possess functional benefits beyond those that traditionally accompany food ingredients, the categorization approach of the FDC Act may appear arbitrary, if not problematic, when applied with full vigor (and rigor) to probiotic products. Nevertheless, the FDC Act reflects the understandable congressional judgment that claims made on behalf of a product should be subject to a scale of increasingly demanding scientific scrutiny and substantiation requirements that depends, in large part, on the nature and context of the benefit claimed. This structure helps create an environment that fosters scientific investigation. As scientific investigation of probiotics continues and as the safety and benefits of probiotics become more clear, the varied nature of the existing regulatory system may lead (as seen in the context of some products of biotechnology) to flexible agency policies and practices that tend to encourage rational but innovative product categorizations designed to encourage the development of beneficial probiotic products.

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