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Food and microbiota in the FDA regulatory framework

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Abstract

Ongoing efforts to develop microbiota-directed foods (MDF) provide potentially new ways for improving health status. A MDF could alter the structural and functional configuration of a consumer's gut microbial community, provide substrates for microbial transformation to biomolecules necessary for a healthy state, or act through a combination of these mechanisms. The development of MDFs promises to expand our view of 'essential nutrients' and prompt questions about how they should be classified and regulated.

There is increasing evidence that many features of our gut microbial communities (microbiota) are affected by our dietary practices. New understanding of how the microbiota transforms dietary ingredients into metabolic products that affect numerous aspects of human biology is altering our definitions of the nutritional value of foods [1,2]. Current work indicates that the manner of formation of the gut microbiota during early postnatal life, and the traits encoded by its set of several million microbial genes (microbiome) are important determinants of healthy growth and of various facets of our metabolic, physiologic, immune and perhaps neurologic phenotypes [3,4]. As such, this microbial community can be viewed as an intimate component and determinant of our human biology. Together, these advances are spawning efforts to develop foods that promote healthy community development during early postnatal life, prevent the loss of microbial diversity associated with Western diets, and repair structural and functional abnormalities associated with various disease states [5–8].

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Challenges posed by the current regulatory framework

Microbiota-directed foods (MDFs) can be defined as those designed to alter the properties of a consumer's gut community. It has been over 20 years since the last major revision of regulatory definitions for food ingredients in the US was issued. When the Dietary Supplement Health and Education Act of 1994 was signed into law, knowledge of the role of the gut microbiota in health and disease was limited.

Growing appreciation of how the microbiota generates biomolecules that are not produced by any of our human cell lineages and that affect our health status is forcing us to evolve our concept of essential nutrients to include some of these microbial products [9,10]. Moreover, a microbiota that cannot generate these products in adequate quantities may lead to disease and is therefore a target for reconfiguration by a MDF. Provision of a MDF could serve to alter the representation of existing members of the consumer's microbiota in a deliberate manner to affect the community's functional properties/capabilities, or it may provide a direct substrate that is transformed by the microbiota to a product or products necessary for a healthy state, or through a combination of these mechanisms.

Given the mechanisms by which MDFs may achieve their desired effect, the existing regulatory framework presents significant challenges in determining how a MDF should be classified. The FDA defines 'conventional food' as "(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article." (21 U.S.C. §321 (f)). Foods are further described to include substances ingested primarily for their taste, aroma or nutritive value. If a MDF is designed primarily to provide nutritive value to the consumer, a key question is whether such nutritive value has to be provided *directly* by the MDF for it to be classified as a food. For example, if the MDF functions to affect targeted members of the microbiota in ways that increase microbial production of a nutrient necessary for a healthy state, would it be considered a food?

An additional way of distinguishing a 'conventional food' from a MDF is that the former is not designed to specifically alter the properties of the microbiota while the latter is intentionally formulated with this goal in mind. In practice, ingredients that target the microbiota may be added to existing food products; for example, incorporation of human milk oligosaccharides into infant formula [11]. From a regulatory perspective, the distinction between conventional food and MDF may be inconsequential if the use of the MDF satisfies the criteria for Generally Recognized as Safe (GRAS). Importantly, by law, it is not the substance itself that underlies its designation as GRAS but rather its manner use (either based on scientific evaluation, or the fact that it was commonly used in food prior to 1958). There is no definitive list of substances established as GRAS under conditions of intended use [sources include, for example, 21 CFR Part 182, 21 CFR Part 184 and FDA's Inventory of voluntary GRAS Notices (GRNs) (<https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices>)]. To establish GRAS status for the use of a MDF as a human food ingredient, qualified food safety experts would have to consider the effects of the MDF, its constituents and the products of its microbial biotransformation on the gut microbiota. These latter considerations could influence future definitions of food safety.

A ‘dietary supplement’ is defined as a “product (other than tobacco), intended to supplement the diet, that bears or contains one or more of the following dietary ingredients; (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid, (E) a dietary substance for use by people to supplement the diet by increasing total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any of the above ingredient described in clause (A), (B), (C), (D) or (E)” (21 U.S.C. §321 (ff)). If a MDF contains a substance not normally found in the diet, or one that has not been reviewed by FDA under a New Dietary Ingredient (NDI) Notification, its classification as a dietary supplement may be precluded [12].

A ‘medical food’ is formulated to be “consumed or administered enterally under the supervision of a physician and intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation” (21 U.S.C. §360ee(b)(3)). If a MDF is designed for a condition where insufficiency of a product of a consumer’s microbiota, or chemical entities generated by host cell metabolism of that product, is recognized to be causally related to the condition, then that product might be considered an ‘essential nutrient’ in the context of that condition. In this scenario, a MDF that promotes microbial production of the essential nutrient may meet the current regulatory definition of a medical food if the condition cannot be addressed through modification of a normal diet alone (or one that includes a dietary supplement). However, key questions for such a classification include whether the health condition is recognized by the scientific community as having ‘distinctive nutritional requirements’, and the extent to which the definition of ‘essential nutrient’ is expanded to include products of microbial metabolism.

The regulatory definition of a ‘drug’ includes “articles (other than food) intended to affect the structure or any function of the body of man or other animals” (21 USC §321(g)(1)). Since dietary practices are known to alter microbiota configuration and metabolic output [e.g., refs. 1,8,13], classification as a drug would seemingly require specific claims that the MDF mediates a reconfiguration to a state or states known to cure, treat, mitigate or prevent a disease, *and* that the MDF not be classified as a food. Classification as a drug would also entail rigorous evaluation of safety, efficacy and CMC (Chemistry, Manufacturing and Controls) under an Investigational New Drug application (IND). If in the future, a consensus arises in the scientific community that the FDA, and importantly lawmakers in Congress, should define the (gut) microbiota as a human organ from a regulatory perspective, the question will arise as to whether a claim that a MDF promotes reconfiguration of community structure or function might lead to its classification as a drug.

Claiming the health benefits of MDFs

It is entirely possible that MDFs will have specific health benefits that extend beyond the more generic claims permitted by the FDA for foods. Claims such as ‘three grams of soluble fiber from oatmeal consumed daily in a diet low in saturated fat and cholesterol may reduce the risk of heart disease’ are allowed for foods, while ‘structure-function claims’ are allowed for dietary supplements (e.g., ‘calcium builds strong bones’) [14]. Importantly, foods may not bear disease claims, explicit or implied, unless the claim has undergone premarket

review by the FDA and the claim has been authorized or approved under the rules for health claims or drugs, as appropriate. Classification of a MDF as a ‘medical food’ would provide a route for making claims for dietary management of a disease or condition without premarket approval as a drug. However, the FDA applies specific criteria to medical foods relating to their composition/processing and the medical conditions for which distinctive nutrient requirements have been determined [15].

One regulatory approach for evaluating claims for MDFs that provide specific health benefits would be to create a monograph analogous to that used for over-the-counter (OTC) drugs, as has been suggested for probiotics [16]. A MDF monograph would include descriptions of acceptable doses of active ingredients, and allowable product claims and labeling, based on recommendations from expert panels. ‘Acceptable dose’ would include considerations of safety and efficacy in the target populations. While marketing a new product under the current OTC drug monograph system can be complex undertaking, if a MDF is comprised entirely of existing commonly consumed foodstuffs, an abbreviated review process could focus on defining allowable claims and labeling.

MDFs in the context of the public’s view of the role of food and the microbiota in health

Development of MDFs is being enabled by progress in defining various features of human gut microbial communities, and the extent to which these features vary within and across individuals as a function of host and environmental factors. MDFs themselves offer opportunities to (i) further delineate how these communities and their members affect our biology, (ii) determine the extent to which it is possible to deliberately reshape community functions through dietary interventions, (iii) characterize the generalizability of these effects and their short and long term safety and efficacy, and (iv) catalyze efforts to identify bioactive natural products derived from the gut microbiota. Whether intended or not, the development of MDFs will likely help change concepts and definitions of nutritional requirements, nutritional benefits and food safety. They will also likely raise questions in the minds of consumers of what effect a food has (or should have) on their gut microbiota, and what constitutes a ‘healthy’ food. Addressing these questions and issues will necessitate well controlled human studies with measurements of microbiota as well as host parameters. The regulatory classification of MDFs used in these trials will influence their development plans and future uses.

A revolution has already started; it exploits advances in analytic methods such as mass spectrometry to characterize food ingredients at an unprecedented level of molecular resolution. For example, efforts are underway to define the structures of complex polysaccharides present in different crops, and how they vary as a function of different cultivars of that crop and what processes are used to incorporate it into various foods. This capacity to define what we eat not only provides a new dimension to studies of the anthropology of food, but promises to change how we define ‘nutritive value’. As we learn more about the molecular features of the foods we consume, we can gain greater understanding of how microbial communities transform them into products, and which of

these products are important contributors to ‘normal’ (healthy) physiologic functions. The definition of ‘normal’ becomes an important yet daunting problem; the challenge is to determine which of these microbiota-derived products are common features of a healthy human being, how the term common is related to age, gender, and anthropologic features of a population, what concentration range is associated with a healthy state and, whether deficiency of one or more of these products is causally linked to an unhealthy state. This knowledge could not only expand how we define what constitutes a healthy food, but would also enable design of MDFs and provide biomarkers to establish their efficacy.

The public is increasingly aware of the role of the microbiota in health and disease. At the same time, the number of products claiming to provide benefits through their effects on the microbiota is growing rapidly. Therefore, there is a pressing need for consumers and health care professionals alike to have access to an evidence-based framework that allows them to make informed decisions. During this period of increasing globalization, wider consideration should be given to how policies that address the issues described above can be applied and harmonized across national boundaries. Classification schemes that are ultimately adopted will likely have broad societal implications for testing, labeling, branding, and advertising of products that target the microbiota. In addition, they could affect efforts designed to develop future nutritious foods ‘from the inside out’, based on knowledge of the effects of these foods on the properties and metabolic output of consumers’ gut microbial communities.

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