

There is rapid growth in the number of products that claim to affect the gut microbiota and benefit health.

microbiota in ways that increase microbial production of a nutrient necessary for a healthy state, would the MDF be considered a food? One way of distinguishing a conventional food from an MDF is that the former is not designed to specifically alter the properties of the microbiota, whereas the latter is intentionally formulated with this goal in mind. In practice, ingredients that target the microbiota may be present in, or deliberately added to, existing products [e.g., human milk oligosaccharides in infant formula (12)].

The distinction between conventional food and an MDF may be inconsequential from a regulatory perspective if the use of the MDF satisfies criteria for being deemed Generally Recognized as Safe (GRAS) and claims fall within the scope allowable for food. Note that it is not the substance itself that underlies GRAS designation but rather its manner of use; moreover, there is no definitive list of substances established as GRAS under conditions of intended use. To establish GRAS status, qualified food-safety experts would have to consider the effects of the MDF, its constituents, and the products of its microbial biotransformation. If an MDF is composed of ingredients with GRAS status, it could be classified as a conventional food. If any components do not have GRAS status, they cannot be added to conventional food without petitioning the FDA for approval as a new food additive. This requires extensive safety testing (13).

If an MDF were classified as a “dietary supplement,” it would be possible to make certain claims related to its nutrient content and its effects on health or the structure and function of the body but not claims regarding the treatment, prevention, or diagnosis of a disease. However, if an MDF contains a substance not normally found in food or one that has not been reviewed by the FDA as a new ingredient under a New Dietary Ingredient (NDI) Notification, its classification as a dietary supplement would likely be precluded (14).

A “medical food” is designed for dietary management of a disease or condition with “distinctive nutritional requirements” (e.g., for management of inborn errors of metabolism, such as phenylketonuria). If an MDF is designed for a condition where insufficiency of a product of a microbiota—or chemicals 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. An MDF that promotes microbial production of the

Downloaded from <http://science.sciencemag.org/> on July 13, 2017

POLICY FORUM

SCIENCE AND REGULATION

Food and microbiota in the FDA regulatory framework

How should microbiota-directed foods be regulated?

By **Jonathan M. Green**,^{1,2*}
Michael J. Barratt,^{3,4*} **Michael Kinch**,⁵
Jeffrey I. Gordon^{3,4}

New understanding of how our gut microbial communities (microbiota) transform dietary ingredients into metabolic products that affect human biology is altering our definitions of the nutritional value of foods (1, 2). We are coming to appreciate how much formation of the gut microbiota during early postnatal life and the traits encoded by its several million microbial genes (microbiome) are important determinants of healthy growth and of our metabolic, physiologic, immune, and perhaps neurologic phenotypes (3, 4). These advances are spawning efforts to develop foods that promote healthy microbiota development during early postnatal life, prevent the loss of microbial diversity associated with Western diets, and repair abnormalities associated with various disease states (5–8). But given the mechanisms by which such microbiota-directed foods (MDFs) may achieve their desired effects, the existing U.S. regulatory framework presents challenges in determining how MDFs should be classified. How these challenges are addressed will affect innovation incentives, product quality, consumer access, and public health. Although

approaches to regulation vary among countries (9), we focus on the U.S. Food and Drug Administration (FDA) because of its global influence and because the products it regulates are often widely distributed.

It has been more than 20 years since the last major revision of regulatory definitions for food ingredients in the United States. 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 (10, 11). A microbiota that cannot generate these products in adequate quantities may lead to disease and is thus a target for reconfiguration by MDFs, which can be defined as foods designed to alter properties of a microbiota. An MDF could alter existing members of the consumer's microbiota in a deliberate manner to affect the community's functional properties, and/or it may provide a substrate that is transformed by the microbiota to products necessary for a healthy state.

POTENTIAL CLASSIFICATIONS

If an MDF is designed primarily to provide nutritive value, a key question is whether such nutritive value has to be provided directly by the MDF for it to be classified as a “conventional food” by the FDA (i.e., substances ingested primarily for their taste, aroma, or nutritive value). For example, if the MDF affects targeted members of the

¹Department of Medicine, ²Institute for Public Health, ³Center for Genome Sciences and Systems Biology, ⁴Center for Gut Microbiome and Nutrition Research, ⁵Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine, St. Louis, MO 63110, USA.
*These authors contributed equally to this work.
Email: jgordon@wustl.edu

essential nutrient may meet the 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). Key questions include whether the 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.

Because dietary practices are known to alter microbiota configuration and metabolic output [e.g., (1, 8, 15)], classification of an MDF as a “drug” would seemingly require specific claims that it mediates reconfiguration to a state known to cure, mitigate, or prevent a disease and that the MDF not be classified as a food. Classification as a drug would, among other implications, entail rigorous evaluation of safety, efficacy, and Chemistry, Manufacturing, and Controls under an Investigational New Drug application. If a consensus arises in the scientific community that the FDA and 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 HEALTH BENEFITS

MDFs may have specific health benefits beyond the more generic claims permitted by the FDA for foods (e.g., “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, ...”). “Structure-function claims” are allowed for dietary supplements (e.g., “calcium builds strong bones”) (16). Note that conventional foods may not bear disease claims, explicit or implied. Classification of an MDF as a medical food would provide a route for making claims for dietary management of a condition without premarket approval as a drug. However, the FDA requires medical foods to meet specific criteria related to their formulation, processing, and the medical conditions for which distinctive nutrient requirements have been determined (17).

One approach for regulating MDFs that provide specific health benefits would be to create a monograph analogous to that used for over-the-counter drugs, as has been suggested for probiotics (18). This approach would allow MDF manufacturers to make health and/or disease claims that have been substantiated without going through what is, to many, a prohibitively costly drug development process, while providing the public with trustworthy products. An MDF monograph would include descriptions of

acceptable doses of active ingredients and allowable product claims and labeling, based on expert panel recommendations. “Acceptable dose” would include considerations of safety and efficacy in target populations. Although marketing a new product under the over-the-counter drug monograph system can be complex, if an MDF is composed entirely of existing foodstuffs, an abbreviated review process could focus on defining allowable claims and labeling.

FOOD AND THE MICROBIOTA

To what extent will scientific advances in microbiota research affect public attitudes and governmental regulation? How will regulatory decisions, in turn, affect scientific progress and society? MDFs offer research opportunities to (i) delineate how microbial

“Classification schemes that are ultimately adopted will likely have broad societal implications for...products that target the microbiota.”

communities affect our biology, (ii) determine the extent to which it is possible to 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 gut microbiota. Development of MDFs will likely help change concepts and definitions of nutritional requirements, nutritional benefits, and food safety. They will also likely raise questions about what effect a food has (or should have) on the microbiota, and what constitutes a “healthy” food. Addressing these issues will necessitate well-controlled human studies with measurements of microbiota and host parameters. Regulatory classification of MDFs used in these trials will influence their development plans and future uses.

A revolution has already started, exploiting advances in analytic methods, such as mass spectrometry, to characterize food ingredients at an unprecedented level of molecular resolution. For example, efforts are under way to define structures of complex polysaccharides present in different crops and how they vary as a function of different cultivars and the processes used to incorporate them into various foods. This capacity to define what we eat provides a new dimension to studies of the anthropology of food and promises to change how we define “nutritive value.” We can gain greater

understanding of how microbial communities transform foods into products and which of these products are important contributors to “normal” (healthy) physiologic functions. 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 a healthy food but would also enable design of MDFs and provide biomarkers to establish their efficacy.

The number of products claiming to provide benefits through effects on the microbiota is growing rapidly. Consumers and health care professionals need an evidence-based framework to inform decisions. Wider consideration should be given to how policies that address these issues 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 consumers’ gut microbial communities. ■

REFERENCES AND NOTES

1. J. L. Sonnenburg, F. Bäckhed, *Nature* **535**, 56 (2016).
2. A. Koh, F. De Vadder, P. Kovatcheva-Datchary, F. Bäckhed, *Cell* **165**, 1332 (2016).
3. B. O. Schroeder, F. Bäckhed, *Nat. Med.* **22**, 1079 (2016).
4. G. Sharon et al., *Cell Metab.* **20**, 719 (2014).
5. L. V. Blanton, M. J. Barratt, M. R. Charbonneau, T. Ahmed, J. I. Gordon, *Science* **352**, 1533 (2016).
6. J. A. Gilbert et al., *Nature* **535**, 94 (2016).
7. K. Honda, D. R. Littman, *Nature* **535**, 75 (2016).
8. E. D. Sonnenburg et al., *Nature* **529**, 212 (2016).
9. H. Kumar et al., *Curr. Opin. Biotechnol.* **32**, 99 (2015).
10. M. S. Donia, M. A. Fischbach, *Science* **349**, 1254766 (2015).
11. L. B. Bindels, N. M. Delzenne, P. D. Cani, J. Walter, *Nat. Rev. Gastroenterol. Hepatol.* **12**, 303 (2015).
12. G. Puccio et al., *J. Pediatr. Gastroenterol. Nutr.* **64**, 624 (2017).
13. Center for Food Safety and Applied Nutrition, FDA, “Ingredients, additives, GRAS & packaging guidance documents & regulatory information” [U.S. Department of Health and Human Services (HHS), 2016].
14. Center for Food Safety and Applied Nutrition, FDA, “Guidance for industry: Dietary supplements: New dietary ingredient notifications and related issues: Draft guidance” (HHS, 2016).
15. D. Zeevi et al., *Cell* **163**, 1079 (2015).
16. T. Brody, *Compr. Rev. Food Sci. Food Saf.* **15**, 92 (2016).
17. Center for Food Safety and Applied Nutrition, FDA, “Frequently asked questions about medical foods, Guidance for industry” (HHS, ed. 2, 2016).
18. D. E. Hoffmann et al., *Science* **342**, 314 (2013).

ACKNOWLEDGMENTS

The authors thank R. Sachs for comments and members of the Institute for Public Health at Washington University, notably J. Van Rhoenen, A. Hanten, and W. Powderly, for their support.

10.1126/science.aan0836

Food and microbiota in the FDA regulatory framework

Jonathan M. Green, Michael J. Barratt, Michael Kinch and Jeffrey I. Gordon

Science **357** (6346), 39-40.

DOI: 10.1126/science.aan0836

ARTICLE TOOLS

<http://science.sciencemag.org/content/357/6346/39>

RELATED CONTENT

<http://stm.sciencemag.org/content/scitransmed/9/390/eaal4069.full>
<http://stm.sciencemag.org/content/scitransmed/9/379/eaaf6397.full>
<http://stm.sciencemag.org/content/scitransmed/9/376/eaaf9412.full>
<http://stm.sciencemag.org/content/scitransmed/8/366/366ra164.full>

REFERENCES

This article cites 15 articles, 3 of which you can access for free
<http://science.sciencemag.org/content/357/6346/39#BIBL>

PERMISSIONS

<http://www.sciencemag.org/help/reprints-and-permissions>

Use of this article is subject to the [Terms of Service](#)