Regulation of Probiotic Substances as Ingredients in Foods: Premarket Approval or “Generally Recognized as Safe” Notification

Antonia Mattia¹ and Robert Merker²
¹Division of Biotechnology and GRAS Notice Review and ²Division of Petition Review, Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, US Food and Drug Administration, College Park, Maryland

This article discusses options and examples of regulations or “generally recognized as safe” determinations that are related to microorganisms in food. A balanced picture of information about the microorganism and its characteristics is needed to make conclusions about its safety.

Food additives and substances that are “generally recognized as safe” (GRAS) are the main categories of ingredients intentionally added to conventional food. The evaluation of such ingredients from the perspective of their safety is accomplished by the Center for Food Safety and Applied Nutrition’s Office of Food Additive Safety, via the food additive petition approval process or the GRAS notification procedure. Either regulatory route might be appropriate for a submission to the US Food and Drug Administration (FDA) for the use of a probiotic as a food ingredient. The purpose of this article is to discuss these options and to consider examples of regulations or GRAS determinations that are related to microorganisms in food, not probiotics per se. Although there has been much interest in probiotics as food ingredients in recent years, the FDA has received few submissions for probiotics.

GUIDE TO FDA TERMS REGARDING INGREDIENTS IN FOOD

The following is an alphabetical list of terms relating to the FDA’s premarket submissions for food ingredients.

1. Common knowledge element: for a GRAS determination, the information supporting the GRAS determination is generally available (e.g., published) and is generally accepted by the scientific community.
2. Food additive (a legal term): in the United States, ingredients in food are food additives, which require FDA safety review and approval, unless they are GRAS for their intended use or otherwise exempt from the definition of food additive.
3. Generally recognized as safe (GRAS) (by qualified experts for the intended use in food).
4. GRAS notice: a voluntary submission to the FDA for which the FDA responds to information about the notifier’s conclusion that the intended use of a substance is GRAS.
5. Notifier: the person or company who voluntarily submits a GRAS notice to the FDA.

REGULATORY CATEGORIES OF INGREDIENTS ADDED TO FOOD

There are 4 regulatory categories of ingredients added to conventional food: food additives, color additives, GRAS substances, and prior sanctioned substances. Food additives are substances without a proven record of safe use; they must be approved by the FDA before use. GRAS substances are substances for which the use in food has a proven record of safety, on the basis of either published scientific evidence or history of use before 1958. GRAS substances need not be approved by the FDA. The other 2 categories are color additives.
and prior sanctioned substances. Color additives impart color to food and are regulated in a fashion analogous to that used for food additives. Prior sanctioned substances are those deemed to be safe by either the FDA or the US Department of Agriculture before 1958 for use in specific products. For example, the preservative nitrate can be used in meat because it was sanctioned before 1958, but it cannot be used in vegetables, which were not covered by that prior sanction. Food contact substances are packaging materials, such as polymers. They fall within the food additive definition but differ in that they unintentionally may become components of food. A probiotic ingredient intentionally added to a conventional food would probably be classified as either an “intentional” food additive or a GRAS substance.

**FEDERAL FOOD, DRUG, AND COSMETIC ACT**

The FDA derives its authority to regulate food additives and GRAS substances from the Federal Food, Drug, and Cosmetic Act. The act was written in 1938 but underwent numerous amendments. The 1958 amendments are most relevant to the FDA’s authority to regulate food additives and GRAS substances. They define food additives (with a GRAS exemption), require premarket approval, establish the standards of safety and review, and establish formal rule-making procedures for food additives.

**PREMARKET APPROVAL PROCESS**

The statutory definition of a food additive is found in section 201(s) of the Food, Drug, and Cosmetic Act. The term “food additive” is broadly defined to mean “any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food…” [1]. If no regulation authorizing the use of an additive exists, information (usually privately held by the sponsor) is submitted to the FDA in the form of a food additive petition. The FDA reviews the petition and makes the decision about safety. For a successful petition, the FDA writes a regulation describing the conditions under which the food additive may be used legally and publishes the regulation in the Federal Register.

The information in a food additive petition includes but is not limited to the following:

1. Identity and composition of the additive
2. Proposed use in food
3. Amount to be added to food
4. Data establishing its intended effect
5. Quantitative detection methods in food
6. Full reports of toxicological and other safety studies
7. Proposed tolerances, if needed
8. Environmental information

The additive must be well characterized. Data to establish the intended effect and the methods of detection in food permit the determination of how much of the additive will be in food. The food matrix can complicate such determinations, and methods that work well in a laboratory setting sometimes need modifications. Safety studies are largely toxicological studies, but microbiological, preclinical, and clinical studies are often part of a data package. The FDA does not list required safety tests. Rather, the FDA recommends a testing strategy to generate data appropriate for addressing safety questions that arise from the intended use of an additive and other considerations, such as the method of manufacture. Typically, food additive petition workgroups are interdisciplinary, including a chemist, toxicologist, and regulatory scientist at a minimum. Microbiologists, molecular biologists, epidemiologists, physicians, or scientists with specialized expertise are included as appropriate.

The steps (simplified) in the review process for food additive petitions are as follows.

1. The petitioner submits information and raw data to the FDA.
2. Communication occurs between the FDA and the petitioner (usually for clarification).
3. The FDA reviews the petition and prepares scientific or other memoranda.
4. The FDA prepares the preamble to the final rule, summarizing its findings.
5. The FDA publishes a final regulation in the Federal Register, which lays out the FDA’s reasoning in reaching a decision and also
   A. authorizes specific uses,
   B. must withstand legal and scientific challenge, and
   C. bears the FDA’s credibility.

**USES OF MICROBES IN FOOD**

Microbes have been used in food for millennia. Fermented foods were traditionally prepared as a means of preservation. Uncharacterized microorganisms from environmental sources were used first; later, pure cultures were developed. With the development of pure cultures, the manufacture of natural starters and spontaneous fermentations has evolved into a large industry. Over the years, the FDA has published a number of regulations in the Code of Federal Regulations title 21 that detail the allowed uses of microorganisms, often as sources of enzymes used to produce food (table 1) [2].

These regulations concern lactic acid–producing bacteria, flavor-producing bacteria, and glucose-fermenting bacteria used in the production of a variety of dairy products or for the removal of glucose from dried egg whites. In examining these regulations, it is apparent that none regulates probiotic uses of active cultures.
Table 1. Types of microorganisms that are the subject of regulations in the Code of Federal Regulations title 21 [2].

<table>
<thead>
<tr>
<th>Type of microorganism</th>
<th>Regulated uses in food (regulation number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harmless lactic acid (–producing) bacteria</td>
<td>Sour cream and acidified sour cream (parts 131.160 and 131.162); cheese (part 133); bread, rolls, and buns (part 136.110)</td>
</tr>
<tr>
<td>A “characterizing bacterial culture that contains the lactic acid–producing bacteria Lactobacillus bulgaricus and Streptococcus thermophilus”</td>
<td>Yogurt, lowfat and nonfat (parts 131.200, 131.203, and 131.206)</td>
</tr>
<tr>
<td>Harmless flavor-producing bacteria</td>
<td>Cheeses (part 133) (with separate regulations for hard grating, hard, soft ripened, semisoft, and semisoft part-skim cheeses)</td>
</tr>
<tr>
<td>Glucose-fermenting bacteria</td>
<td>Dried egg whites (optional glucose-removal procedure) (part 160.145)</td>
</tr>
</tbody>
</table>

GRAS

A food additive is any substance that may become a part of food, unless that substance is GRAS. GRAS status is therefore an exemption from the food additive definition. In 1997, the FDA published a proposed rule that established the GRAS Notification Program to receive and review GRAS submissions. The quantity and quality of data needed to support a GRAS determination are the same as those needed for approval of a food additive petition, which are referred to as the “technical element.” What distinguishes a GRAS substance from a food additive is the “common knowledge element.” The common knowledge element means that data and information supporting a GRAS determination must be generally available (e.g., published) and must be generally accepted by the scientific community. In other words, scientists qualified by training and experience must have access to pertinent information and must agree that the intended use of the substance is GRAS. If a substance is GRAS, premarket approval by the FDA is not required, so participation in the GRAS Notification Program by submission of a GRAS notice is voluntary.

The FDA has responded to >200 GRAS notices to date; some related to microorganisms are listed in table 2. This table, which is not comprehensive, demonstrates that few probiotics per se have been the subjects of GRAS notices. Several GRAS notices are for uses of microbially derived ingredients, including enzymes from organisms considered safe but new to food. To date, the FDA has received few submissions for probiotics. Although there is no legal requirement for companies to interact with the FDA regarding GRAS substances, the FDA encourages companies to consult with the FDA regarding any information that they may wish to provide on the safety of uses of new ingredients in food or questions they may have regarding probiotic microbes for use in food.

There are key concepts to remember about GRAS status. First, a GRAS determination is time dependent, necessarily based on information available at the time. As science evolves, new information that could challenge GRAS status may become available. Second, GRAS is not an inherent property of substances; rather, the intended use of the substance makes it GRAS, so different uses of the same substance may or may not be GRAS. Third, unlike in the review of a food additive petition, the notifier, not the FDA, makes the safety decision for the subject of a GRAS notice. Finally, a GRAS determination is not a license, nor is it company specific. If a notifier chooses to notify the FDA of a GRAS determination, others may use the information in the notice to support the safe use of the substance for the same intended purpose.

GRAS notices are reviewed by the FDA using a multidisciplinary team approach similar to the review teams used for food additive petitions. In reviewing a GRAS notice for a microor-

Table 2. Generally recognized as safe (GRAS) notices related to microorganisms.

<table>
<thead>
<tr>
<th>GRAS notice number</th>
<th>Subject of notice</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td><em>Streptococcus thermophilus</em> and <em>Bifidobacterium lactis</em> in infant formula</td>
</tr>
<tr>
<td>91</td>
<td>Mycoprotein from <em>Fusarium venenatum</em></td>
</tr>
<tr>
<td>120</td>
<td>Genetically engineered wine yeast with a malate permease from <em>Schizosaccharomyces pombe</em> and a malolactic enzyme from <em>Oenococcus oeni</em></td>
</tr>
<tr>
<td>159</td>
<td><em>Carnobacterium maltaromaticum</em> for use in meat products to inhibit <em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td>171</td>
<td>Lactic acid bacteria mixture (<em>Lactobacillus acidophilus</em> [NP35, NP51], <em>Lactobacillus lactis</em> [NP7], and <em>Pediococcus acidilactici</em> [NP3]) to control growth of pathogenic bacteria in meat products</td>
</tr>
<tr>
<td>175</td>
<td>Wine yeast (<em>Saccharomyces cerevisiae</em>) with enhanced production of urea amidolyase</td>
</tr>
<tr>
<td>198</td>
<td>Bacteriophage for reduction of <em>L. monocytogenes</em> on cheese</td>
</tr>
</tbody>
</table>

NOTE. The FDA’s response letters and other information about GRAS notices are posted on its Web site [3].
ganism, the FDA considers general aspects of safety (e.g., exposure and method of manufacturing), as well as taxonomy, pathogenicity, potential toxin production, antibiotic-resistance potential, safe history of use in food, reports of adverse events, metabolic considerations, environmental presence, and any other information deemed relevant to the safety assessment. Notices are evaluated on a case-by-case basis by a weight-of-the-evidence approach, which is particularly relevant to microorganisms, because model test systems may be lacking. Feeding studies using microorganisms, although occasionally conducted, tend to be technically difficult and are often of dubious value. Viability is an important consideration, and whether the microorganism is viable in the food itself and whether it survives transit or is a common resident in the gut are also components of a safety assessment.

In general, the FDA responds to a GRAS notice with 1 of 3 types of letters: (1) a letter with no questions about the notifier’s determination, (2) a letter stating that the notice does not provide a basis for GRAS, or (3) a letter that the notice, at the request of the notifier, was withdrawn. A notice will not provide a sufficient basis to determine GRAS status if the common knowledge element is lacking, if safety concerns exist, or if the submission is deficient. A notifier may withdraw a notice for any reason; some may be business related. If a notice is withdrawn, a new or related notice may be resubmitted at the notifier’s discretion.

CONCLUSION

The framework for evaluating food additives and GRAS substances in the United States contrasts with other regulatory systems. GRAS is a concept unique to the United States, which does not have a novel food category. If the intended use of a substance, including probiotics, is as an ingredient in food, then the substance must be approved as a food additive or must be determined to be GRAS. In evaluating the safety of the intended use, the FDA considers only safety; benefits are not evaluated, although health claims may be considered by the FDA under a separate petition process. In any case, a balanced picture of information about the microorganism and its characteristics is needed to reach a conclusion about safety. Traditional uses of microorganisms in food have a long history of safety, but there is recent interest in new microorganisms or new uses of old organisms that is largely a result of developments in the field of probiotics.

Acknowledgments

We are appreciative of help and comments from Paulette Gaynor, Robert Martin, and Laura Tarantino.

Supplement sponsorship. This article was published as part of a supplement entitled “Developing Probiotics as Foods and Drugs: Scientific and Regulatory Challenges,” sponsored by the Drug Information Association, the National Institutes of Health National Center for Complementary and Alternative Medicine (1R13AT003805-01 to Patricia L. Hibberd), the California Dairy Research Foundation, Chr. Hansen, the Dannon Company, General Mills, Institut Rosell, and Yakult International.


References