FDA’s Generally Recognized As Safe (GRAS) Notification Program:
Live Microbial Cultures Used in Food

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Overview

• Define “live microbial cultures”
• GRAS substance uses vs. food additive uses—what is common, and what are the distinctions?
• What is FDA’s GRAS Notification Program and how does it work?
• What data and information does FDA consider during its evaluations of GRAS notices for the food uses of live microbial cultures?
• Examples
Live Microbial Cultures are Added to a Variety of Conventional Food Products

- Yogurt
- Juice
- Cereal
- Snack Bar
- Infant Formula
Question & Answer #1

“Live microbial cultures” are the same as “probiotics”.

a. True
b. False
GRAS Substance Uses vs. Food Additive Uses—What’s Common, and What Are the Distinctions?
The Act Defines GRAS Substances and Food Additives

Under the Federal Food, Drug, and Cosmetic Act, anything added to food is a food additive…unless it is GRAS.
GRAS Substance Uses vs. Food Additive Uses—What’s Common?

• The chemical nature of GRAS substances and food additives is the same (e.g. live microbial cultures and other substances may be used as GRAS substances or food additives).

• Regardless of whether a substance is used as a GRAS substance or as a food additive, there must be adequate evidence showing that the substance is safe for the intended use in food.

• For GRAS substances and food additives, safety is based on the intended use (including the use level).
GRAS Substance Uses vs. Food Additive Uses—What are the Distinctions?

Generally Recognized As Safe

Common Knowledge Element
Are the safety data and information generally available to everyone and generally accepted by qualified scientific experts?

Technical Element (Safety)
Are the safety data and information adequate for the intended use?

Technical Element + Common Knowledge Element = GRAS Standard
The Common Knowledge Element Distinguishes GRAS Uses from Food Additive Uses

Technical Element (Safety)
Are the safety data adequate for the intended use?

Yes

Common Knowledge Element
Are the data and information generally available to everyone and generally accepted by experts?

Yes

GRAS Status

No

Need Data

No

Food Additive
What is FDA’s GRAS Notification Program and How Does It Work?
FDA’s GRAS Notification Program

- Framework laid out in FDA’s 1997 GRAS Proposal.
- Manufacturer makes a determination that a use of a substance is GRAS.
- Manufacturer may voluntarily submit a GRAS notice to FDA.
  - FDA responds by letter (goal = 180 days).
- Transparent – an inventory of GRAS notices and FDA’s responses are listed on our website at: [http://www.fda.gov/grasnoticeinventory](http://www.fda.gov/grasnoticeinventory).
FDA’s Responses to GRAS Notices

• 3 types of endpoints:
  – FDA has no questions
  – Notice does not provide a basis for GRAS
  – Manufacturer stops the review process and withdraws the GRAS notice
## GRAS Notices vs. Food Additive Petitions--Outcomes

<table>
<thead>
<tr>
<th></th>
<th>GRAS Notice</th>
<th>Food Additive Petition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End result</strong></td>
<td>FDA issues an opinion letter</td>
<td>FDA issues a regulation</td>
</tr>
<tr>
<td><strong>Who owns the safety decision?</strong></td>
<td>Manufacturer</td>
<td>FDA</td>
</tr>
</tbody>
</table>
Types of Substances Notified to FDA as of May 31, 2014

- Lipids: 20%
- Enzyme Preps: 14%
- Chemicals: 22%
- Carbohydrates: 16%
- Microbials: 8%
- Proteins: 8%
- Other: 6%
- Extracts: 6%

*Includes 22 GRAS notices for the uses of live microbial cultures.
Information About Microbes
Microbes Have Long Been Used in Foods

- Safe use of microbes in fermented foods dates to 6000 B.C.
  - Cheeses
  - Beer, wine
  - Breads
  - Pickled vegetables
  - Wine/cider vinegar
Microbes Are Abundant and Diverse in the Human Body

- Humans have evolved with microbes
  - There are more bacterial cells in the colon \((10^{14})\) than there are human cells in the human body \((10^{13})\)
  - The stomach and small intestine contain a few bacterial species
  - Human gastrointestinal tract contains thousands of bacterial strains
Evaluations of GRAS Notices for the Uses of Live Microbial Cultures in Food
### Live Microbial Cultures Whose Uses Have Been Evaluated Under FDA's GRAS Notification Program

<table>
<thead>
<tr>
<th>GRAS Notice Number</th>
<th>Name of Live Microbial Culture(s)</th>
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<tbody>
<tr>
<td>49</td>
<td><em>Bifidobacterium lactis</em> and <em>Streptococcus thermophilus</em></td>
</tr>
<tr>
<td>171, 463</td>
<td><em>Lactobacillus acidophilus</em>, <em>Lactobacillus lactis</em>, and <em>Pediococcus acidilactici</em></td>
</tr>
<tr>
<td>231, 429</td>
<td><em>Lactobacillus casei</em></td>
</tr>
<tr>
<td>254, 409, 410, 440</td>
<td><em>Lactobacillus reuteri</em></td>
</tr>
<tr>
<td>268</td>
<td><em>Bifidobacterium longum</em></td>
</tr>
<tr>
<td>281, 288</td>
<td><em>Lactobacillus rhamnosus</em></td>
</tr>
<tr>
<td>357, 502</td>
<td><em>Lactobacillus acidophilus</em></td>
</tr>
<tr>
<td>377, 445</td>
<td><em>Bifidobacterium animalis</em></td>
</tr>
<tr>
<td>399, 526</td>
<td><em>Bacillus coagulans</em> spores*</td>
</tr>
<tr>
<td>455, 454, 453</td>
<td><em>Bifidobacterium breve</em></td>
</tr>
<tr>
<td>457</td>
<td><em>Bacteroides xylanisolvens</em></td>
</tr>
</tbody>
</table>
Where have microbes used in foods originally been isolated from?

a. Plants
b. Naturally-fermented foods
c. Fecal material
d. All of the above
Live Microbial Cultures Must be Fully Identified and Characterized

- Identity
  - Unambiguously identified using genetically-based techniques
  - Named using current nomenclature
- Method of Manufacture
  - Appropriately maintained
    - Pure cultures/genetically stable
  - Appropriate fermentation methods
    - Use of food grade materials
    - Discarding contaminated batches
Definition of Safety in 21 CFR 170.3(i):

“Reasonable certainty in the minds of competent scientists that a substance is not harmful under the intended conditions of use.”
Live Microbial Cultures Must be Nonpathogenic and Nontoxigenic

- Nonpathogenic - not able to cause disease or infection in a healthy individual (e.g. unlike *Escherichia coli* O157:H7)

- Nontoxigenic - does not produce injurious substances at levels that are detectable or demonstrably harmful under ordinary conditions of use or exposure (e.g. *Clostridium botulinum*)
  - Consideration of the potential to cause opportunistic infections in immunocompromised individuals
Live Microbial Cultures Should Not Contain Transmissible Elements that Confer Resistance to Clinically-Relevant Antibiotics

- There should be adequate evidence to show that:
  - If present, the antibiotic resistance gene(s) would not affect therapeutic use of antibiotics in the human population.
  - It is unlikely that any genes conveying resistance to clinically relevant antibiotics would be transferred to other microorganisms.
Live Microbial Cultures Reportedly Confer Many Human Health Benefits

- Suppress pathogens
- Treat/prevent diarrhea
- Control irritable bowel syndrome
- Alleviate food allergy symptoms
- Strengthen immunity
- Decrease serum cholesterol
- Improve lactose tolerance
- Reduce risk factors for colon cancer…
- And more
Question & Answer #3

When evaluating a GRAS notice for the food use of a live microbial culture, FDA considers the reported health benefits conferred by the live microbial culture.

a. True
b. False
Review: The Common Knowledge Element Distinguishes GRAS Uses from Food Additive Uses

Technical Element (Safety)
Are the safety data adequate for the intended use?

Yes

Common Knowledge Element
Are the data and information generally available to everyone and generally accepted by experts?

Yes

No

Need Data

Food Additive

GRAS Status
Example #1

Company A has generated data and information supporting the safe use of a novel live microbial culture they intend to use in food. None of the data are publicly available—Company A considers them to be confidential.

Which of the following is true?

a. Company A’s food use of their live microbial culture may be a GRAS use.

b. Company A’s food use of their live microbial culture may be a food additive use.

c. Company A’s food use of their live microbial culture may either be a GRAS use or a food additive use.
Example #2

Company B wants to send a submission to FDA for the company’s intended use of a live microbial culture. The company has published a lot of safety data, but these do not address all of the relevant safety questions. What should Company B do?

a. Submit a GRAS notice to FDA and let the agency “fill in the blanks”.
b. Submit a food additive petition to FDA.
c. Conduct studies to address the remaining safety questions.
Wrap-Up

- The use of GRAS substances and food additives must be supported by adequate safety data (i.e. meet the technical element).
- The uses of GRAS substances must also meet the common knowledge element.
Wrap-Up, continued

- To date, FDA has reviewed 22 GRAS notices for the uses of live microbial cultures.
  - GRAS notices for the uses of live microbial cultures must demonstrate that a culture is thoroughly identified, nonpathogenic, nontoxigenic, and does not contain transmissible antibiotic resistance elements.
- More information on food ingredient safety and FDA’s food ingredient regulatory programs is available at http://www.fda.gov/Food/IngredientsPackagingLabeling/default.htm