The GRAS Concept, Food Additives, and Food Safety: How the Concept Has Served FDA and the Public and the Basis for and Implications of Possible Changes in Its Application

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Fred H. Degnan
fdegnan@kslaw.com
Preliminary Points

• The FDC Act has 3 GRAS provisions (§§ 201(p) (new drugs), 201(s) (food additives), (201(w)) (new animal drugs) and 2 GRAE provisions (201(p) and 201(w))

• Our primary focus today is the GRAS concept as it has evolved in the context of Section 201(s)
Background Considerations Regarding FDA Regulation of Food “Safety”

• The food supply is complex and presents an array of safety issues:
  – natural toxins in food
  – physical contaminants
  – microbial contaminants
  – pesticide residues
  – animal drug residues
  – ingredients: intentionally “added” substances
The statutory scheme of the FDC Act for regulating the safety of food reflects the complexity of the food supply.

As a result, the FDC Act contains a number of different “safety” standards.

These standards vary and focus on:

- the food itself
- the use in food to which a substance may be put
- the conditions under which the food is made and held
- ingredients or substances migrating into the food
- the presence in food of the residues/metabolites of animal drugs.
The difference in rigor that accompanies the different “safety” standards in the FDC Act depends in large part upon whether pre-market approval requirements or post-market enforcement authorities apply.

For example: “reasonable certainty of no harm” v. “may render injurious to health.”

The “reasonable certainty of no harm” safety standard applies to food additives and to GRAS substances.
Pre-Market Approval Systems: “Food Additives”

• The 1958 Food Additives Amendment (“FAA”) replaced the existing ad hoc arrangements whereby new ingredients had been tested voluntarily.

• At the heart of the process was the shift to formal agency pre-market review of the safety of such ingredients.

• The expressly stated purpose of the FAA was twofold: to ensure safety and to foster innovation.
The FAA defined “food additive” as follows:

“any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component … of any food … if such substance is not generally recognized among experts qualified by scientific training and experience to evaluate its safety as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use …”
GRAS: What Did Congress Intend?

• An exception to the broad definition of “food additive” and the ensuing requirement of pre-market review

• Congress sought
  – to ensure safety by permitting the reasonable exercise of scientific judgment
  – to balance safety with the practical needs of not disrupting the food supply
  – to wisely allocate scientific and regulatory resources
“Gems of Ambiguity”

• The vagueness of the “general recognition” terminology
  – provided a flexible tool for excluding from food additive coverage a number of compounds already in use
  – gave FDA discretion to proceed against compounds it considered problematic as well as against any new, untested compounds
“Gems of Ambiguity” (cont.)

• In excluding GRAS substances from the definition of “food additive,” Congress recognized that
  – priorities had to be set
  – too much regulation might disrupt the food supply
  – the safety of many food ingredients could be assured without pre-market approval
The GRAS Exception

- The GRAS exception to the food additive definition embodies the congressional recognition in 1958 that an all encompassing reading of the definition of food additive would not be the best way to ensure the safety and integrity of the entire food supply.
Criteria for GRAS Status of a Food Substance

• Two basic routes are available:
  – “Scientific procedures” (our focus today)
  – Safety based upon common use in food prior to 1958

• Under “scientific procedures” toxicological testing must demonstrate safety
  – Safety data must be publicly available.
  – Consensus must exist among qualified experts regarding the conclusion to be drawn from the data.
Brief History of Food
“GRAS”-Based Regulation

- 1958 - Present: “Self” GRAS Determination
- 1958 - Present: FDA Food Additive (not GRAS) Litigation
- 1973 - 1997: GRAS Affirmation Process
- 1997 - Present: GRAS Notification Process (CFSAN)
- 2010 - Present: GRAS Pilot Program (CVM)
GRAS Notification Program

• Voluntary GRAS Notification Program (proposed April, 1997; comment period reopened December, 2010)

• Developer presents basis for GRAS determination
  – “Safe” = reasonable certainty of no harm
  – Notifier’s determination and responsibility
  – Summary document, not raw data or complete reports
    ➢ Based usually on expert panel review

• FDA responds by letter and posts response on the Internet
  – “No questions”
  – “Does not provide a sufficient basis for a determination ….”
GRAS

“Generally” …

• Among experts qualified by scientific training and experience to evaluate safety
  – Consensus? Yes
  – Unanimity? No

• Key function, therefore, of an expert panel is to represent scientific community at large
GRAS

“Recognized” ...

• Based on “common knowledge”
  – general availability of key information
  – general acceptance of key information

• Usually entails peer-reviewed scientific literature, may include secondary literature (textbooks, abstracts, reports of scientific proceedings)
GRAS

“As Safe” …

• Reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use
  – based on the totality of the relevant information
  – NOT zero risk (“absolute harmlessness” can never be shown and not a criterion for “safety, 21 CFR 170.3(i))
  – in determining safety, relevant factors include:
    ➢ probable consumption/exposure
    ➢ cumulative effect over time
    ➢ need for appropriate safety factors (usually to accommodate uncertainties in extrapolating from animal data to humans)
Summary: GRAS Status

Safety standard is the same as that for food additives, “reasonable certainty of no harm”

Evidence of safety is the same as is required to support approval of a food additive petition (or new animal drug application)

- breadth and quantity of information
- quality of information

Information must be publicly

- available (i.e., published - preferably peer-reviewed)
- accepted (by expert community)

May be supported by non-publicly available data
“GRAS” and “Safe”

Upshot:

Because of the common knowledge/“publication” component of the GRAS standard, “GRAS,” in effect, presents a more demanding standard than that for food additives.
GRAS: So What Is It, Really?

• A meaningful safety standard
• A flexible regulatory tool
• A mechanism for
  – dealing with administrative challenges and
  – concentrating resources
What GRAS Is Not - Really

• A loophole

• A shortcut

• A lower standard of safety assurance
Commonly Advanced Criticisms of GRAS Notification Policy

• Lacks scientific rigor
• Fails “BPA test”
• Inhibits innovation
• Absence of guiding criteria for conducting an expert panel, e.g., no assurance of independent/objective expert input
• Not sufficiently transparent
• Relegates food additive approval process to secondary role
Sampling of 2010 GAO Recommendations re: FDA’s “Oversight” of GRAS Substances

- FDA should *require* submissions with respect to *any* GRAS self-determination
- FDA should “develop a strategy” to minimize the potential for conflicts of interest in GRAS determinations
- FDA should finalize its 1997 GRAS notification proposal
- FDA should develop a strategy to conduct reconsiderations of currently authorized GRAS determinations
December, 2010: FDA’s Reopening of the Comment Period on the 1997 Proposed GRAS Notification Rule

• FDA requested comments on a number of issues, notably:
  – The role of “publication” in determining GRAS status
  – The appropriate definition of “scientific procedures”
  – Whether and how trade secret information can/should be a part of a GRAS determination
  – Whether information about dietary exposure (i.e., the amount of the substance that consumers are likely to eat or drink) should be a required element of any submission
December, 2010: FDA’s Reopening of the Comment Period on the 1997 Proposed GRAS Notification Rule (cont.)

– Whether FDA should clarify its coordination with FSIS in GRAS review
– Whether FDA should develop a strategy to minimize the potential for conflicts of interest
Observations of Michael R. Taylor re: Strength of GRAS Rubric ("Regulating the Products of Nanotechnology" (2006))

- Capacity to obtain early information on products in the pipeline - “Weak”
- Capacity to enforce safety and testing requirements - “Moderate”
- Capacity to place burden to prove safety on sponsor - “Moderate”
- Capacity to review safety prior to marketing - “Weak”
- Capacity to require needed monitoring and testing (post-market functions) - none
- Capacity to remove unsafe products from the market - “Strong”
Current Pew Initiative: Enhancing FDA’s Evaluation of Science & Improving Hypothesis-Based Research

- Notable issues presented:
  - Adequacy of currently relied upon studies and endpoints
  - Adequacy of current “concepts of harm and adverse health effects”
  - Redbook as a “living guide”
  - Cyclic review concept
  - Lack of criteria for evaluating products of nanotechnology

- Resolution of each issue could, logically, impact substance and adequacy of GRAS assessments