Safety Evaluation for Substances Directly Added to Food

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How Does FDA Regulate Food Ingredients?

• Federal Food, Drug, and Cosmetic Act (FD&C Act) (1938)

• Food Additives Amendments (1958) provided:
  – Definition for “food additive”
  – Pre-market review authority for food additives
  – Standard of safety, standard for data review, and formal rulemaking procedures

www.fda.gov
Food Additives

“...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...”

- Exempts generally recognized as safe (GRAS) substances
- Require pre-market approval by FDA
- FDA reviews data and makes a safety determination
- Results in a food additive regulation in 21 CFR

Food Additive Authority
(FD&C Act Section 409)

- Defined “unsafe food additive” - A food additive is considered unsafe unless the substance and use conform to:
  - an exemption for investigational use
  - a regulation that prescribes the conditions under which such additive may be safely used; or
  - in the case of a food additive that is a food contact substance, conforms to a regulation issued prescribing the conditions under which the additive may be safely used; or an effective food contact notification

- Foods containing unapproved food additives are considered adulterated under section 402 of the Act

- Established food additive petition process
Food Additive Exemptions (FD&C Act Section 201(s))

- Substances whose use is Generally Recognized As Safe (GRAS)
  - Based on history of use prior to 1958
  - Scientifically confirmed as safe (general recognition)
- Prior sanctioned ingredients (substances whose use was approved by FDA or USDA prior to 1958)
- Color additives
- Dietary ingredients in dietary supplements
- Contaminants not added intentionally to food
- Pesticide chemicals or pesticide chemical residue
- Animal drugs (that may remain in food)

Food Additives vs. GRAS Substances

“Safe” means *a reasonable certainty of no harm under the intended conditions of use*
Food Additives vs. GRAS Substances

- **Same Safety Standard**: Are the safety data and information adequate for the intended use?
  - Yes → Continue
  - No → Need Data

- **General Recognition for GRAS**: Are the data and information generally available \(\text{AND}\) generally accepted?
  - Yes → GRAS
  - No → Food Additive

FDA Evaluation Standards

- **Review Standard**: “fair evaluation of the data”

- **Safety Standard**: “reasonable certainty of no harm”

*FDA evaluates the additive’s intended technical effect, but does not consider possible benefits*
Basics of the Food Additive Petition Process

- Requirements in Title 21 of the Code of Federal Regulations, Part 171.1 (21 CFR 171.1)

The petition serves as the scientific, administrative, and legal basis for issuing a food additive regulation.

Required Information for Food Additive Petitions

- Identity, properties, and composition
- Proposed use in food
- Amount to be added to food
- Manufacturing method and specifications
- Data establishing its intended effect
- Methodology for analysis of the additive in food
- Estimated exposure

- Full reports of safety studies
- Proposed tolerances, if needed

- Environmental information
Petition Review Team

- A multidisciplinary workgroup
- Members include:
  - Regulatory Scientist (Consumer Safety Officer)
  - Toxicologist
  - Chemist
  - Environmental Scientist
  - May also include: Microbiologist, molecular biologist, physician, statistician, nutritionist, etc. depending on the nature of the additive and its use

Safety Assessment

- What is it and how much is there in food?
  - Identity and composition
  - Method of manufacture
  - Specifications
  - Use level and exposure

- Is it safe for its intended use?
  - Safety/toxicity studies as appropriate

- Other case-specific information as needed

The burden is on the petitioner to establish safety
Consumer Exposure

• An estimate of consumer exposure to the additive (and by-products of concern) resulting from ingestion of food containing the additive must be made
  – FDA recommends that the petitioner perform an estimate

• The exposure is calculated as an estimated daily intake (EDI)
  – It is an “eaters-only” estimate
  – Represents a chronic or average daily lifetime intake of the food additive
  – EDI is typically calculated for the mean and 90th percentile consumer

Consumer Exposure (cont’d)

• In calculating an EDI, FDA considers:
  – Specific foods in which the additive is to be used
  – Typical and maximum use levels
  – Subpopulations that might be particularly affected by the use of the additive
  – Any anticipated increase in consumption from currently regulated uses, natural/background sources, and proposed uses (i.e., a cumulative estimate)

• Data sources used for estimating exposure:
  – Food consumption surveys (NHANES 3-day survey)
  – Food disappearance figures
  – Market basket surveys
Safety Information

- FDA provides recommendations for assessing safety (see Redbook)
  - Recommended safety studies are based on the nature of the additive and expected exposure (i.e., concern level)
- A No Observed Adverse Effect Level (NOAEL) is established from toxicology data (i.e., animal studies)
- An Acceptable Daily Intake (ADI) is estimated by applying a safety factor
  - Estimate of the amount of a food additive which may be consumed daily over a lifetime with reasonable certainty of no harm
  - Derived from toxicological data

\[ \text{ADI} = \frac{\text{NOAEL}}{\text{Safety factor}} \]

Safety Decision

- Compare EDI with the ADI
- Proposed use of additive is safe if \( \text{EDI} \leq \text{ADI} \)
- Preparation of scientific memoranda documenting the basis for the safety decision
Publication of a Food Additive Regulation

- Preparation of a final rule (the preamble summarizes the data supporting the safety decision)
- Publication of final rule in the Federal Register to promulgate a food additive regulation
  - Must withstand legal/scientific challenge
  - Agency may receive objections
- Anyone who can meet the requirements of the regulation may lawfully use the additive

Data Needed to Support Safety Determination for a Food Additive

- Information relied upon may be:
  - Data generated by the petitioner
  - Data generated by a contract lab
  - Literature in peer-reviewed journals
  - Data in FDA's files obtained through a Freedom of Information (FOI) Act request
  - Other sources
Basics of the GRAS Notice Process


- An interested party submits a GRAS notice to FDA
- FDA evaluates the submitted notice
- FDA sends a response letter
- GRAS Inventory on fda.gov updated

FDA Response to a GRAS Notice

Successful or Unsuccessful

1. No questions*
   - FDA does not question the basis for the notifier’s GRAS conclusion

2. Insufficient basis
   - FDA concludes that the notice does not provide a sufficient basis for a GRAS conclusion

   Cease to evaluate
   - Notifier requests that FDA cease evaluation of the notice

*Includes a subcategory: FDA has no questions; some uses may require a color additive listing.
Regulatory Status of a Food Ingredient

- Consider identity, specifications, and limitations on use
- Consult 21 CFR Parts 172-179
- If not listed as a food additive, check other inventories such as:
  - GRAS Ingredients (21 CFR Parts 182-184)
  - Color Additives (21 CFR 73-74)
  - Food Contact Notifications
  - GRAS Notifications
  - Everything Added to Food in the United States (EAFUS)

Resources

- Ingredients, Packaging, and Labeling homepage:
  https://www.fda.gov/Food/IngredientsPackagingLabeling/default.htm
  (Contains helpful links to program areas, guidance, regulations, and databases related to the work of the Office of Food Additive Safety)

- Food and Color Additives homepage:
  https://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/default.htm
  (Contains helpful links specific to the petition process, including guidance)

- Food Additive Status List:
  https://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm091048.htm

- Everything Added to Food in the United States (EAFUS):
  https://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm115326.htm

- GRAS Notice Inventory:
  https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/default.htm

- Inventory of Effective Food Contact Substance Notifications:
  https://www.accessdata.fda.gov/scripts/fdcc/?set=FCN
