Procedures and Data Requirements for Food Additive Approval in the U.S.

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Statutory Definition of "Food Additive" FFDCA Section 201(s)

"…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…"

"…(including any substance intended for use in producing manufacturing, processing, preparing, transporting or holding food; including any source of radiation intended for such use),

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Statutory Definition of "Food Additive" FFDCA Section 201(s) (cont.)

. . . 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 exemption)

Prior Sanctioned Prior to 1958

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Elements of FDA's Food Additive Premarket Review

- A food additive regulation is required prior to marketing.*
- Industry must petition FDA and demonstrate safety under the "intended conditions of use."
- FDA must reach its own safety decision.
- FDA must publish a regulation permitting the intended use.*

*Processing aids may also be authorized through the food contact notification process

- If the use is GRAS premarket approval is not required.

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Review Processes

- Food Additive Petition Process
  - FDA safety determination and regulation in 21 CFR 172
- Self-determined GRAS status
  - No FDA review
- GRAS Notification
  - FDA review of manufacturer's safety decision
- Food Contact Notification*
  - FDA safety determination and listing on FDA web site
  - Manufacturer specific
  - Food Contact Notification becomes "effective"
  - 120-day review deadline

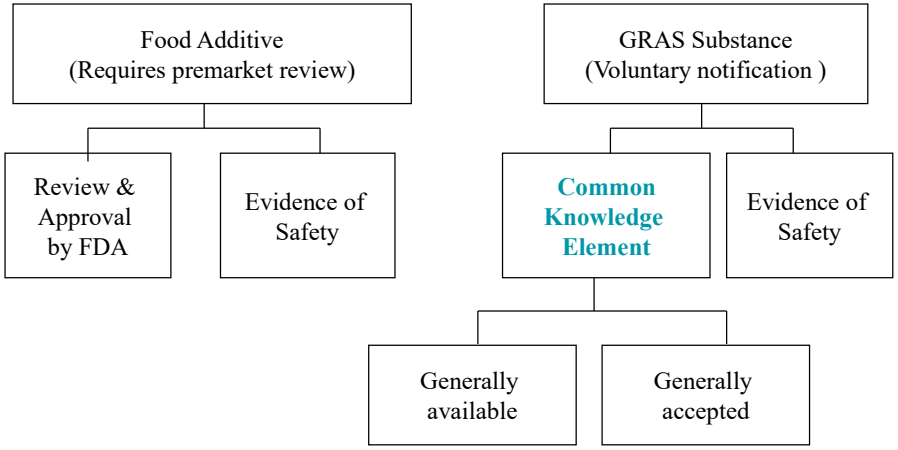
The GRAS Provision

- By definition, anything added to food is a food additive unless it's use is ***generally recognized as safe*** (GRAS).
- It is a ***legal concept*** derived from Section 201(s) and Section 409 of the FD&C Act.
- Is a flexible regulatory tool.
  - The Congressional intent was to provide a practical approach to allocating resources using scientific judgment without giving away FDA's post-market authority.
- The standard of safety is the same as for a food additive.
- GRAS additionally requires that supportive information is publically available.

GRAS Factors: Section 170.30

- Views of qualified scientific experts
- Common knowledge in the scientific community about the safety of the substance
- Same quantity and quality of scientific evidence required for food additive approval
- Based on published studies
- Examples: JECFA/EFSA reviews; reviews of other national authorities

GRAS Criteria: Comparing a GRAS Substance and a Food Additive



GRAS Notification Program

- FDA reviews the assessment and other publically available data
- To save resources, FDA stops short of making its own safety determination and leaves responsibility with the manufacturer
- FDA raises questions or objects if there are any safety concerns for the ingredient use
- GRAS notices are posted on FDA's internet site
- Possible responses include
  - No Basis letter; Notifier stops FDA review; No Questions letter

Safety Standard

"Reasonable certainty of no harm . . ."

- The legislative history reflects that an effect is harmful if it affects health, not if it is simply an undesirable or unexpected effect that has no adverse health consequences.
- Labeling is generally relied upon to address undesirable or unexpected effects.
- From the legislative history, "It does not -- and cannot -- require proof beyond any possible doubt that no harm will result under any conceivable circumstance."
- Safety decisions are always made under some level of uncertainty

Standard of Review

"Fair evaluation of the data . . ."

From the legislative history, "… should not be based on isolated evidence in the record, which evidence in and of itself may be considered substantial without taking account of the contradictory evidence of equal or even greater substance …"

Standards Against Which to Judge Review

- Existing guidelines on types of data which ordinarily relate to safety.
- Established quality factors for judging the rigor of individual studies for safety determinations. e.g., Bradford Hill criteria, FDA's Redbook, OECD or USEPA guidelines
- Existing guidelines for the conduct of a study. e.g. GLP
- The whole body of data.
- Rely on the best most relevant data.

Contents of a Food Additive Submission

- Identity and composition of the food ingredient.
- Manufacture and specifications.
- Use in food must consider -
  - Types of foods,
  - Levels in those foods, and
  - Intended effects.
- Estimated Daily Intake (EDI).
- Analytical methodology.
- Full reports of safety data, including toxicological and other studies – Acceptable Daily Intake (ADI).
- Proposed tolerances, if needed.
- Environmental information.

The Review "Team"

- Core Disciplines
  - Chemist/Exposure Expert
  - Toxicologist
  - Environmental scientist
  - Regulatory expert
- Additional Disciplines
  - Pharmacologist
  - Nutritionist
  - Pathologist
  - Specialized toxicologist e.g., reproduction, development
  - Clinical data reviewer
  - Microbiologist

Data "Requirements"

- FDA has Guidelines, Not Requirements
  - Guidelines are a Benchmark
  - Allows for Flexibility to Use the Newest Science
- FDA's Initial Review Is About Basic Data Adequacy
  - Are There Enough Data?
  - Is the Data Appropriate: Does it Address the Correct Questions?
- FDA's In Depth Review is Also About the Adequacy of the Data
  - Can Raise Additional Questions
  - Require Additional Data Development

Chemistry Data and Information

Identity
- Chemical Name and CAS Number
- Structure and Molecular Weight
- Physical Characteristics

Manufacturing Process
- Full description of process
- List of chemicals/reagents used

Specifications
- Typically proposed by petitioner or reference published specs (FCC)
- Should include description of the additive, identification tests, purity assay, and limits for impurities/ contaminants

Stability
- Data demonstrating the stability
- Discussion of the fate of the additive

Technical Effect and Use
- Type of food and use level
- Data to show that the use level accomplishes the technical effect

Analytical Methodology
- If a use limitation of the additive is required for safe use, the petition must include a method able to quantify the substance for the purpose of enforcing the limit

Chemistry Review

Identity
- Correct nomenclature for regulation
- Relevance of other data
- Potential reactants/ degradants

Stability
- Exposure to degradants

Manufacturing Process
- Exposure to reactants/ degradants
- Need for safety related controls
- Normally not specified

Technical Effect and Use
- Establish that there is a reason for addition to food
- Is the use self limiting?
- Is the use deceptive?

Specifications
- Ensure identity consistent with what is reviewed
- Necessary for safe use?

Analytical Methodology
- Ensure validation of any required tests

Assessment of Dietary Intake

- Estimate of dietary intake by consumers to the food additive (and by-products of concern) resulting from eating food(s) containing the additive.
- Petitioner provides an estimate, which FDA confirms.
- Calculated as an estimated daily intake (EDI)
  - Assumes chronic or average daily intake over a lifetime, and
  - Is typically calculated for the mean and 90th percentile consumer.

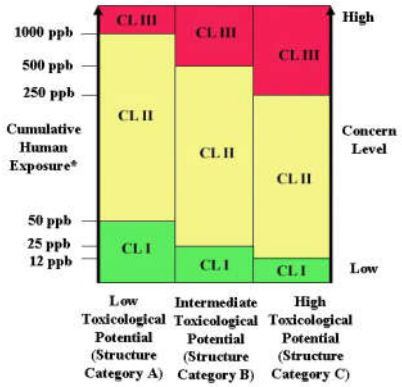
Sources of Data for Estimating Exposure

- Food Consumption Surveys
  - Ex.: USDA Continuing Survey of Food Intakes by Individuals (CSFII) USDA Retail Commodity Consumption Estimates.
- Food/component disappearance figures
  - Ex.: Market disappearance data from industry or contracts.
- Market basket Surveys
  - Ex.: FDA Total Diet Study.
- Body burden/excretion measurements: "Biomarkers"

Exposure Assessment Assumptions

- Assumes 100% market capture
- Can assume everyone is an eater or a small part of the population
- Assumes all foods contain the additive at the highest level (theoretical maximum)
- Use disappearance data to ground truth exposure estimates or as a point of comparison

FDA's Redbook Testing Tiers (1982)



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Concern Levels

- CL1
  - In vitro and in vivo mutagenicity testing
  - Short-term toxicity tests including neurotoxicity and immunotoxicity
- CL2
  - All studies necessary for CL1
  - Metabolism and pharmokinetic studies*
  - 2 Subchronic toxicity tests one in rodent and one in non-rodent**
  - Study of reproductive toxicity including teratology phase

*Possible to resolve by structure activity analysis

**Often possible to justify one versus two test

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Concern Levels

- CL3
  - All studies necessary for CL2 (may omit one subchronic toxicity test)
  - One-year study in nonrodents
  - Carcinogenicity study in rodents
  - Chronic toxicity/carcinogenicity study with rodents
- All testing may not be necessary if earlier tests prove sufficient to establish safety

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Toxicology Data and Information

- Review of safety studies presented to identify relevant studies
- Review of all other available data to identify relevant studies
- Exposure based testing requirements
  - Is there sufficient data to address all normal concerns or are there data gaps?
  - Are any data gaps significant?
  - Does the nature of the additive suggest the need for special data?

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Toxicology Data and Information

- Evaluation of relevant safety studies to determine adequacy of the data set to support estimated exposure
  - Evaluation of the rigor of the study: Do the studies meet minimum standards?
  - Identification of any additional questions raised by data
  - Determination of a safe exposure level (ADI) or suitable margin of exposure

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Safety Evaluation of Food Ingredients

- Data from longest duration; most appropriate highest quality study– used for deciding NOAEL.
- NOAEL=No Observed Adverse Effect Level.
- ADI-Acceptable Daily Intake
- ADI=NOAEL/Safety Factor (Uncertainty Factor)
- Safety Factor: 1000, 100, or 10…also x2 and x3
- ADI>EDI or a suitable margin of exposure; Food Additive approved
- Uncertainty and Conservative Estimates

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The Safety Decision

- Must protect public health by addressing the probative questions associated with the intended use.
- A consensus decision based on a fair evaluation of all the available data.
- Must withstand scientific, procedural, and legal challenge from all sides.

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Safety and Uncertainty

- Decisions must be made in the face of uncertainty
- The uncertainty cannot be out-of-line with what has been previously tolerated in the context of all previous similar safety decisions

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Other Guidance and Guidelines

- EPA - http://www.epa.gov/
- EFSA - http://www.efsa.europa.eu/
- FSANZ - http://www.foodstandards.gov.au/
- JECFA - http://www.who.int/ipcs/food/jecfa/en/
- OECD - http://ntp-apps.niehs.nih.gov/iccvampb/OECD.cfm
- Health Canada - http://www.hc-sc.gc.ca/index-eng.php

This is certainly not an all inclusive list; there are many other valuable documents relevant to food ingredient safety used by FDA scientists and technical reviewers.

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Questions?

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