

FDA's Food Additives Program



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Food Additives: A Global Perspective on Safety Evaluation and Use
Procedures for Approval of Food Additives
New Delhi, India
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Office of Food Additive Safety (OFAS)



What We Regulate

Why We Regulate

How We Regulate



FDA

What We Regulate

ADMINISTRATION

Substances added to food

Legal distinctions within the Federal Food, Drug, and Cosmetic Act

– Color Additives

- Substances added to food to impart color

– Direct Food Additives

- Substances intentionally added to food (Sweeteners; preservatives; nutrients; fat substitutes; texturizers (e.g., thickeners, emulsifiers); flavoring agents)



Substances added to food

Legal distinctions within the Federal Food, Drug, and Cosmetic Act

– Indirect Food Additives

- Food Contact Substances: Coatings (paper, metal, etc.); new/recycled plastics including polymers and monomers; paper; adhesives; colorants, antimicrobials, and antioxidants in packaging; packaging materials used during food irradiation; packaging “formulations”
- Processing Aids: Antimicrobials; enzymes; de-foaming agents; ion exchange resins

Substances added to food

Other “Ingredients”

- GRAS Substances
 - Enzymes; fibers; proteins; lipids; carbohydrates
- Foods/Ingredients Derived from Plants Produced via Biotechnology
 - Plants with enhanced agronomic properties (herbicide or pest resistance) or enhanced production properties (delayed ripening, delayed browning, etc.)
- Food Irradiation Equipment
 - To process food or to inspect food




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Why We Regulate

U.S. FOOD & DRUG
ADMINISTRATION

Why We Regulate

Federal Food Drug and Cosmetic Act. Sec. 201(s) Food Additives

201(s) The term **“food additive”** means 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, packing, processing, preparing, treating, packaging, transporting, or holding food**; and **including any source of radiation intended for any such use**), 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**; except that such term does not include—

- (1) a pesticide chemical residue in or on a raw agricultural commodity or processed food; or
- (2) a pesticide chemical; or
- (3) a color additive; or
- (4) any substance used in accordance with a sanction or approval granted prior to September 6, 1958, pursuant to this chapter, the Poultry Products Inspection Act [21 U.S.C. 451 et seq.] or the Meat Inspection Act of March 4, 1907, as amended and extended [21 U.S.C. 601 et seq.];
- (5) a new animal drug; or
- (6) an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement.

Why We Regulate

FFDCA Sec. 201(t) Color Additives

201(t)(1) The term **“color additive”** means a material which—

(A) is a **dye, pigment, or other substance** made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source, and

(B) when **added or applied to a food, drug, or cosmetic, or to the human body** or any part thereof, is capable (alone or through reaction with other substance) of **imparting color** thereto;

except that such term does not include any material which the Secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring.

(2) The term **“color”** includes **black, white, and intermediate grays**.

(3) Nothing in subparagraph (1) of this paragraph shall be construed to apply to any pesticide chemical, soil or plant nutrient, or other agricultural chemical solely because of its effect in aiding, retarding, or otherwise affecting, directly or indirectly, the growth or other natural physiological processes of produce of the soil and thereby affecting its color, whether before or after harvest.

Why We Regulate

FFDCA Sec. 409(h) Food Contact Substance

409(h)(6) In this section, the term “**food contact substance**” means any substance intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use is not intended to have any technical effect in such food.




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How We Regulate

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Regulatory Divisions in OFAS

- Division of Petition Review (DPR)
 - Color Additives
 - Direct Food Additives
- Division of Biotechnology and GRAS Notification Review (DBGRN)
 - Biotechnology Reviews
 - GRAS Notifications
- Division of Food Contact Notifications (DFCN)
 - Indirect Food Additives (Food Contact)
 - Threshold of Regulations (TOR)

Review Teams for Regulatory Submissions

- Multidisciplinary workgroup
 - 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

**Environmental Scientists are not part of the GRAS Notice review teams

■ Current USA Regulatory Mechanisms for Substances Added to Food

Based on use:

- Intent to color food → Color Additive Petition
- Direct addition to food → Food Additive Petition
- Migration to food from use → Threshold of Regulation
- → Food Contact Notification

Based on availability of and consensus on data:

- Publically available data & consensus → GRAS Notification

How We Regulate

	Petition Process	GRAS Notice	Food Contact Notice/ Threshold of Regulation
Inception of Regulatory Approval Process	Color additives since 1960 Food additives since 1958	1997 to now (previously a GRAS affirmation petition process)	1997 to now (previously handled as “indirect” food additive petitions)
Regulation	Color additives 21 CFR 71.1 Food additives 21 CFR 171.1	21 CFR 170.203-285	FCN 21 CFR 170.100-106 TOR 21 CFR 170.39
Mechanism for Request	Industry submits a petition asking FDA to issue a regulation	Notifier informs FDA of their view that a use of a substance is GRAS	Industry submits a notification
Is submission to FDA required before marketing product?	Required	Not Required	Required
Safety decision	FDA owns the safety decision	Notifier owns the safety decision; FDA evaluates the notifier’s basis	FDA owns the safety decision
Length of time for a review	(180 days) No regulation is published. Food or Color Additive <u>cannot be used in food</u>	(180 days) Substance is considered GRAS until FDA says otherwise	(120 days) Food contact substance cannot be used in food contact applications
Where is the result published?	Federal Register and Code of Federal Regulations	Agency Website	Agency Website
Exclusivity	No exclusivity	No exclusivity	By law, exclusive to manufacture or supplier

How We Regulate

Color Additive Petitions (21 CFR 71.1) – Required Content

- Identity and Composition of the color additive
- Proposed use in food, drugs, cosmetics, device
- Amount (concentration) to be added
- Data establishing its Intended Technical Effect
- Analytical quantitative detection methods to determine amount (concentration) in food
- Full reports of Safety studies (data and narrative)
- Proposed tolerances (if needed)
- Environmental review information (NEPA)
- \$3,000 Deposit (foods)/\$2,600 Deposit (drugs)

How We Regulate

Food Additive Petitions (21 CFR 171.1) – Required Content

- Identity and Composition of the food additive
- Proposed use in food
- Amount (concentration) to be added to food
- Data establishing its Intended Technical Effect
- Analytical quantitative detection methods to determine amount (concentration) in food
- Full reports of Safety studies (data and narrative)
- Proposed tolerances (if needed)
- Environmental review information (NEPA)

How We Regulate

Safety Evaluation: Color Additive & Food Additive Petitions

- “An Iterative Process”
 - Consult early and often
 - Share plans before initiating testing
- Food and Color Additive Master Files
- Discussing the safety package as it is developed can eliminate roadblocks to approval

How We Regulate

Safety Evaluation: Color Additive & Food Additive Petitions

- Lifetime-average Estimated Daily Intake (ADI)
- Highest No-Effect Level (HNEL) from lifetime animal studies
- Threshold behavior for toxic effects
- Application of appropriate safety (uncertainty) factor (e.g., 100x)
- Acceptable Daily Intake (ADI)
- Comparison of the EDI to the ADI
- No effects at estimated consumption levels

How We Regulate

Food Contact Notifications (1 CFR 170.100-106) – Required Content

- Identity and Composition of the food contact substance
- Intended Use (single-use or repeat-use food contact articles)
- Amount (concentration) to be added to the food contact article
- Data establishing its Intended Technical Effect
- Analytical quantitative detection methods to determine migration to food (FCS and any residual impurities)
- Full reports of Safety studies (data and narrative)
- Environmental review information (NEPA)

How We Regulate

Food Contact Notifications (21 CFR 170.100-106)

- Exposure ≤ 0.5 ppb (TOR)*
 - No toxicology studies recommended
 - Comprehensive literature search
- Exposure > 0.5 ppb and ≤ 50 ppb
 - As above plus genetic toxicity tests
- Exposure > 50 ppb and ≤ 1 ppm
 - As above plus 2 subchronic oral studies (rodent and non-rodent)
- Exposure > 1 ppm
 - Comprehensive tests including bioassays

How We Regulate

Threshold of Regulation (TOR) (21 CFR 170.39)

- A policy developed in the mid-1990's in CFSAN using “notice and comment” rulemaking
- Exempts from petition review, situations where the dietary exposure to an ingredient is below a “threshold level,” (Exposure—EDI <1.5 µg/p/d; DC <0.5 ppb)
- Applied to non-carcinogens but precludes non-negligible upper-bound carcinogenic risk

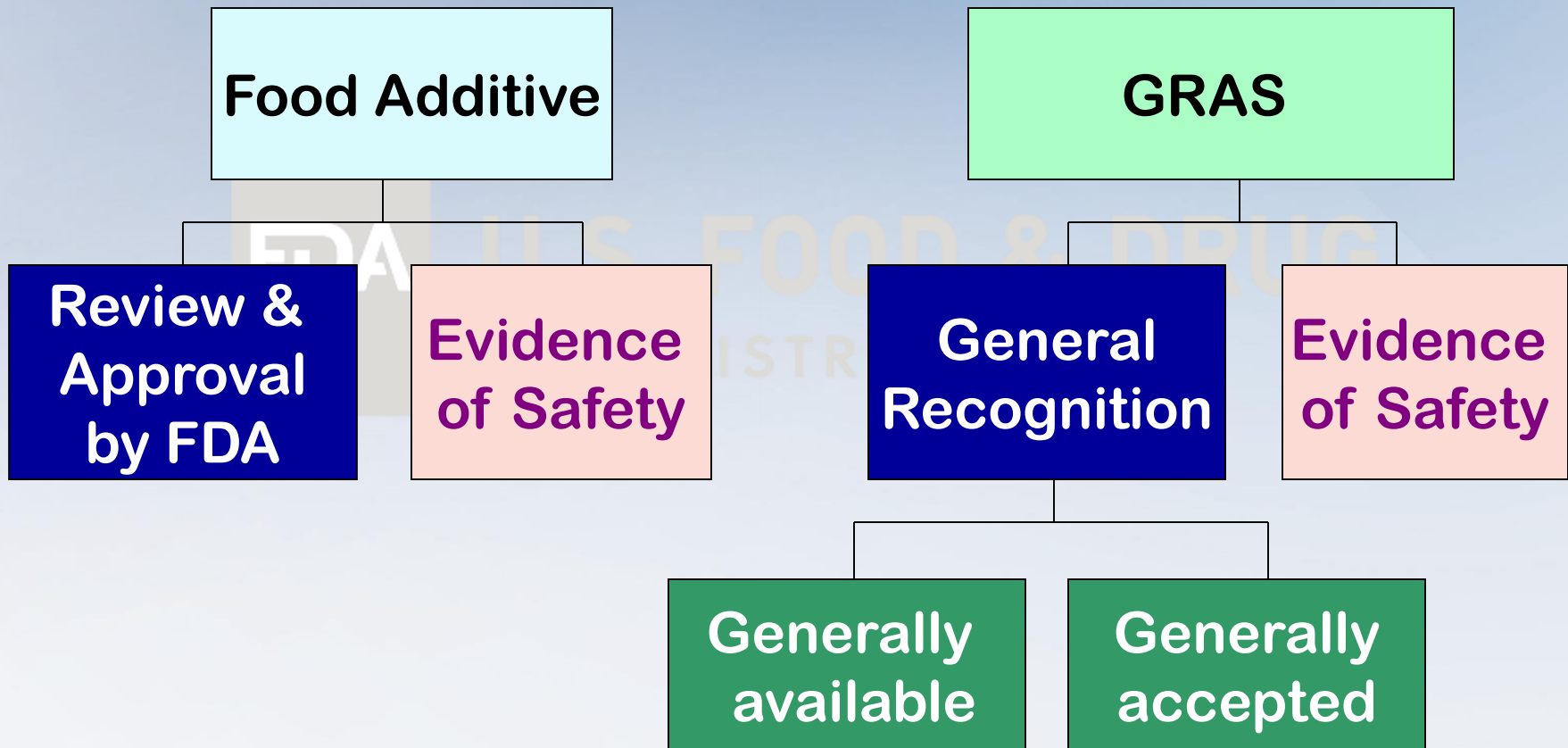
■ Submission of a GRAS notification to FDA is not required prior to marketing

Industry can reach a “*Self-Determination*” that the use of a substance is GRAS.

- From a use perspective GRAS substances are food additives, however legally they are exempt and can be used without prior FDA approval
 - History of safe use prior to 1958 or general recognition of safety
 - **Exempting** GRAS substances prevented disruption of US food supply in 1958, and reduces burden on Agency and Industry for substances which are truly “generally recognized” as safe
- The statutory standard for GRAS must be met **regardless** of GRAS Notice vs Self-Determination
 - FDA has recently published a Final rule which defines the criteria for GRAS (81 FR 5490 – August 17, 2016)
 - FDA offers GRAS Notice review – useful for instances where consensus on safety may be questioned.
- Self-Determination can be problematic (e.g., Partially Hydrogenated Oils)

How We Regulate

Food Additive vs. GRAS



How We Regulate

Food Additive vs. GRAS

Food Additive

- Data and information may not be generally available
- FDA reviews the data and “owns” the safety decision

GRAS

- Data and Information are generally available
- Reviewed by experts qualified by training and experience to evaluate the safety of the substance
- Reflects the general acceptance (or consensus) of experts
- Although manufacturers can self-determine that the use of a substance is GRAS, that determination is not binding on FDA
- It is not a license or company-based determination

How We Regulate

GRAS Notices (21 CFR 170.203-285)

- Identity, method of manufacture, specifications and physical or technical effect
- Dietary Exposure
- Self-Limiting levels of use
- Experience based on common use in food before 1958
- Narrative
- List of supporting data and information
- Signed statements & certifications

■ Safety and Review Standards are same across all regulatory mechanisms

- Standard of Safety

- Requires “Reasonable Certainty of No Harm”

“a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use” (21 CFR 170.3)

“It does not – and cannot – require proof beyond any possible doubt that no harm will result under any conceivable circumstance” (H.R. report No. 2284, 85th Congress, 1958)

- Information necessary to demonstrate safety is dependent on exposure and determined by intended use

- Standard of Review

- Fair evaluation of all of the data

Regulatory Progress Since 1958

- Food Additive Petitions >4800
- Color Additive Petitions >300
- GRAS Affirmation Petitions >400
- Food Contact Notifications ~1870 (since 2000)
- GRAS Notifications ~800 (since 1998)
- Biotechnology Consultations ~160 (since 1995)



Total: >8200 petitions/notifications/consultations

■ Links to Guidance Documents and Inventories

Guidance documents for GRAS Notifications, Food and Color Additive Petitions, and Food Contact Notifications can be found at:

<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/default.htm>

Inventory of Effective Food Contact Substance (FCS) Notifications are available at:

<https://www.accessdata.fda.gov/scripts/fdcc/?set=FCN>

Other uses may also be GRAS, but are not necessarily so Inventory of all GRAS Notices available at:

<https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices>

Contact The Office of Food Additive Safety

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