U.S. FOOD & DRUG ADMINISTRATION

Center for Food Safety and Applied Nutrition

Introduction to GRAS Ingredients and the FDA GRAS Notification Program

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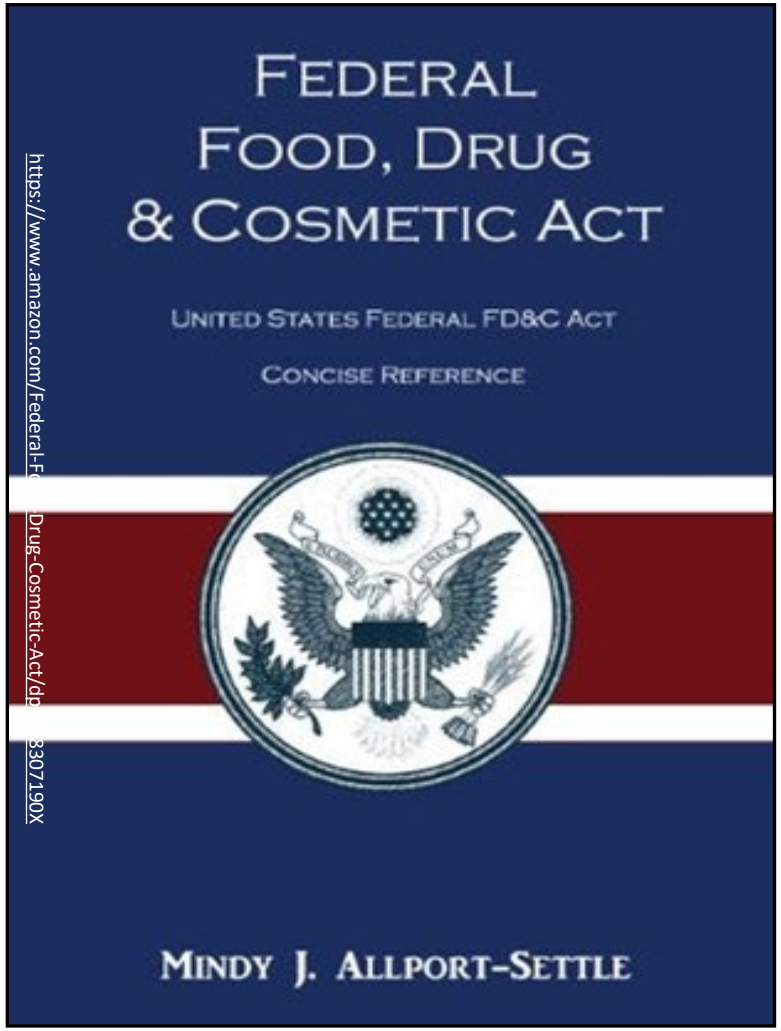
Ensures the 

of substances added to food

AUTHORITY TO REGULATE

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

Federal Food, Drug, and Cosmetic Act



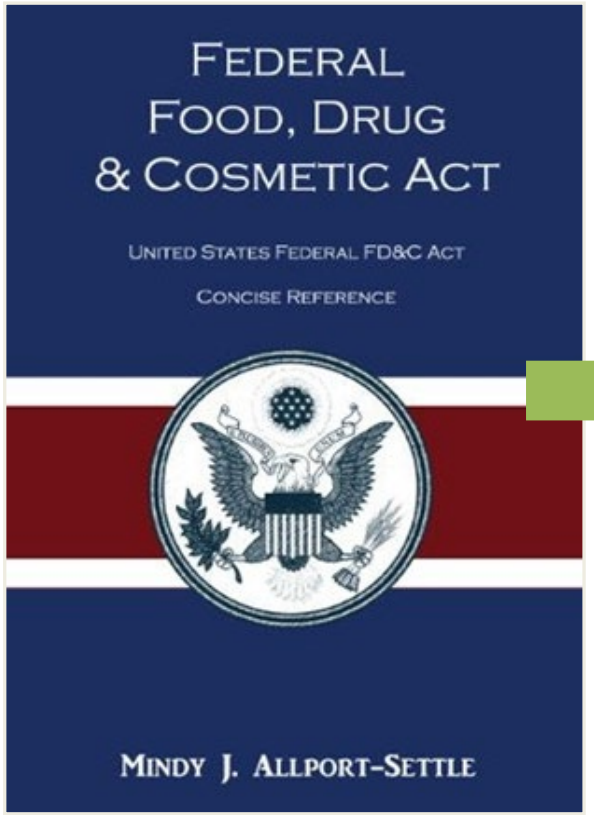
https://www.amazon.com/Federal-F Drug-Cosmetic-Act/dp 830719 0X

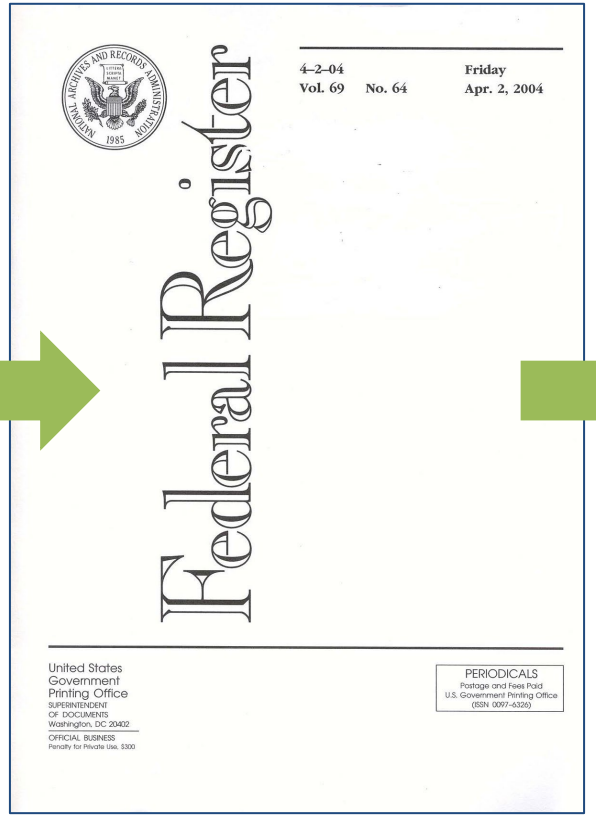
- The FD&C Act was passed in 1938
- In addition to drugs and cosmetics, the Act also gives FDA the legal authority to regulate food and food ingredients.
- It also gives FDA the authority to oversee the safety of the food supply.

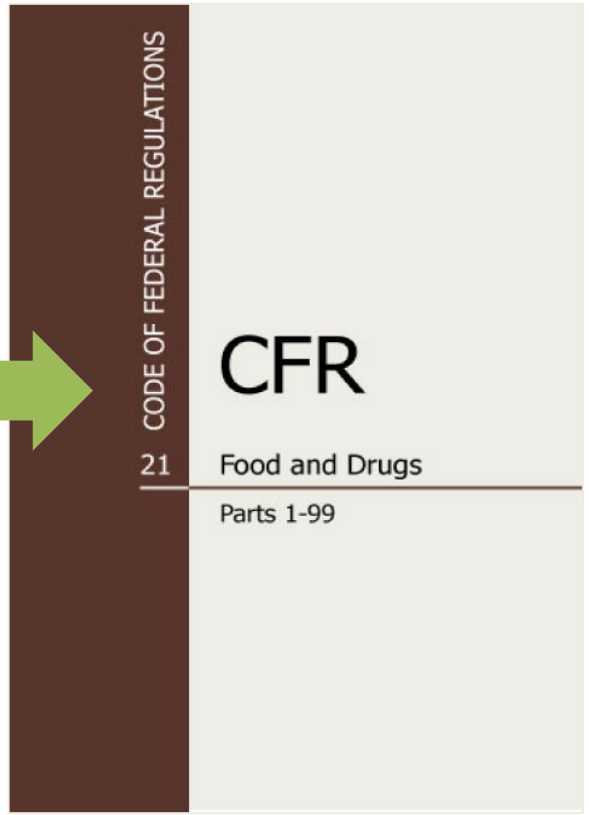
Federal Food, Drug, and Cosmetic Act- Amendments

- In 1958, the Food Additives Amendment to the FD&C Act was passed by Congress
  - Defines “food additive”, with a provision for “GRAS”
  - Requires pre-market approval of new uses of food additives
  - Establishes the standard of review
  - Establishes the standard of safety
  - Establishes formal rulemaking procedures
- In 1960, the Color Additives Amendment to the FD&C was passed by Congress

The Law and Regulations







Regulations.gov

www.ecfr.gov

Navigating the Code of Federal Regulations (CFR)

Accessed online at www.ecfr.gov

TITLE PART/ SECTION

21 CFR § 182.10

Title 21 Food & Drugs
Subchapter B Food for Human Consumption
Part 182 Substances Generally Recognized as Safe
Section 10 Spices and Other Natural Seasonings and Flavors

Statutory Definitions

Food Additive and GRAS Provision

FD&C Act §201(s) - Food Additive	FD&C Act §201(s) – GRAS Provision
"… 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 a 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), …"	A substance is excluded from FDA's premarket review and approval requirement for food additives if it is "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures… or experience based on common use in food [prior to January 1, 1958] to be safe under the conditions of its intended use"

Exceptions to the Definition of "Food Additive"

- Prior sanctioned ingredients; 21 CFR 181
  - Explicit approval for the use of a substance in food prior to September 6, 1958, under the FD&C Act, MIA, or PPIA (21 CFR 170.3(l))
- Color Additives
- Pesticides (EPA)
- Animal drugs that may remain in food
- Dietary Ingredients in dietary supplements

Comparison of Food Additives and GRAS Substances

Food Additives

Similarities:

- Safety standard of Reasonable Certainty of No Harm (see 21 CFR 170.3(i))

Differences:

- Petition Process
- Subject to pre-market review and approval by FDA
- Successful food additive petitions result in a regulation number in Title 21 of the Code of Federal Regulations (21 CFR)
- **General recognition requirement is not applicable to petitions.**

GRAS Substances

Similarities:

- Safety standard of Reasonable Certainty of No Harm (see 21 CFR 170.3(i))

Differences:

- GRAS Notification Program
- Not subject to pre-market review and approval by FDA
- **General recognition requirement: The data are published/public and there is consensus among experts**

FD&C Act: prohibited acts

Section 301

The following acts and the causing thereof are prohibited:

-> the introduction or delivery for introduction into interstate commerce of any food that is adulterated

-> the adulteration of any food in interstate commerce

-> the receipt in interstate commerce of any food that is adulterated, and the delivery or proffered delivery thereof for pay or otherwise

Section 402

Any food that is, or bears or contains, an unapproved food or color additive is deemed **unsafe** (per Sections 409 and 721) and is therefore **adulterated** under the FD&C Act.

Color Additives

Per section 201(t) of the FD&C Act:

"… 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 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 to another substance) of imparting color thereto …"

- Color additives also require pre-market approval under a different part of the law
- Color additive approval is handled through a separate petition process to food additive approval
- Color additives cannot be GRAS

Is it a color additive?

Food ingredients such as cherries, green or red peppers, chocolate, and orange juice which contribute their own natural color when mixed with other foods are not regarded as color additives; but where a food substance such as beet juice is deliberately used as a color, as in pink lemonade, it is a color additive. [21 CFR 70.3(f)]

For a material otherwise meeting the definition of color additive to be exempt from section 721 of the Act, on the basis that it is used (or intended to be used) solely for a purpose or purposes other than coloring, the material must be used in a way that any color imparted is clearly unimportant insofar as the appearance, value, marketability, or consumer acceptability is concerned. [21 CFR 70.3(g)]

Food Additive Petitions

- To market a new food additive, or before using an approved additive for a new intended use, a manufacturer must submit a petition proposing:
  - A regulation prescribing the conditions under which a food additive may be safely used

    OR

  - An amendment of an existing food additive regulation

- Petition must include an assertion of facts, supported by data, showing that new information exists with respect to the food additive; or, that new uses have been developed or old uses abandoned
- If a petition is granted for a new use- results in regulation in the CFR

GRAS Ingredients and GRAS Notices

Generally Recognized as Safe (GRAS)

Per section 201(s) of the FD&C Act:

"…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…"

A substance whose use meets GRAS criteria does not require pre-market approval by FDA

BUT must meet the same safety standard as food additives

Under FDA's GRAS notification program, any person can notify FDA of their conclusion that a substance is GRAS under its conditions of use (21 CFR part 170 subpart E)

Use of an ingredient may be GRAS either through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food

Two Ways to Establish GRAS Status

Scientific Procedures
21 CFR 170.3(b)

- The information contained in a GRAS notice is of the same quality and quantity as contained in a food additive petition

History of Common use in Food Prior to 1958
21 CFR 170.3(c)

- Current use of substance is identical in quality, manufacture, use, and use levels as it was prior to 1958
- New uses in food that were common prior to 1958 are increasingly rare

General Recognition of Safety
21 CFR 170.3(a)

Generally Available

- Publication in peer-reviewed, scientific journals, textbooks, scientific reports, etc.
- The information supporting a GRAS conclusion cannot be confidential

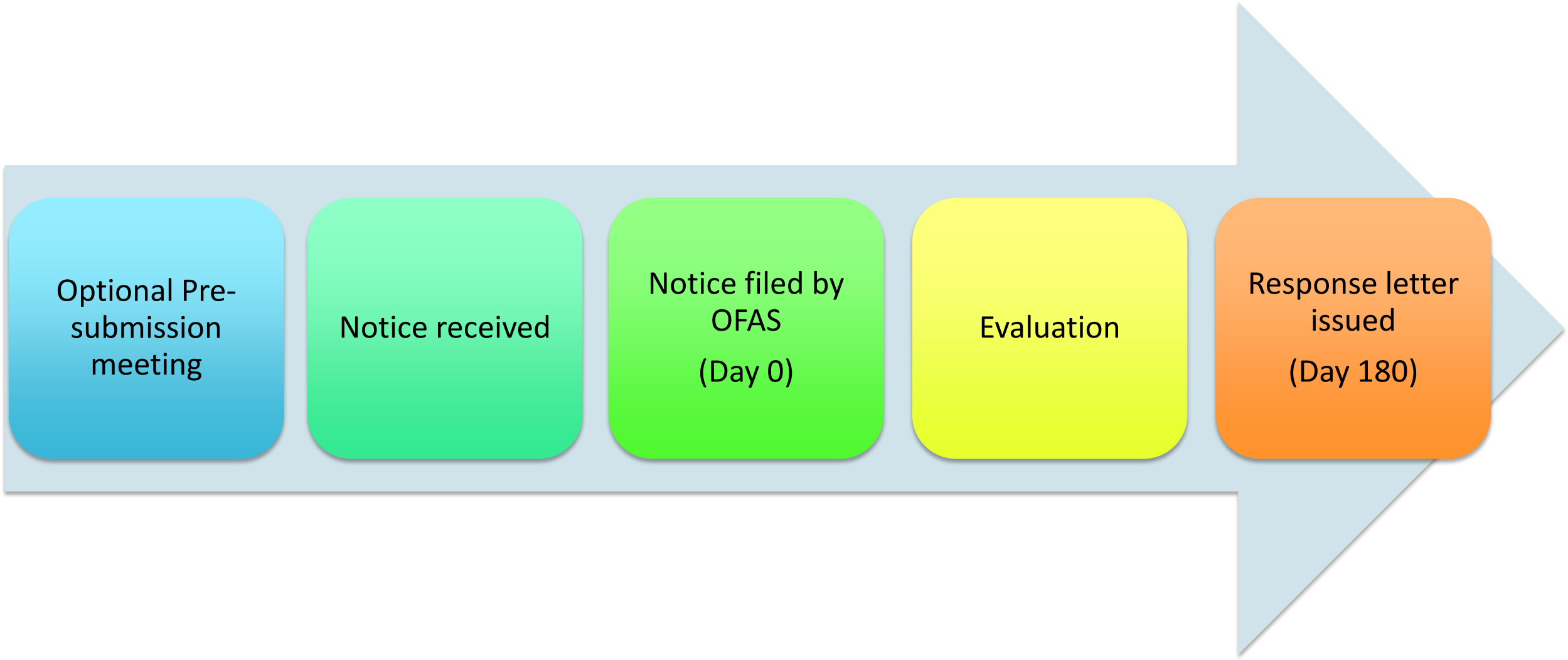
Generally Accepted

- Consensus among qualified scientific experts regarding safety

Narrative and Supporting Data

- Should provide the basis of a GRAS conclusion
- Explains why the data and information provide basis of the notifier's view that:
  - the substance is safe under the conditions of its intended use
    - ADME, toxicology, allergenicity, pre-clinical data, clinical data, etc.
  - there is a general recognition among qualified experts that the substance is safe under the conditions of its intended use
    - Peer reviewed publications, textbooks, authoritative body opinions
- Must include the good, bad, and indifferent
- Safety of a food ingredient is not a risk-benefit balance
- Provide bibliography of data used to provide the basis for the GRAS conclusion

GRAS Notice Review Timeline



GRAS Panel Guidance

- **GRAS panel:** "… a panel of qualified experts who independently evaluate whether the available scientific data, information, and methods establish that a substance is safe under the conditions of its intended use in human food or animal food as part of an evaluation of whether adding that substance to food is lawful under the GRAS provision of the FD&C Act"
- Our regulations do not specify a requirement for GRAS panels
- In most cases, a well-supported GRAS conclusion will not require analysis by a panel
- Consider whether it would be useful in supporting the GRAS conclusion before using resources to convene a panel
  - A GRAS panel is just one mechanism to provide evidence of general acceptance
  - If published results in the primary scientific literature raise no questions that experts need to interpret and resolve, a GRAS panel is likely unnecessary

Common Misconceptions About GRAS

- An ingredient on its own cannot be GRAS
  - **GRAS is based on the *intended use* of an ingredient**
- Notifying FDA of a GRAS conclusion is not mandatory; however, in the absence of an authorizing regulation or explicitly sanctioned in writing from either USDA or FDA prior to 1958, then a GRAS conclusion for the safe use of a substance is **mandatory** to lawfully add the substance to conventional food
  - *A manufacturer is legally responsible* to ensure that all ingredients added to food are safe for their intended uses.
- FDA response to a GRAS notice is not a certification, license, authorizing regulation, or an approval
- Color additives cannot be GRAS
- Dietary supplements and dietary ingredients in dietary supplements have their own regulatory pathways outside of GRAS

Regulations

Regulation	Topic
21 CFR 73	Listing of Color Additives Exempt from Certification
21 CFR 74	Listing of Color Additives Subject to Certification
21 CFR 172	Food Additives Permitted for Direct Addition to Food for Human Consumption
21 CFR 173	Secondary Direct Food Additives Permitted in Food for Human Consumption
21 CFR 175	Indirect Food Additives: Adhesives and Components of Coatings
21 CFR 176	Indirect Food Additives: Paper and Paperboard Components
21 CFR 177	Indirect Food Additives: Polymers
21 CFR 178	Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers
21 CFR 180	Food Additives Permitted in Food or in Contact with Food on an Interim Basis Pending Additional Study
21 CFR 181	Prior-Sanctioned Food Ingredients
21 CFR 182	Substances Generally Recognized as Safe
21 CFR 184	Direct Food Substances Affirmed as Generally Recognized as Safe
21 CFR 186	Indirect Food Substances Affirmed as Generally Recognized as Safe
21 CFR 189	Substances Prohibited From Use in Human Food

RESOURCES

- eCFR: https://www.ecfr.gov/
- GRAS Inventory: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices
- SCOGS Database: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=SCOGS
- Food & Color Additive Petitions Under Review Or Held In Abeyance: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=FAP-CAP
- Substances Added to Food Inventory: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=FoodSubstances
- Food Additive Status List: https://www.fda.gov/food/food-additives-petitions/food-additive-status-list
- Color Additive Status List: https://www.fda.gov/industry/color-additive-inventories/color-additive-status-list
- Import Alerts: https://www.fda.gov/industry/import-alerts/search-import-alerts
- Warning letters: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters

THANK YOU

For questions about the regulation of food additives, please reach out to **premarkt@fda.hhs.gov**

(please note, no last “e” in premarket)

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