Food Additives, Color Additives, GRAS and Dietary Ingredients – How are they different?

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Food Additives

- 1958 Food Additives Amendment to the Food, Drug & Cosmetic Act
  - Must prove that new additives are safe before FDA will approve them.
  - Included the Delaney Clause: if a substance caused cancer in animals or humans, it could not be added to food.
  - Formalized GRAS exception for substances considered safe by experts or long use.
  - Broadened the definition to include substances included in producing, processing, packaging, or holding food, including sources of radiation.

Food Additives

- Defined in the FD&C Act as:

"Any substance the intended use of which results or may reasonably be expected to result – directly or indirectly – in it becoming a component or otherwise affecting the characteristics of any food."

- Exceptions or substances subject to additional requirements:
  - GRAS Ingredients (Generally Recognized As Safe)
  - Prior-sanctioned substances authorized for use prior to the 1958 Food Additives Amendment
  - Color Additives
  - Dietary Ingredients in dietary supplements
  - Pesticides

Food Additives

- Direct Food Additives

Added to a food for a specific purpose, e.g., xanthan gum added to add texture. Direct additives are listed in the ingredient list on the label of a food.

- Must be authorized by FDA before it can be used in food on the market – 1958 Food Additive Amendment
- Must submit a food additive petition
  - To market a new direct food additive
  - To use a direct food additive in a different way than how the FDA has currently approved it.
- Food additive petitions must provide evidence that the substance is safe for the ways in which it will be used – including the foods it will be used in and the intended levels of use.

Food Additives

- Example: 21CFR172.490 Yellow prussiate of soda

§ 172.490 Yellow prussiate of soda.

(a) The food additive yellow prussiate of soda (sodium ferrocyanide decahydrate; $Na_4Fe(CN)_6 \cdot 10H_2O$ contains a minimum of 99 percent by weight of sodium ferrocyanide decahydrate.

(b) The additive is used or intended for use as an anticaking agent in salt and as an adjuvant in the production of dendritic crystals of salt in an amount needed to produce its intended effect but not in excess of 13 parts per million calculated as anhydrous sodium ferrocyanide.

[42 FR 14491, Mar. 15, 1977, as amended at 58 FR 17098, Apr. 1, 1993]

Food Additives

- Direct Food Additives

When evaluating the safety of an ingredient submitted in a food additive petition, the FDA considers:

- What is the food ingredient?
- How will the food ingredient be made?
- How much of the ingredient will be in food?
- What types of foods will the ingredient be used in?
- How much of the food ingredient will consumers eat?
- How does the body metabolize the food ingredient (including absorption, digestion, metabolism, and excretion)?
- What are the results of relevant scientific studies on the safety of the ingredient?

Food Additives

- Direct Food Additives
  - The safety of food additives must be supported by science that demonstrates its use meets the FDA's safety standard – a reasonable certainty of no harm.
  - For every food additive the FDA approves, a regulation is issued and is available in the U.S. Code of Federal Regulations (CFR)
  - FDA does consult with USDA during the review process for food additives that are proposed for use in meat and poultry products.

Food Additives

- Indirect Food Additives

Food Packaging & Other Substances that come in contact with food (Food Contact Substances)

  - Prevent grease from leaking through paper or cardboard food packaging
  - Prevent discoloring from repeated use of repeat use plastic containers
  - Make cookware non-stick
  - Adhere stickers to produce

Food Additives

- Indirect Food Additives

A substance that is expected to migrate to food because of its intended use in the food contact material must be covered by one of the following:

- a regulation listed in Title 21 Code of Federal Regulations
- meeting the criteria for GRAS status (including but not limited to a GRAS regulation or GRAS notice)
- a prior sanction letter
- an effective Food Contact Substance Notification (FCN)
- a Threshold of Regulation (TOR) exemption request

Food Additives

- Indirect Food Additives

Food Contact Notification (FCN)

- An FCN is effective for:
  - The manufacturer/supplier identified in notification
  - The Food Contact Substance
  - The conditions of use identified in the notification
- An FCN is proprietary to the manufacturer for which the notification is effective
- List of current FCNs can be found on FDA's website.

Threshold of Regulation Exemptions (TOR)

- 21CFR170.39
- Food contact article at extremely low levels and no health or safety concerns
- No technical effect in the food to which it migrates
- No significant adverse impact on the environment

Food Additives

- Irradiation

Regulated under the 1958 Food Additives Amendment

- 21CFR179 addresses the provisions for use of irradiation
- Limited foods and packaging that can be irradiated. Sometimes a food in a package can be irradiated but the safety in all cases must have been assessed.
- Retail foods in package form that have been irradiated must be labeled with a statement of “Treated with radiation” and the Radura symbol.

Other Additives

- GRAS Ingredients
  - Do not (currently) require pre-market review by FDA
  - All data necessary to establish safety must be publicly available
  - Safe use must be generally recognized by qualified experts
  - Must meet the same safety standard as for food additives
    - Reasonable certainty of no harm under the conditions of intended use
    - Same quantity and quality of information that would support the safety of a food additive
  - Any person that has concluded that the use of an ingredient can meet the standard for GRAS may notify the FDA through the FDA's GRAS Notification Program – not mandatory but strongly encouraged.
  - If FDA has no questions on the GRAS notification, the information is stored in the GRAS Notice Inventory.

Other Additives

- GRAS Notice Inventory

GRN No. (sorted Z-A)	Substance	Date of closure	FDA's Letter	Date of add'l correspondence	Resubmitted as GRN No.
1219	Recombinant bovine lactoferrin isolate produced by *Komagataella phaffii* M020 expressing the gene encoding bovine lactoferrin	May 7, 2025	FDA has no questions (in PDF) (580 kB)		
1218	*Bacillus subtilis* NRRL 68054	Apr 29, 2025	FDA has no questions (in PDF) (192 kB)		
1217	Algal oil (≥40% docosahexaenoic acid) from *Aurantiochytrium limacinum* CCAP A1	May 7, 2025	At the notifier's request, FDA ceased to evaluate this notice (in PDF) (202 kB)		
1216	Galacto-oligosaccharides		Pending		
1215	Bacteriophage (phage) preparation specific to *Listeria monocytogenes*	Jun 6, 2025	FDA has no questions (in PDF) (163 kB)		
1214	*Bacillus clausii* UBBC-07 spore preparation	May 7, 2025	FDA has no questions (in PDF) (179 kB)		

Other Additives

- GRAS Ingredients
  - Once an ingredient is accepted as GRAS, it can still have that status rescinded if subsequently deemed unsafe.
    - Caffeinated alcoholic beverages
    - Cannabidiol (CBD)
    - Gingko Biloba
    - Tara Flour
    - Partially hydrogenated oils

Other Additives

- Prior Sanctioned Substances 21CFR181

Authorized for use by the FDA or USDA prior to the 1958 Food Additives Amendment

- A number of substances present in food packaging materials
- Sodium Nitrate
- Potassium Nitrate

A number of ingredients prior to the 1958 Food Additives Amendment were considered GRAS. However, it wasn't until 1969 that a select committee (SCOGS) was formed to evaluate the safety of these substances. By 1982, after 10 years of work, SCOGS had produced 151 detailed reports covering over 400 substances. The current database holds the opinions and conclusions from 115 SCOGS reports on the safety of over 370 GRAS food substances.

Color Additives

- A color additive must be shown to be safe and be listed in the CFR before it may be used to color foods, drugs, cosmetics, or certain medical devices. No GRAS provisions for color additives.
- Defined in the FD&C act as:
  - "a material which ... 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 ... [that] 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 [an]other substance) of imparting color thereto ... The term 'color' includes black, white, and intermediate grays..."

Color Additives

- Listed in 21CFR73 and 74, however the FDA website provides some additional information such as the E number and the year approved.
- The current administration has been very active in trying to restrict the use of the certified colors.
  - January 15, 2025: FDA issued an order to revoke the authorization of Red 3 for food and drugs.
  - April 14, 2025: A petition was filed to repeal the use of titanium dioxide in foods.
  - April 22, 2025: HHS and FDA announced a series of measures to phase out petroleum-based synthetic dyes from the nation's food supply.
  - May 9, 2025: FDA granted 3 new color additive petitions: Galdieria extract blue, Butterfly pea flower extract (blue), Calcium phosphate (white).
  - September 17, 2025: FDA proposed to revoke the authorization of the use of Orange B.

Dietary Ingredients

- If you want to market a “new dietary ingredient” in a dietary supplement, you must be sure that the substance is considered to be a dietary ingredient. Defined as
  - A vitamin
  - A mineral
  - An herb or other botanical
  - An amino acid
  - Dietary substance for use by man to supplement the diet by increasing total dietary intake
  - Concentrate, metabolite, constituent, extract, or combination of any of the above dietary ingredients.

Dietary Ingredients

- New Dietary Ingredient: a dietary ingredient that was not marketed in the US in a dietary supplement before October 15, 1994. (Note: There is no authoritative list of dietary ingredients that were marketed in dietary supplements before October 15, 1994. However, a list of 1400 new dietary ingredients since 1995 can be found on FDA's website.)
- You must submit a premarket notification if you are a:
  - Manufacturer or distributor who intends to market a new dietary ingredient;
  - Manufacturer or distributor who intends to market a dietary supplement that contains a new dietary ingredient
- Dietary ingredients cannot be used in foods unless there is a separate regulation permitting their use in food.

Pesticides

- The EPA (Environmental Protection Agency) along with FDA set maximum legal limits (tolerances) for residues in foods to ensure food is safe for consumption.
- The FDA monitors and enforces these tolerances in the food supply
- Regulations require a waiting period between when a pesticide is applied and when the crop can be harvested, allowing residues to decrease to safe levels.

Summary

- Food Additive
  - Direct (added to a food for a specific purpose- Food Additive Petition)
  - Indirect (part of processing or packaging – Food Additive, GRAS, Prior-Sanctioned, Food Contact Notification, or Threshold of Regulation Exemption)
- GRAS Ingredients (Generally Recognized As Safe) – Voluntary Notification
- Prior-sanctioned substances authorized for use prior to the 1958 Food Additives Amendment
- Color Additives – Color Additive Petition
- Dietary Ingredients in dietary supplements – New Dietary Ingredient Notification
- Pesticides - EPA