U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY & APPLIED NUTRITION

OFAS Pre-Market Review Programs

Regulatory Decision-Making Tools for Novel Food Technologies

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Disclosure Statement

- No conflicts of interest to declare

Summary

- Innovations in science and technology continue to generate new food production technologies
  - Precision fermentation (e.g., proteins, carbohydrates)
  - Animal cell culture for food and feed production
- FDA combines long-standing authorities with policy and scientific knowledge to regulate food safety

Food safety – definitions, tools, and programs

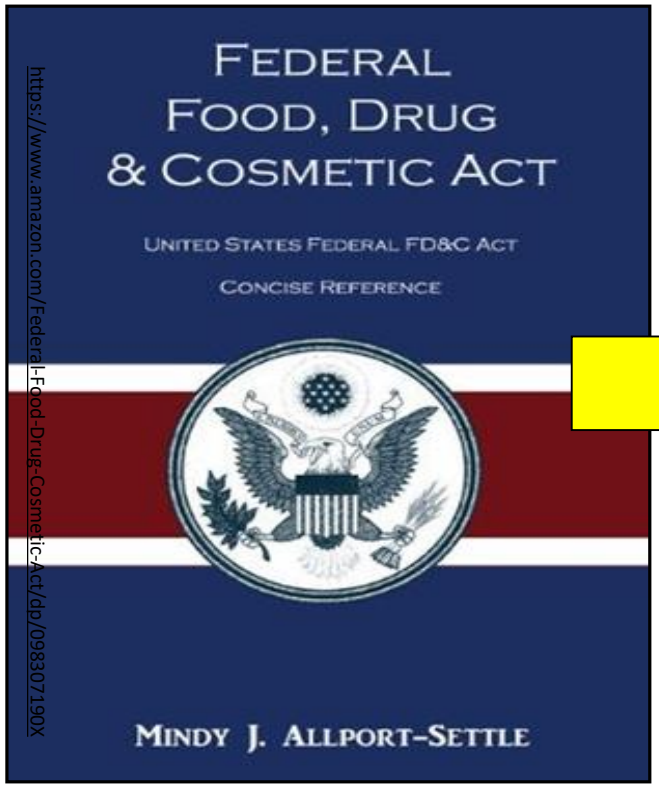
Example: Precision Fermentation

Example: Cell Culture

FOOD SAFETY

Definitions, Tools, and Programs

Federal Food, Drug & Cosmetic Act



https://www.amazon.com/Federal-Food-Drug-Cosmetic-Act/dp/098307190X

The Law

Foods, Food Ingredients, Drugs & Cosmetics

Federal Food, Drug & Cosmetic Act

---------- 1958 Amendments ----------

- Defines “food additive”, and the “GRAS” provision
- Requires pre-market approval of new uses of food additives
- Establishes the standard of review
- Establishes the standard of safety
- Establishes formal rulemaking procedures

Statutory Definition of Food Additives

Any substance the intended use of which

results or may reasonably be expected to result

in its becoming a component

or otherwise affecting the characteristic of any food

including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting or holding food

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 (separate regulations)
- Pesticides (EPA)
- Animal drugs (that may remain in food)
- Dietary Ingredients in dietary supplements

Food Additive

"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."

GRAS

… ***Unless*** the substance is generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as adequately shown to be safe under the conditions of its intended use.

Food Additive

- Subject to pre-market review & approval by FDA
  - Regulation prescribing the conditions under which a food additive may be safely used
- Successful food additive petitions result in a regulation number

GRAS

GRAS Provision

- Not subject to pre-market approval requirements of the Act
- Some GRAS substances listed in Parts 182, 184, 186
- No regulation number for GRAS notices
- Notices, response letters posted to GRAS Notice Inventory on FDA site

Two Components of GRAS

General Recognition of Safety	Evidence of Safety
GRAS	Food Additive GRAS

Safety data, information must:

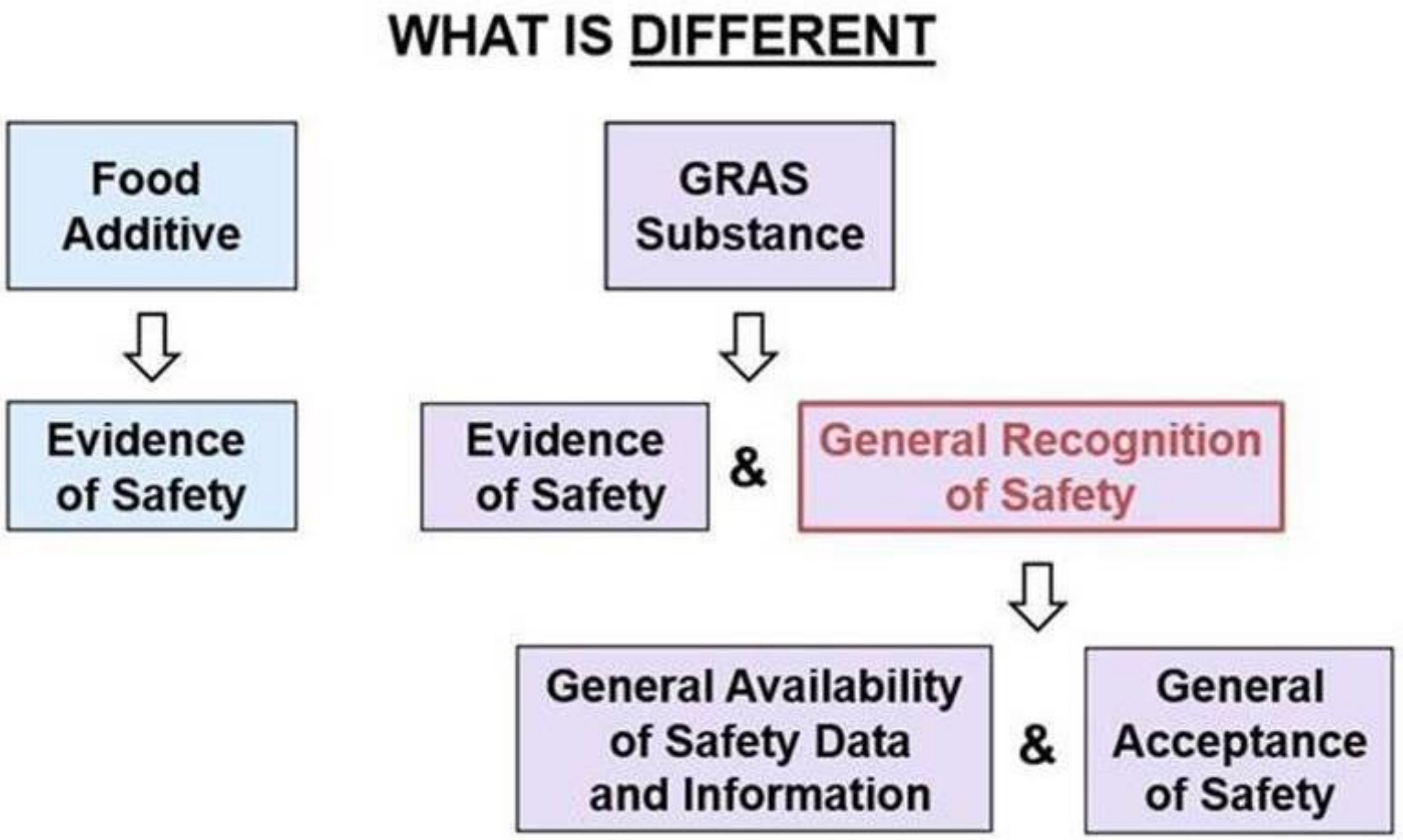
1. Be generally available

2. Be generally accepted

The information supporting the GRAS conclusion must be generally available; it **cannot** be confidential.

- **Availability:** Publication in peer-reviewed scientific journals, text books, scientific reports *etc.*
- **Acceptance:** Consensus among qualified scientific experts regarding safety

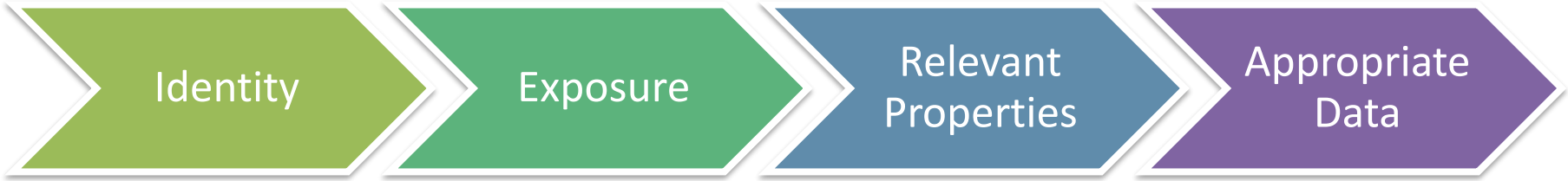
Food Additives and GRAS Substances



Safety Standard

- Legislative History of the FD&C Act:
  - "The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive."
  - "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
- It is the burden of the petitioner to demonstrate a "… reasonable certainty of no harm …" from the intended use of the additive; the safety decision is ultimately FDA's

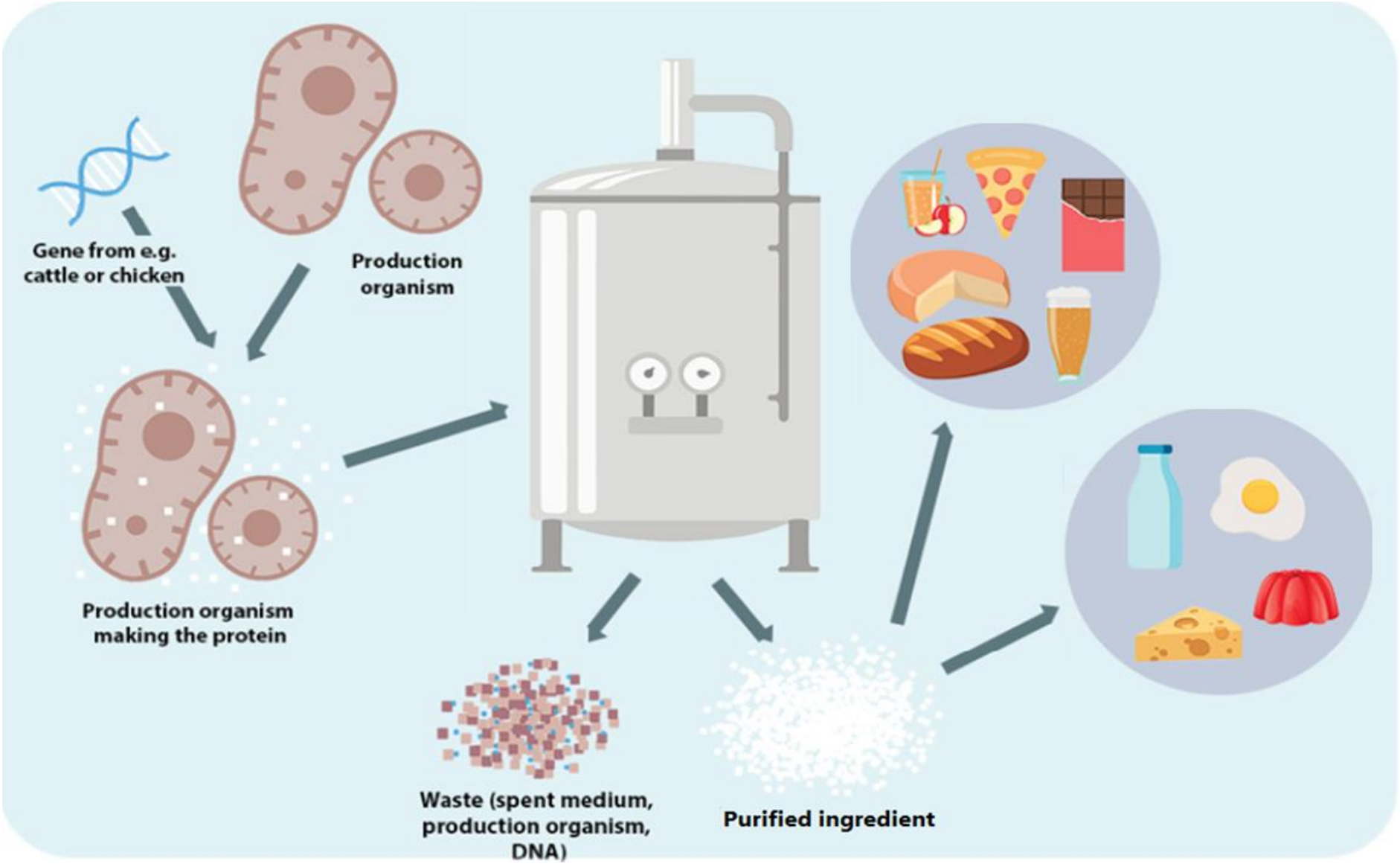
Approach to Safety Assessment of Substances Added to Food



Safety Assessment: Basic Elements

- **What is it?**
  - Identity, properties, and composition
  - Manufacturing process
  - Specifications, limits on impurities/contaminants
- **What are its intended uses?**
  - Purpose or technical effect (why is it added to food?)
  - Food categories
  - Use levels
- **How much will people consume of it?**
  - Exposure estimate based on maximum intended use levels and food consumption data
- **Will amounts consumed be safe?**
  - Data and information supporting safety at estimated exposure levels
  - Appropriate data informed by exposure, biochemical properties, functional properties

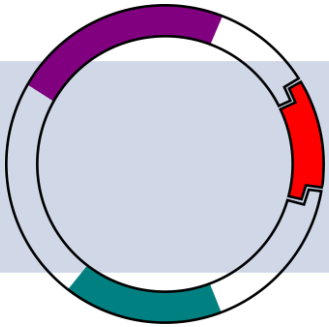
PRECISION FERMENTATION



This figure has been republished from “Cellular Agriculture: An extension of common production methods for food” https://gfi.org/images/uploads/2018/03/Cellular-Agriculture-for-Animal-Protein.pdf

Precision Fermentation

- Bacteria and fungi have been used traditionally in food processing (e.g., yogurt, cheese, pickles, wine, bread)
- Can also be used as a source of ingredients
  - Microorganisms as direct ingredients in conventional food
  - Microorganisms as vehicles for production of an ingredient used in conventional food (e.g., protein, carbohydrate)
  - Plant-derived protein production
    - GRN 000944 – rice protein hydrolysate – production includes treatment with a subtilisin enzyme preparation from a non-pathogenic and non-toxigenic strain of *Bacillus amyloliquefaciens*



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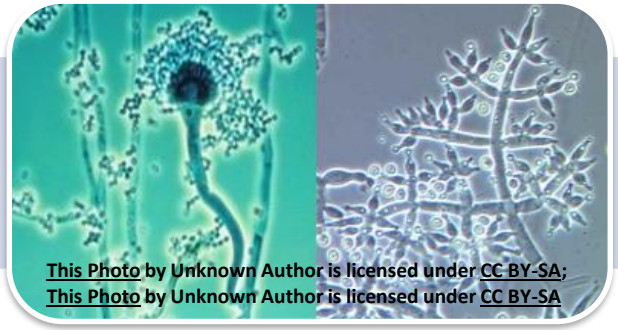

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Precision Fermentation, cont'd.

- Chymosin preparation derived, via fermentation, from a non-pathogenic and non-toxigenic strain of *Escherichia coli* K-12 containing the prochymosin gene (21 CFR 184.1685)
  - First genetically engineered microorganism evaluated by FDA, and affirmed as GRAS, to produce an ingredient for use in conventional food (55 FR 10932, March 23, 1990)
- Since 1990, FDA has routinely evaluated ingredients derived from microbial fermentation through its premarket programs
  - Various enzyme preparations
    - Often produced by fermentation of genetically engineered microorganisms, many with a history of use in food, including various strains of *Trichoderma reesei* and *Aspergillus niger*

Precision Fermentation, cont'd.

- Other examples include:
  - Steviol glycoside preparations (rebaudioside A, rebaudioside M)
    - Produced by heterologous expression of steviol glycoside biosynthetic enzymes from *Stevia rebaudiana* introduced into *Saccharomyces cerevisiae, Yarrowia lipolytica, Komatagella phaffii*
  - Human milk oligosaccharides (e.g., 2'-fucosyllactose)
    - Often produced by fermentation of different strains of genetically engineered microorganisms, such as *Escherichia coli*
  - "Novel" food ingredients
    - GRN 000737 – soy leghemoglobin produced by a strain of *K. phaffii*
    - GRN 000966 – soluble egg-white protein (comprised of ovomucoid) produced by a strain of *K. phaffii*

ANIMAL CELL CULTURE USED FOR FOOD AND FEED PRODUCTION

Cultured Animal Cell Foods

- FDA and the U.S. Department of Agriculture, Food Safety Inspection Service (FSIS) jointly oversee human food products incorporating cultured cells from livestock (including Siluriformes fish) and poultry
  - FDA oversees cell collecting and culturing, and conducts premarket consultations on production processes
  - FDA and FSIS share oversight of harvesting of live cellular material
  - FSIS oversees processing, packaging, and labeling of harvested cellular material
- FDA oversees both cell culture and food processing, packaging, and labeling for human foods incorporating cultured fish and seafood cells
- FDA oversees both cell culture and food processing, packaging, and labeling for all animal feeds incorporating cultured animal cells and their byproducts
- The division of roles and responsibilities are outlined in the March 2019 Formal Agreement, available at the following webpage:
  - https://www.fda.gov/food/domestic-interagency-agreements-food/formal-agreement-between-fda-and-usda-regarding-oversight-human-food-produced-using-animal-cell

FDA's Roles and Responsibilities

- Conduct premarket consultations
- Oversee cell collection, cell banking, cell culture
- Coordinate with FSIS on oversight at harvest of cellular material for livestock (including Siluriformes fish) and poultry
- Enforce applicable FDA requirements
- Conduct inspections and related activities
- Oversee food products incorporating cultured fish and seafood cells
- Share information with FSIS

FDA's Premarket Consultation

- FDA conducts premarket consultations to evaluate:
  - Production materials/processes and manufacturing controls
  - Initial tissue collection
  - Development and maintenance of cell lines and banks
  - Proliferation and differentiation of cells through the time of harvest
  - Components and inputs
- FDA will engage with FSIS on consultations involving livestock (including Siluriformes fish) and poultry cell lines, and share the results of consultations. FDA will help to coordinate the transfer of regulatory oversight to FSIS

SUMMARY

Consistent Approach Over Time

Production process considered only insofar as it affects properties or safety of food

Important to understand potential impacts on properties relevant for safety

Information needed to establish safety may change if process changes

Conclusion

- Innovations in science and technology continue to generate new ways of producing food
  - E.g., precision fermentation, animal cell culture
- FDA combines long-standing authorities with policy and scientific knowledge to regulate food safety
- This approach is flexible and adaptable to a wide variety of new food production technologies
- Established framework (e.g., FAPs, GRAS) may be applied to "innovative" ingredients added to conventional food
  - E.g., ingredients derived from microbial fermentation
- New frameworks developed, as science and technology evolve, but rely on established standard of safety

Where are the Regulations Found?

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: PAPER AND PAPERBOARD COMPONENTS

21 CFR 177: INDIRECT FOOD ADDITIVES: POLYMERS

21 CFR 178: INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS

21 CFR 179: IRRADIATION IN THE PRODUCTION, PROCESSING AND HANDLING OF FOOD

21 CFR 180: FOOD ADDITIVES PERMITTED IN FOOD OR IN CONTACT WITH FOOD ON AN INTERIM BASIS PENDING ADDITIONAL STUDY

Where are the Regulations Found?

21 CFR 181: PRIOR-SACTIONED 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

GRAS NOTICE INVENTORY:
https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices

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