EAS Consulting Group
A Certified Group Company

Framework for Food Ingredient Regulation; Food Additives Amendment of 1958

Presenter: Tom Jonaitis, DABT
Independent Consultant
EAS Consulting Group
tjonaitis@easconsultinggroup.com

Tues. March 16, 2021
1:15 to 2:20 PM

Respected • Experts • Ethical • with Integrity

EAS Consulting Group
A Certified Group Company

AGENDA

- Definition of a “food additive”?
- Generally Recognized as Safe (GRAS) Substances
- Food Additive Approval Requirements
- Food Contact Substances
- Regulation of Color Additives

Learning Objectives:

1. Have a clear understanding of the regulations relevant to food additives in the US,

2. Provide some of the tools for you to help food/related companies navigate their obligations.

EAS Consulting Group
A Certified Group Company

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**."

New food additives require premarket approval by FDA *via* food additive petition, with the exception of …..

1) Prior sanctioned substances/ingredients,
2) Substances that are Generally Recognized as Safe (GRAS),
3) Substances otherwise exempted from the definition of a "food additive".

Color additives are not "food additives".

Food Additives Amendment of 1958

- Amendment to Food, Drugs, and Cosmetic Act of 1938.
  - Gave the FDA authority and responsibility to require manufacturers to provide safety assessments for all new food additives,
  - This is where the GRAS exemption was formalized,
  - Also included the Delaney Clause:
    - prohibits the FDA from approving the use of any food additive found to cause cancer in animals or humans *i.e.*, zero tolerance (synthetic flavor ban).
    - Not applicable to GRAS substances.

EAS Consulting Group
A Certified Group Company

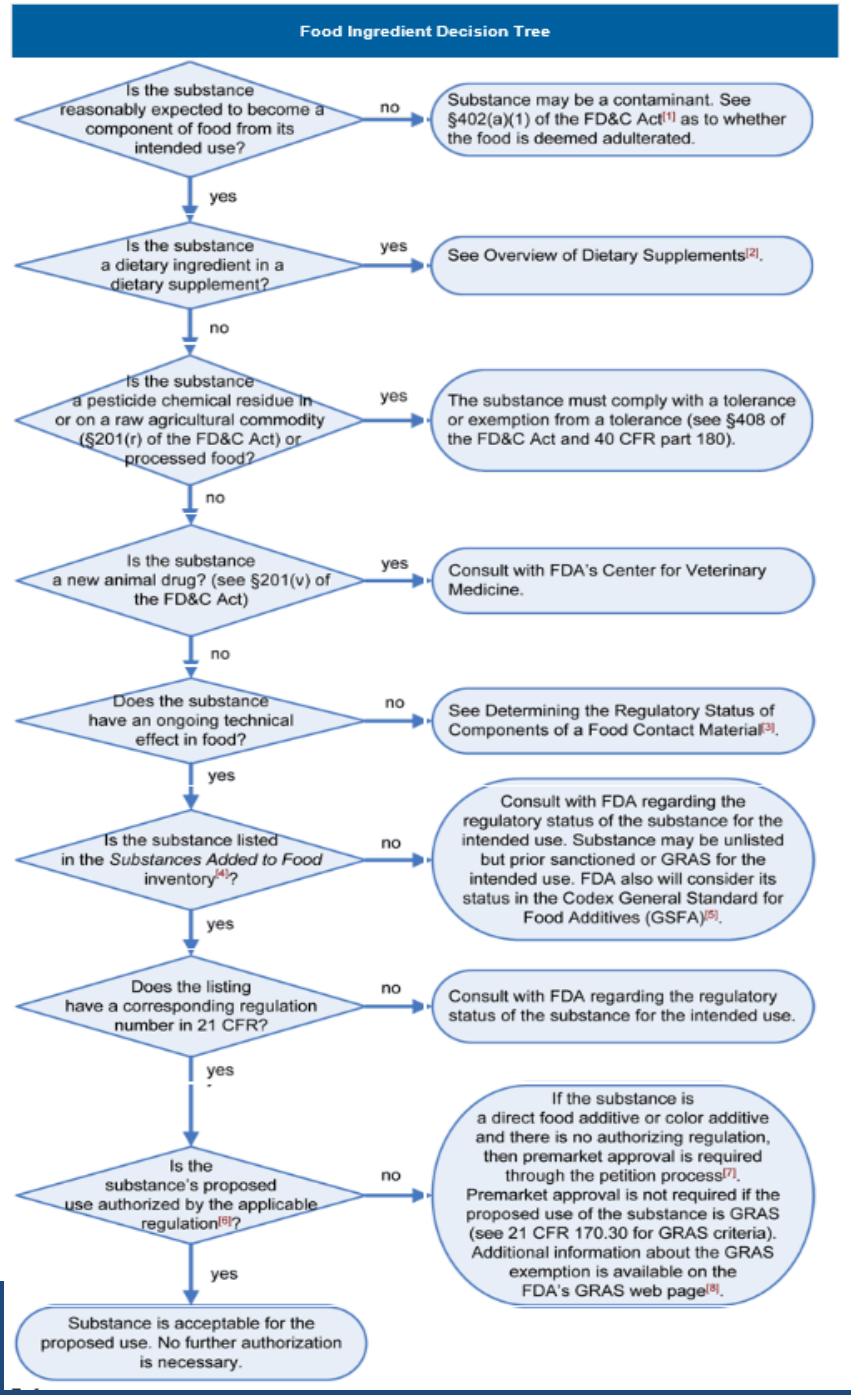
Food Additive Breakdown

a. Direct Food Additive
   - added to a food for a specific purpose in that food (most found on ingredient labels)

b. Indirect Food Additive (Food Contact Substances; 21 CFR Parts 175 to 178)
   - become part of the food in trace amounts due to its packaging, storage, or other handling

c. Secondary Direct Food Additive (21 CFR 173)
   - technical effect in food during processing but not in the finished food (*e.g.,* processing aids)

EAS Consulting Group
A Certified Group Company



[FDA Decision Tree]

EAS Consulting Group
A Certified Group Company

Not “Food Additives”: Prior Sanctioned Substances

Prior Sanctions (21 CFR 181):

a. Excludes “any substance used in accordance with a sanction or approval granted prior to enactment of the Food Additives Amendment (*i.e.*, prior to September 6, 1958);

b. FDA and USDA provide a list of known prior sanctions (*e.g.*, nitrites/nitrates in meat, various food contact substances);

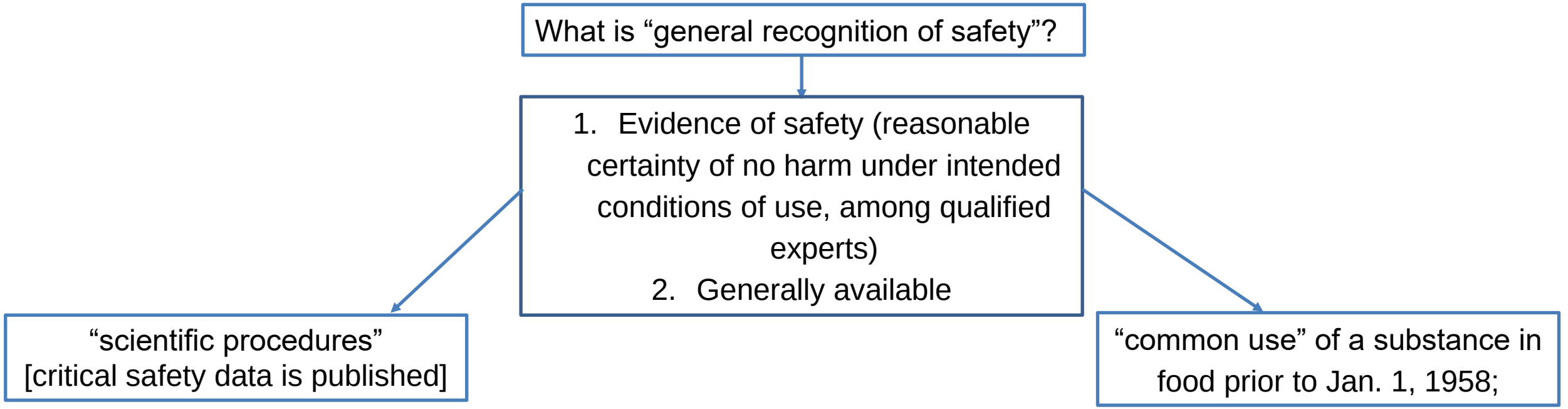
c. Burden on company to establish the ingredient meets the requirement,

d. Cannot expand uses.

EAS Consulting Group
A Certified Group Company

Substances that are Generally Recognized as Safe (GRAS)

A GRAS substance is “one that is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use.” (21 CFR 170.30)



Previously described as “consensus” (not unanimity) but the final rule, only refers to “generally recognized” (open to debate?)

GRAS Substances

- Some GRAS substances are listed in 21 CFR Parts 182, 184, 186.

- Other sources of GRAS substances:
  - FEMA GRAS (~3000 flavoring substances evaluated)

EAS Consulting Group
A Certified Group Company

Self-Conclusion of GRAS Status

1. Compile necessary data to establish that the ingredient is safe, including
   i. chemistry/identity/characterization,
   ii. manufacturing,
   iii. quality and purity (batch analysis),
   iv. Technical effect, intended uses and levels, and consumer exposure,
   v. Safety/toxicology data and risk assessment, as applicable.

2. Typically to confirm the GRAS status of an ingredient, an expert panel is convened (3 to 5 members) that consists of individuals:

- qualified by scientific training (pertinent areas like toxicology, microbiology, statistics) and experience and familiarity with US food law;

- free from conflict of interests (*i.e.*, not involved in the dossier preparation, honoraria not contingent on positive outcome).

Common Use in Food (prior to 1958)

- Substantial history of consumption of a substance for food use by a significant number of consumers (US or outside of US).
- Generally difficult to prove: requires published or other information (generally available) that is corroborated by information from a second, independent source that confirms the history and circumstances of use of the substance.
- Still requires qualified experts to evaluate.

GRAS CONCLUSION

- Upon completion of the GRAS conclusion, the ingredient can be legally marketed.
- It is not the Panel that makes the GRAS determination but the company (final GRAS rule also notes that FDA considers the expert panel opinion as secondary scientific literature).
- Company is responsible for ensuring the GRAS status of the substance remains so – *i.e.*, evolving science.

GRAS Notification

- Notifying the FDA (Center for Food Safety and Applied Nutrition) of the GRAS conclusion (with submission of a GRAS Notice) is OPTIONAL.
  - *i.e.,* not required but strongly encouraged by the FDA,
  - many companies choose not to notify.
- Company informs U.S. FDA of its GRAS conclusion and provides all supporting information to FDA (can meet prior to notice filing to get agency input).
- The entire notice is published online (sufficient details need to be provided for FDA to review, so proprietary data will become public).

EAS Consulting Group
A Certified Group Company

GRAS NOTIFICATION

Contains seven parts (guidance) that are required to be addressed.

FDA reviews notification and responds with a letter stating ("within 180 days", not statutory):

1. FDA has no questions (positive outcome)

2. The notifier has not provided a basis that the substance is GRAS,

3. FDA has ceased to review the notification at the request of the notifier.

- If ingredient is used in meat, poultry, and/or egg products, the Food Safety and Inspection Service (FSIS) of the United States Department of Agriculture (USDA) will also be involved and may have specific requirements.

GRAS Notices

- U.S. GRAS Notice Inventory lists substances that have been notified since 1998;

  https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=GRASNotices

  – This is a valuable resource for technical and scientific details.

EAS Consulting Group
A Certified Group Company

GRAS Notification Strategy

- Most companies do not notify FDA (not required).
- Benefits of notification:
  - Increased transparency for customers (some demand it),
  - Avoids potential for FDA enforcement (confirms GRAS conclusion).

Food Additive Petitions (FAP)

Food Additive Petition: Requirements and Feasibility

a. Formal safety determination and writing of a new regulation.
b. Typically takes 2 to 4 years to accomplish!

Safety Standard Applied to Food Additives

a. Exact same as GRAS substances = “reasonable certainty of no harm”

b. Quality of safety data is same as GRAS, except only technical evidence of safety needed (not general recognition) = can use unpublished data!

c. Many of the details of the FAP (including proprietary data) will be published in the “final rule” or may otherwise be accessible through FOIA requests.

Safety Data GRAS vs. FAP

- Although same standard – actual studies may vary…
- Generally, which toxicology tests are necessary will depend on:
    - the specific ingredient composition,
    - the availability of existing/published data (is there a scientific rationale to support why published data is applicable to a company's ingredient – is it the same ingredient? Sufficiently similar?)
    - specific concerns associated with the ingredient.

GRAS vs. FAP

- For GRAS: ultimately up to company/expert panel to make a judgement if standard met.

- For FAP: FDA refers to the Redbook (2000) to interpret the toxicology needs for an ingredient…

  – prescriptive/rule-based: equation of human exposure vs. chemical structure => list of studies triggered.

  – can result in greater studies than might have been required otherwise.

Dietary Ingredients (under FFDCA)

i. a vitamin;
ii. a mineral;
iii. an herb or other botanical;
iv. an amino acid;
v. a dietary substance for use by man to supplement the diet by increasing total dietary intake; or
vi. a concentrate, metabolite, constituent, extract, or combination of any of the above dietary ingredients.

- Foods may only contain food additives or GRAS substances.
- Dietary supplements are a subset of “food” but are regulated separately (Dietary Supplement Health and Education Act of 1994 or DSHEA) => different approval process (for dietary ingredients [new vs. old], everything else as food additive [excipients etc]), different GMP implications.
- Ingredients that are GRAS can be used in supplements but permitted supplement ingredients are not permitted for food unless GRAS.

Food vs. Supplement

- Supplements can be:
  - powder, pill, tablet, liquid, bar (must not represent the product as a conventional food or a sole item of a meal or diet).
  - Sometimes it is obvious (pills/capsules)….sometimes not (powder, liquids).

e.g., FDA guidance on beverages/liquid supplements – comes down to claims and other factors.

Food Contact Substances (FCS)

Food Contact Substances (FCS)

Food contact article vs. food contact material vs. food contact substance

If substance is reasonably expected to become part of food…needs to be:

- already approved,
- an FAP/FCSN, or
- be exempt

Already Approved

Numerous classes of food packaging (*e.g.*, coatings, adhesives, paper) and their regulatory permissions are captured in 21 CFR Parts 170-199 under Food Additive Regulations (indirect).

- companies can start here to determine compliance of their materials (if compliant, no further action required),

- Rarely updated/are out-dated with regards to current innovations.

EAS Consulting Group
A Certified Group Company

Food Contact Substance Notification (FCSN)

For new FCS or new uses

Submitted to FDA:

- Includes chemistry, migration data, estimated dietary exposure (could trigger need for FAP, if exposure is high enough), toxicological review, and environmental impact (like other federal decisions, subject to NEPA).
- FDA has statutory 120 days to review/raise objections, otherwise, FCS is considered legally permissible,
- Successful notifications published in the FCS Database (specific to notifier).

Specific Testing/Analysis

- Migration Testing:
  - Quantifying the extent that an FCS might become part of food (typically up to 1 ppm);
  - Use different food simulants (oil, ethanol), under various conditions to simulate contact with different types of foods (can be complex analytically),
  - Protocols (and specific simulants) may be stipulated based on type of material, conditions of use (repeat or single-use etc).

Dietary Exposure

Complex calculations that include:

- "Consumption Factors" (CFs) that describe the fraction of the daily diet expected to contact specific packaging materials and

- "food-type distribution factors" that reflect the fraction of all food contacting each material that is aqueous, acidic, alcoholic and fatty.

– Need to also address cumulative exposure to FCS (if already present in packaging).

Food Contact Formulation (FCF) Notification

- Can also request FDA to review and verify compliance of the components of a particular food contact material (when all substances are established to be permitted).
  - If using an effective FCN as part of this, must establish that the entity is allowed to use such data.

EAS Consulting Group
A Certified Group Company

Food Contact Substances (FCS): Exemptions

Threshold of Regulation (TOR) (21 CFR 170.39)

Exempt migrating substances from “food additive definition” if levels in foods are below TOR, which means:

- Substance (or any impurities) are not carcinogenic, including chemical structure analysis, etc.
- Dietary concentration of ≤0.5 ppb, corresponding to ≤1.5 µg/person/day or approved as a direct food additive (and exposure ≤1% of ADI),
- No technical effect in food,
- No effect on the environment.

- Make submission to FDA with robust data/evidence (usually <90 days),
- Database of TOR exemptions granted (not manufacturer-specific).

FCS: Other Exemptions

- Prior sanctions (21 CFR 181),

- Houseware Articles exemptions:
  - products in contact with food (utensils, dishes); must still be safe!

- FCS that are GRAS:
  - substances deemed GRAS by FDA is set forth at 21 C.F.R. § 182, 184 and 186.
  - Self-GRAS conclusions/notifications

- “No migration” exemption
  - what does “no migration mean”? “insignificant” migration = < 50 ppb, unless special safety concern (heavy metals, carcinogens), so could be much lower.
  - company itself makes this determination, based on
    - robust migration/extraction studies, worst-case 100% migration estimates, diffusion principles.

Other Exemptions

- Functional Barrier (substances separated from food by appropriate barrier)
- Basic Resin/Polymer Doctrine (as long as basic resin is permitted, this applies to variable constituents, like catalysts, etc used at low levels to make the resin and become part of resin/washed away).
- Mixture Doctrine: allowed to mix substances that are individually permitted (as long as all requirements/limitations are met for each substance and process is purely physical).

Color Additives

Regulation of Color Additives (21 CFR Part 71)

Definition: any dye, pigment or substance which when added or applied to a food (or drugs, cosmetics, to the human body), is capable (alone or through reactions with other substances) of imparting color.

Caveat: unless the substance is used solely for a purpose other than coloring.

No GRAS exemption = only formal rule writing.

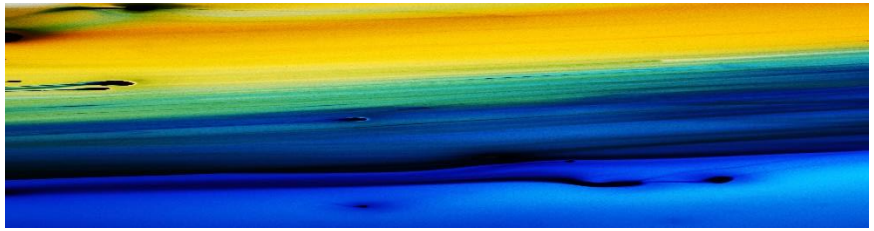
Color Additives

Breakdown

a. **Certified colors (synthetically produced)** these are permitted only if they are from batches that FDA has certified; also have specific labeling requirements (21 CFR 70.25).

   i. FD&C Blue Nos. 1 and 2, FD&C Green No. 3, FD&C Red Nos. 3 and 40, FD&C Yellow Nos. 5 and 6, Orange B, Citrus Red No. 2

   ii. Color additives that are subject to batch certification are listed in FDA's regulations, in 21 CFR Parts 74 and 82.



Color Additives

b. Colors that are exempt from certification: include pigments derived from natural sources, such as vegetables, minerals or animals; may impart unintended flavors to food.

i. annatto extract (yellow), dehydrated beets (bluish-red to brown), caramel (yellow to tan), beta-carotene (yellow to orange), grape skin extract (red, green).

ii. Color additives that are exempt from certification are listed in the regulations in 21 CFR Part 73.

Color Additives

FDA Premarket Approval

- All color additives and new uses for listed color additives must be approved by the FDA (listed in the color additive regulations) before they may be used in foods,
- Need to submit a color additive petition (21 CFR Part 71; guidance),
- Requires: detailed chemistry, characterization/purity, manufacturing, toxicology data, safety of intended uses, tolerance (if needed), samples (if requested).
- Same standard as food additives (reasonable certainty of no harm).

Summary

- Clear understanding of the composition of the substance/ingredient and intended use is an important first step in order to be able to interpret its regulatory status,
- If not obvious, follow the decision tree to clarify how it might be regulated,
- Look for exemptions!

EAS Consulting Group
A Certified Group Company

Summary

- Review FDA guidance - there's plenty of it!
- Obtain additional expert support in necessary areas to ensure sufficient and robust data is available and/or generated through testing.
- Companies must ensure the continued compliance of their ingredient given evolving science.

EAS Consulting Group

A Certified Group Company

Thank you

www.easconsultinggroup.com