

REGULATORY ELEMENTS OF THE GENERALLY RECOGNIZED AS SAFE (GRAS) PROCEDURE

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GENERALLY RECOGNIZED AS SAFE (GRAS) PROGRAM



any substance that is reasonably expected to directly or indirectly become a component of food or impact the characteristic of a food is a food additive, that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use.

- “GRAS” is an acronym for the phrase **Generally Recognized As Safe**. Under sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act (the Act)
- Concept unique to the United States
- Rapid route to market
 - Shorter time frame than food additive evaluation, which requires FDA approval prior to marketing
- GRAS evaluations completed by manufacturer (‘self-GRAS’)
- Use of the substance, not the substance per se, that may have GRAS status



GRAS PROCEDURE

- Implementing regulations for the GRAS rule are 21 CFR 170.3 and 21 CFR 170.30
- The GRAS use of a food is determined by views of experts qualified by scientific training and experience in the evaluation of food safety
- These “views of qualified experts” must be established through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food Under 21 CFR 170.30(b)

1. Scientific Procedures



- *“shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive.”*
- Based upon the application of **generally available** and **accepted** scientific data, information, or methods, which ordinarily are published

2. Common Use in Food



- Based on **common** use in food in the U.S. prior to January 1, 1958
- Does not require the same quantity or quality of scientific procedures required for approval of a food additive
- Common use in food outside of the United States **should** notify FDA of that view in accordance with 21 CFR 170 subpart E

FINAL GRAS RULE

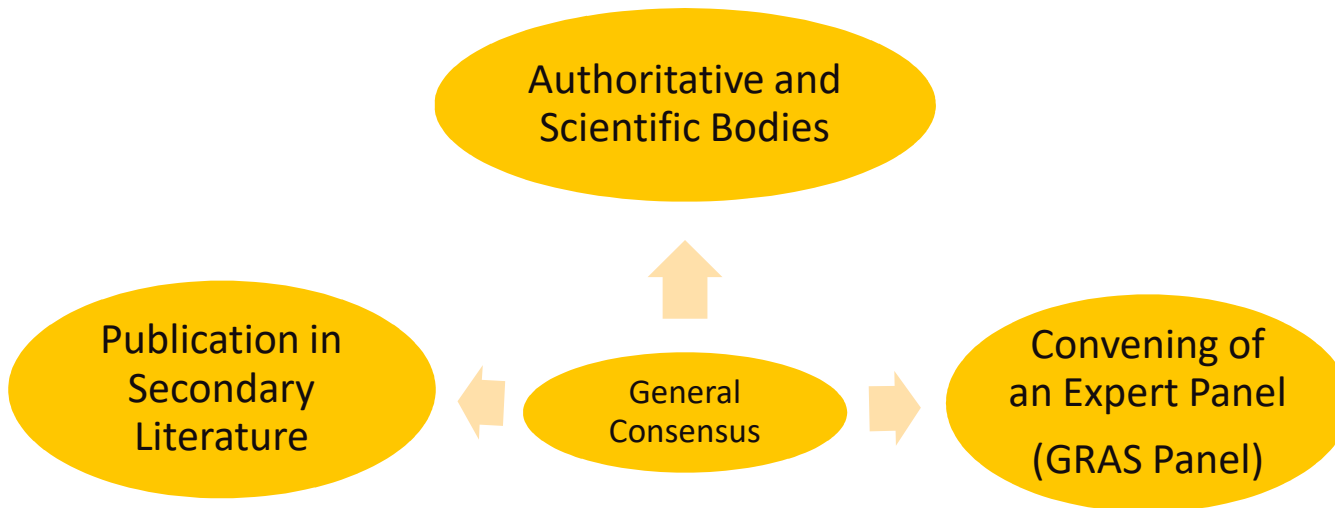


- In 2016 the U.S. FDA issued a final rule amending and clarifying criteria for concluding that the use of a substance in human or animal food is “generally recognized as safe” (GRAS)
- Detailed discussions of the history of the GRAS procedure and clarifications on key regulatory definitions were presented in the supporting federal register notice to the final rule under 81 FR 54960 (95 pages long)
- Extensive discussion on the application of the “*common knowledge*” element of the GRAS standard to a scientific procedures evaluation
- FDA re-iterated that pivotal data that is relied upon by qualified scientific experts must be **Generally Available**
 - Emphasis on publication in **peer-reviewed** journal that is ordinarily accessed by the scientific community
 - Publication should be associated with a “*reputable scientific institution*”
 - Pivotal data must be made available in the “*primary scientific literature*”

FINAL GRAS RULE

Generally Accepted – Consensus in Scientific Community

- Not sufficient that pivotal data supporting safety is generally available
- Must be a basis to concluded that there is expert consensus on the safety of the substance under the conditions of intended use
- Consensus on safety can be established in a variety of ways:



- Once consensus is established the ingredient can be immediately marketed





GRAS PANEL

- FDA recently issued Draft Guidance for Industry: Best Practices for Convening a GRAS Panel
- GRAS panel is to act as a proxy for the larger scientific community
- Expertise of the members of the GRAS Panel should match the pertinent subject matter of interest
 - *E.g.*, general toxicology, reproductive toxicology, genotoxicity, carcinogenesis, chemistry, intake modeling, pediatrics, immunology, allergenicity, nutrition, enzymology, microbiology
- Expert panel often receives a 'reasonable' honorarium for their time
 - Payment of honorarium must not be contingent upon outcome of Panel meeting
- Conflicts of interest and bias should be avoided
 - Individuals having financial ties to the company (*e.g.*, stock options, paid advisory roles)
 - Individuals who's research activities may bias their conclusions
- A written output of the GRAS Panel deliberations should be produced and signed by the Panel
- Agents or consulting firms co-ordinating the GRAS procedure on behalf of client must **not** participate as a member of the GRAS Panel



FDA NOTIFICATION

- The final GRAS rule also included provisions to officially replace the GRAS Affirmation process with a “new” administrative procedure for notifying the agency of the basis for a conclusion that a substance is GRAS under conditions of use
- Filing a GRAS Notification with the FDA is voluntary, however ...
- FDA has stated that ***“The FDA strongly encourages companies to inform the agency of GRAS conclusions through the notification procedure finalized with today’s rule.”***
- GRAS Notice has seven parts:

1	Signed statements and certifications	5	Experience based on common use in food before 1958
2	Identity, method of manufacture, specifications, and physical or technical effect	6	Narrative
3	Dietary Exposure	7	List of supporting data
4	Self-limiting levels of use		

- FDA recommends that format of GRAS dossier should be consistent with FDA Notification format

PART 1

§170.225 PART 1 OF A GRAS NOTICE: SIGNED STATEMENTS AND CERTIFICATION





§170.225 PART 1 OF A GRAS NOTICE: SIGNED STATEMENTS AND CERTIFICATION

- Includes general administrative requirements (*e.g.*, name and address of notifier, name of notified substance, statement of statutory basis for GRAS and applicable regulatory verbiage)
- GRAS Notice must include a signed certification statement from the notifier
 - Must “*Certify that, to the best of your knowledge, your GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to you and pertinent to the evaluation of the safety and GRAS status of the use of the substance*”
- All data relevant to safety that is available to the notifier must be disclosed
- Part 1 includes a section for identification of confidential data
 - Currently no procedures in place to handle confidential information

PART 2

**§170.230 PART 2 OF A GRAS
NOTICE: IDENTITY, METHOD OF
MANUFACTURE,
SPECIFICATIONS, AND PHYSICAL
OR TECHNICAL EFFECT**





§170.230 PART 2 OF A GRAS NOTICE: IDENTITY, METHOD OF MANUFACTURE, SPECIFICATIONS, AND PHYSICAL OR TECHNICAL EFFECT

Identity and Description of Substance

- Chemical name, CAS registry number, empirical formula, structural formula
- Composition defined in a qualitative (*e.g.*, IR, NMR, MS) and quantitative (*e.g.*, HPLC) manner
- Characterization of impurities (important for substantial equivalence approaches)
- For botanicals and microorganism identification of taxonomic identity at the genus, species, subspecies and strain/cultivar level
- Food-grade specifications need to be established
- Stability data establishing shelf-life and end-product uses where applicable

§170.230 PART 2 OF A GRAS NOTICE: IDENTITY, METHOD OF MANUFACTURE, SPECIFICATIONS, AND PHYSICAL OR TECHNICAL EFFECT



Manufacturing Information

- Raw materials, direct and indirect additives should be food grade (*e.g.*, FCC) or equivalent (*e.g.*, USP, EP)
- **In the United States processing-aids are not excluded from the definition of a food additive!**
- General outline of manufacturing process should be provided
 - Should include only non-confidential information
 - Details of manufacturing steps applicable to safety should be presented (*e.g.*, pasteurization/sterilization time and temp; filter sterilization materials)
- Description of processing controls
- Batch-analyses for 3 to 5 non-consecutive lots demonstrating consistency of the manufacturing process

PART 3

§170.235 PART 3 OF A GRAS NOTICE: DIETARY EXPOSURE



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Exposure/Consumption Data

- Must provide an estimate of dietary exposure to the notified substance that includes exposure from its intended use and all sources in the diet
- Must include exposure estimates for potential contaminants or minor substances of nutritional/toxicological concern that may be present or formed in the food as a result of the GRAS use
- Varied approaches for estimating dietary exposure
 - Per capita disappearance or poundage data
 - Model diets based on national food consumption surveys (*e.g.*, market basket approaches)
 - National food consumption surveys based on individual dietary records (NHANES)
 - Monte Carlo approaches

PART 4

§170.240 PART 4 OF A GRAS NOTICE: SELF-LIMITING LEVELS OF USE

- As applicable identify circumstances where a particular characteristic of a food ingredient may limit the amount that can be added because food containing levels of the notified substance above a particular level would become unpalatable or technologically impractical,



PART 5

§170.245 PART 5 OF A GRAS NOTICE: EXPERIENCE BASED ON COMMON USE IN FOOD BEFORE 1958.

- Only applicable if statutory basis for GRAS is common use prior to 1958
- Include **generally available** evidence of a **substantial** history of consumption of the notified substance for food use by a significant number of consumers prior to January 1, 1958.



PART 6

**§170.250 PART 6 OF A GRAS
NOTICE: NARRATIVE**





§170.250 PART 6 OF A GRAS NOTICE: NARRATIVE

- This section of the notice contains the information relevant to safety
 1. Safety may be inferred for many common constituents of food; *e.g.* amino acids, proteins, sugars.
 2. Safety may be evaluated based on published historical literature on the ingredient or structurally similar compounds
 3. For new substances, complete toxicological studies may be necessary
 4. The test article used in supporting toxicology studies should meet or be very similar to the reported specifications of the substance being evaluated
- **Must** explain why the data and information in the notice provide a basis for a conclusion that the substance is safe
- **Must** discuss what information is generally available and what information is not generally available
- **Must** explain how the generally available data and information that you rely on to establish safety is generally recognized among qualified experts

§170.250 PART 6 OF A GRAS NOTICE: NARRATIVE

- GRAS Notice must include discussion of favorable and unfavorable information as it applies to the GRAS status of the substance
- Identify, discuss, and place in context, data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status, regardless of whether those data and information are generally available; or
- Statement that you have reviewed the available data and information and are not aware of any data and information that are, or may appear to be, inconsistent with your conclusion of GRAS status
- If unpublished safety-related data and information was considered in reaching a conclusion of GRAS status, you must explain how there could be a basis for a conclusion of GRAS status if qualified experts do not have access to such data and information.





PART 7

§170.255 PART 7 OF A GRAS NOTICE: LIST OF SUPPORTING DATA AND INFORMATION IN YOUR GRAS NOTICE.

- Part 7 of the GRAS notice must include a list of all of the data and information that are discussed in Part 6 of your GRAS notice (*i.e.*, reference list and appendices)



§170.265 FDA REVIEW PROCESS

- FDA conducts and administrative review prior to filing (*ca.* 30 days)
- If notice contains all the required administrative and scientific elements required under 21 CFR 170 Subpart E, the agency will inform the notifier in writing that the notice has been filed and issue a filing date and GRN number for the notice
- FDA GRAS team will then carefully review the notice and issue a response within 180 days
- The notifier may be provided the opportunity to send additional data and information upon request from the Agency and an additional 90-days may be added to the review
 - Submission of major data amendments typically not permitted
- If the notifier is unable to respond to questions raised by the FDA to the agency's **satisfaction** the notifier may request in writing that the agency cease to evaluate the GRAS notice
- Resubmission of the GRAS notice at a later time is permitted
- If the agency agrees with the Notifier's conclusion on GRAS status the agency will issue a no questions letter stating that the agency does not object at this time to the notifiers conclusions on the GRAS status
- Full disclosure of all FDA notifications are published on the FDA's GRAS notification inventory

THANK YOU!



QUESTIONS?

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