GRAS Overview

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Introduction

The concept of Generally Recognized As Safe (GRAS) is a key component of food safety regulation in the United States. This document provides an extensive overview of GRAS, including its historical context, determination process, and future directions.

Overview

The GRAS designation used by the Food and Drug Administration (FDA) indicates that experts consider a substance added to food to be safe under its intended use. This designation exempts the substance from the usual FDA food additive tolerance requirements. Essentially, GRAS status allows companies to use certain substances in food without pre-market approval from the FDA, but these substances still need to meet the same safety standards as approved food additives.

The GRAS determination process has evolved significantly since its inception in 1958, with two approaches taken by the FDA to manage the concept. The FDA notification process involves submitting a comprehensive dossier that details the substance's identity, composition, intended use, dietary exposure, and safety information. The FDA evaluates the submission and responds with either a "No Questions" letter, an indication of insufficient basis for GRAS status, or a cessation of evaluation request.

Generally Recognized As Safe status can be determined through an FDA notification or through a self-determination process

In addition, a second option, formalized in 2016 through the FDA's **GRAS Final Rule**, allows self-determination of GRAS status by gathering scientific data, consulting experts, and documenting the decision-making process to be reviewed by the FDA. This self-determination process can be quicker, maintain confidentiality, and allows flexibility in tailoring the process to specific needs but faces challenges related to resource constraints and potential legal disputes. This process can have increased business and litigation risks if later it is determined and becomes public knowledge that the food component has heightened food safety/human health risks compared to those in the original self-determination scientific risk assessment for human safety.

Safety studies are crucial for both GRAS notification and self-determination and cover a wide range of health impacts related to variables such as exposure levels, consumption patterns, and self-limiting factors like taste.

The future direction of GRAS determinations will depend on the FDA's prioritization of resources, external pressures, and the ability to adapt to new scientific evidence.

Historical Context

1958 Food Additves Amendment

The concept of GRAS was first defined in the 1958 Food Additive Amendment. This amendment established the framework for food additive regulation, including the definition of GRAS substances. However, it did not include a specific process for GRAS determination.

FDA's Initial Response

In response to the amendment, the FDA created a GRAS list published in the Federal Register (21 CFR 182). This list included substances like spices and simple extracts recognized as safe based on their long history of common use in food.

Industry Requests and Informal Opinion Letters

As the food system evolved, companies began requesting the FDA's opinion on substances not included in the initial GRAS list. The FDA responded by issuing informal opinion letters confirming the GRAS status of these substances. These letters were based on the available scientific evidence and expert consensus at the time.

Additionally, the The Flavor and Extract Manufacturers Association of the United States (FEMA) established its own GRAS program in 1959 to provide estimates of ingredients used to manufacture flavorings, and established an expert panel to evaluate the safety of these ingredients the following year.

Revocation of Opinion Letters

In the 1970s, the FDA revoked all previous informal opinion letters. This decision stemmed from the need for a more formal and rigorous process for GRAS determinations. The FDA required formal submissions for GRAS status, ensuring each substance underwent thorough evaluation based on scientific evidence.

SCOGS Review

The Select Committee on GRAS Substances (SCOGS) was formed to conduct an independent review of GRAS substances. The committee's findings were made available online, and the FDA issued regulations based on these findings (21 CFR 184, 186). This review process helped formalize the criteria for GRAS determinations and provided a structured approach to evaluating the safety of food additives.

There are 370 food additives in the **SCOGS database** reviewed by the SCOGS committee and approved by FDA for GRAS status. These substances were approved from 1972-1980 based on available science. Over 40 years have passed since that time, and we are finding that current science has identified the existence of more food safety hazards in some food ingredients than was available then.

The removal of some additives from the database is a result of the FDA going back to review GRAS ingredients in light of new scientific evidence or if the safety assessment supporting its previous GRAS status is no longer valid.

2016 GRAS Self-Determination Rule Finalized

The GRAS self-determination process was formally established in 2016 through the FDA's GRAS Final Rule, though a proposed rule was published in 1997. The 2016 rule finalized and codified the voluntary notification procedure, allowing anyone to inform the FDA of their determination that a substance is GRAS. Self-determination is the most controversial part of the GRAS process, because it doesn't have a direct approval process from the FDA staff involved.

GRAS Determination Process

GRAS Notification Process

The GRAS petition process allows companies to submit formal requests for rulemaking to the FDA to affirm the GRAS status of a substance. The FDA reviews the petition, considering scientific evidence and expert consensus, and makes a decision based on that evaluation. This process ensures that GRAS determinations are based on thorough safety assessments and expert opinions.

GRAS Self-Determination Process

This program allows companies to self-determine the GRAS status of substances and submit an optional notification to the FDA. The FDA reviews these notifications to ensure that the determinations are based on the same quality and quantity of evidence required for food additives. The program operated under the proposed rule for nearly two decades before being formalized.

Both GRAS notification and self-determination are viable options for companies to establish the safety of food additives. The choice depends on factors such as substance complexity, regulatory assurance needs, confidentiality concerns, the potential for litigation risk and market strategy. Understanding the science and FDA processes helps companies make informed decisions aligned with their goals and regulatory requirements.

Future Direction of GRAS Determination

Flexibility in GRAS System

The GRAS system is designed to be flexible, allowing the FDA to use various approaches to GRAS determinations. The priorities and resources available to the FDA play a critical role in shaping the future direction of the GRAS system.

Post-Market Assessment

The FDA has the authority to reevaluate substances based on new evidence, even after they have been determined to be GRAS. If new scientific data suggests that a substance may not be safe, the FDA can issue scientific memorandums and take regulatory action to address the potential risks. This post-market evaluation process ensures that GRAS determinations remain current and reflective of the latest scientific knowledge. An update to the post-market assessment process is currently in progress with the FDA.

Resource Constraints

Limited resources affect the FDA's ability to conduct timely evaluations of GRAS substances. The prioritization of resources is critical for future changes to the GRAS system. The FDA must balance the need for rigorous scientific evaluation with the practical constraints of available funding and personnel.

Definitions

Proponent: The entity or person making the GRAS determination.

FDA Notification: FDA Notification means communicating with the FDA regarding a GRAS notification where a dossier is submitted and does not apply to the GRAS Self-Determination approach, where notification is not required. This is optional and not an approval process. It does not address all regulatory issues such as labeling and Good Manufacturing Practices (GMPs).

Required Evidence: Compelling scientific evidence and a consensus of qualified experts that the substance is safe under its intended use. The required evidence is the same regardless of using either the Notification Path or the Self-Determination path. The evidence requires a quantity and quality of scientific data as would be required by the FDA to obtain approval of a food additive.

Experience Based on Common Use: This requires a substantial history of consumption in the USA prior to 1958. One cannot use substantial use history from other countries or cultures, where certain herbs and plants used in food can date back hundreds of years, as a basis for the substantial history exclusion. However, long term use can be useful in supporting appropriate food safety scientific data (for example, toxicological studies).

- **Consensus of Qualified Experts:** There must be a broad agreement among scientifically qualified experts trained in food safety assessment that the data and information establish the substance's safety.
- **Widespread Availability:** Scientific data and information must be widely available (published in peer-reviewed journals), use broadly accepted and available scientific analysis methods, and be generally accepted by qualified experts.
- **Identity and Composition:** Detailed chemical identity, specifications, and method of manufacture. "Identity" refers to the specific chemical description and specifications of a substance, including its purity and composition, compared to the United Nations Food and Agriculture Organization (FAO) standards and other relevant specifications. This ensures the substance is clearly identified and its safety can be evaluated.
- **Intended Use:** The proponent must specify the intended use of the substance and provide evidence that it is safe for that particular purpose.
- **Dietary Exposure:** Based on use levels and food consumption.
- **Safety Information:** Includes metabolism, toxicology, intestinal absorption, and any contradictory information.

Safety Data in GRAS Determinations

- **Safety Studies:** These include acute toxicity, reproductive, genotoxicity, endocrine disruption, and inhalation/dermal exposure.
- **Combining Safety Data:** This involves combining safety data and exposure data to determine the Expected Daily Intake (EDI) and Acceptable Daily Intake (ADI).
- **Margin of Exposure (MOE):** Used to evaluate the safety of a substance by comparing a "no observed adverse effect level" (NOAEL) from animal studies to the estimated human exposure level. A higher MOE generally indicates a greater safety margin, with an MOE of 100 or more often considered protective for substances with health thresholds (not genotoxic or carcinogenic).

Confidential Business Information (CBI): While the FDA discourages including proprietary information in GRAS notices due to potential public disclosure requirements, it does allow for the inclusion of Confidential Business Information (CBI) in certain circumstances. CBI can be included, but not in Part 1 of the notice, and any reliance on such information for a GRAS conclusion must be justified. Qualified experts must have access to the CBI to support the conclusion, or the notifier must explain the basis for the GRAS determination without such access to the FDA.

For GRAS Self-Determination, CBI can be addressed by convening a panel of qualified scientific experts under a confidentiality agreement that allows them to review the data without it being publicly disclosed.

Animal GRAS Regulations: These differ, allowing significant portions of animal GRAS notices to be redacted.

Limiting or Self-Limiting Factors: Substance is considered safe for its intended use but has limitations. These limitations are often based on historical use, data from similar substances, or technological limitations like maximum use levels. Some GRAS substances may have a self-limiting use level, meaning the food becomes unpalatable or undesirable above a certain concentration

Consumption Data: GRAS consumption data is used to assess the safety of ingredients generally recognized as safe and relies heavily on databases like National Health and Nutrition Examination Survey (NHANES). This data provides detailed population breakdowns, including demographics, and allows researchers to understand how much of a substance is consumed by different segments of the population, according to the National Institutes of Health (NIH). The proponent should identify all the potential food uses/food categories-product types that the material might be used in.

Source/Product Identity: Identification of the material source of the food ingredient, including taxonomic and morphological traits.

Certified Labs: For GRAS determinations, using Good Laboratory Practice (GLP)-compliant labs is crucial for ensuring the reliability and validity of the data used to support the GRAS claim. GLP labs provide a framework that ensures data integrity, promotes ethical treatment of animals (if applicable), and meets regulatory requirements for product approval.

Acceptable Daily Intake: The maximum amount of a chemical or ingredient that can be ingested daily over a lifetime with no applicable health risk.

Traditional Culinary Practices: These are not applicable in large-scale production.

Complex Substance: These are not single, pure chemical compounds but rather mixtures or natural extracts containing a variety of chemicals.

Manufacturing Process: A detailed description of the process(es) used to convert the food material from a source raw material to the final material for use as a food component or additive. Should include information regarding the variability of the process (e.g., batch to batch or raw material variability) and mechanisms for its control.

Dietary Exposure: When evaluating dietary exposure related to substances deemed Generally Recognized as Safe (GRAS), it's crucial to consider potential contaminants and byproducts that may be present in the food supply. FDA requires that GRAS notices include estimates of dietary exposure to the substance itself, as well as any other substances expected to be present due to its use, including contaminants and byproducts (e.g., mycotoxins, heavy metals, microbial growth byproducts, secondary metabolites, allergens). This ensures a comprehensive assessment of the substance's safety within the context of the food supply.

Resources

FDA Resources

Guidance from 2014 on assessing significant changes to manufacturing processes: **Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that Are Color Additives**

Guidance for Industry: Estimating Dietary Intake of Substances in Food

Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions

Guidance for Industry: Recommendations for Submission of Chemical and Technological Data for Food Additive Petitions and GRAS Notices for Enzyme Preparations

Guidance for Industry: Regulatory Framework for Substances Intended for Use in Human Food or Animal Food on the Basis of the Generally Recognized as Safe (GRAS) Provision of the Federal Food, Drug, and Cosmetic Act

FDA's Approach to the GRAS Provision: A History of Processes

Food Chemical Safety

FY2015 Regulatory Science Research Report: Complex Mixtures and Peptides

Post-market Determinations that the Use of a Substance is Not GRAS

GRAS Notice for Use of 1-methylcyclopropene "1-MCP"

GRAS Substances (SCOGS) Database

Other Resources

Center for Professional Innovation and Education - Understanding Good Laboratory Practice (GLP) Guidelines

ChemSafetyPRO - What Are Margin of Exposure (MOE) and Margin of Safety (MOS) and How to Calculate

Flavor and Extract Manufacturers Association of the United States (FEMA) - About FEMA GRAS

Food and Agricultural Organization of the United Nations - FAO Specifications and Evaluations for Agricultural Pesticides

U.S Government Accountability Office - Food Safety: FDA Oversight of Substances Used in Manufacturing, Packaging, and Transporting Food Could Be Strengthened

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