INTERNATIONAL FOOD ADDITIVES COUNCIL
GENERALLY RECOGNIZED AS SAFE (GRAS)
BEST PRACTICES GUIDE
ACKNOWLEDGEMENTS

This GRAS Best Practices Guide was developed by the International Food Additives Council (IFAC), a global association representing companies that produce high quality substances used worldwide as food ingredients, including food additives and GRAS substances.

This document represents voluntary guidance for food ingredient producers who wish to establish a Generally Recognized As Safe (GRAS) position on a substance to be used in a food. The guide is also intended for use by food and dietary supplement producers in developing GRAS positions on the ingredients in their products.
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I. Introduction

The U.S. Federal Food, Drug and Cosmetic Act\(^1\) (FFDCA) provides for two regulatory mechanisms for the addition of substances to foods. They are the food additive petition process and the Generally Recognized as Safe (GRAS) process. GRAS is unique to the U.S. and is sometimes not well understood. Though not official, the IFAC GRAS Best Practices Guide is intended to serve as a compilation of available U.S. Food and Drug Administration (FDA) regulations, guidance documents and industry best practices to help determine the GRAS status of a substance.

For more information on FDA regulations and guidance related to GRAS, please visit www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/default.htm.

II. Purpose/Scope

The intended purpose of this Guide is to serve as a resource to food ingredient producers who wish to establish a GRAS position on a substance to be used in a food. The Guide is also intended for use by food and dietary supplement producers in developing GRAS positions on the ingredients in their products.

This Guide provides an overview of U.S. FDA regulations and guidance documents for substances that are considered GRAS, explains and adds clarity to the U.S. GRAS process, describes the options available to producers and users to obtain a food ingredient GRAS determination and recommends best practices.

This Guide does not apply to the following types of ingredients:

- **Flavorings:** The Flavor and Extract Manufacturers Association (FEMA) has established a separate process for establishing the GRAS status of flavor ingredients under their purview. This guide therefore does not apply to the FEMA GRAS process.

- **Food Contact Substances:** FDA’s Food Contact Substance Notification process was created in 1997, which replaced the petition process for food contact substances. FDA defines a food contact substance as ‘any substance intended for use as a component of materials used in manufacturing, packing, packaging,

transporting, or holding food if such use is not intended to have a technical effect
in such food.”\(^2\) This guide is not intended to apply to food contact substances.

- **Color Additives:** GRAS does not apply to color additives. Color additives are subject to separate regulations that include specific procedures for notification and/or approval.\(^3\) They are not within the scope of this guide and therefore are not discussed.

### III. General Information on Food Additives and GRAS Substances

The FDA provides the following succinct guidance for differentiating between food additives and GRAS substances:

> “Any substance that is reasonably expected to become a component of food is a food additive that is subject to premarket approval by FDA, unless the substance is generally recognized as safe (GRAS) among experts qualified by scientific training and experience to evaluate its safety under the conditions of its intended use, or meets one of the other exclusions from the food additive definition in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FFDCA). Any food additive that is intended to have a technical effect in the food is deemed unsafe unless it either conforms to the terms of a regulation prescribing its use or to an exemption for investigational use.”\(^4\)

> “General recognition” is understood to mean that the safety data used to support a GRAS position for a substance under specified conditions of intended use are publicly available and there is consensus by qualified experts in the field that such use does not raise safety concerns. For GRAS determinations based upon scientific procedure, 21 CFR 170.30(b) indicates that “publicly available data” is typically regarded as consisting of published studies. GRAS determinations require scientific evidence of comparable quantity and quality as that needed to support the safety of a food additive.

### A. Food Additives

Food additives follow a premarket review and approval process that involves the submission of a Food Additive Petition (FAP) along with the associated technical data package for review by FDA subject matter experts. Contingent upon the conclusion that the petitioned use and use levels do not present a safety concern, the review step is followed by an administrative procedural step. A new or amended food additive regulation is published in the Federal Register, followed by codification in the Code of Federal Regulations. The technical data submitted can be privately held and does not


need to be publicly available in published sources. The FFDCA provides FDA with 180 days to act on a FAP. However, the process has been known to take years to complete because the review clock is stopped when questions are asked of the petitioner and responses (which may include the generation of additional data) are developed.

B. **GRAS Substances**

Under sections 201(s) and 409 of the FFDCA, and FDA’s implementing regulations in 21 CFR 170.30, substances may be regarded as GRAS and therefore exempt from FDA premarket review and approval based on common knowledge and general acceptance among qualified scientific experts that the substance is safe for its intended use. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958 through experience based on common use in food. Substances that cannot meet the common knowledge criteria are not eligible for GRAS status consideration.

FDA guidance on GRAS further clarifies as follows:

- Under 21 CFR 170.30(b), general recognition of safety through scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive and ordinarily is based upon published studies, which may be corroborated by unpublished studies and other data and information.

- Under 21 CFR 170.30(c) and 170.3(f), general recognition of safety through experience based on common use in foods requires a substantial history of consumption for food use by a significant number of consumers prior to January 1, 1958.

Any substance that meets the specified criteria indicated above can be regarded as GRAS under the conditions of intended use and can be introduced into the U.S. market. The sponsor of a GRAS determination may exercise one of two options for adding their GRAS substance to a food:

- GRAS notice to the FDA; or
- GRAS self-determination.

**GRAS Notices**

A GRAS notice includes information on identity, manufacturing, application, and safety, which forms the basis for the conclusion that the substance is GRAS.

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5 The information in a food additive petition is available to the public through a request under the Freedom of Information Act, except for confidential business information.

6 In 1997, FDA replaced the GRAS affirmation process with a proposed voluntary notification procedure.

Within 30 days of receiving the notice, the Agency informs the notifier that the notice has been received. FDA targets 180 days to respond to a GRAS notice with one of three types of letters:

- The first type of letter advises that the Agency has “no questions” regarding the basis for the notifier’s GRAS determination. This means that the notifier may begin marketing the substance. GRAS Notices that receive a “no questions” letter are listed in FDA’s GRAS Notice Inventory.
- The second type of letter advises the notifier that the GRAS notice does not provide a basis that the substance is GRAS.
- The third type of letter states that the Agency has ceased to evaluate the GRAS notice, at the request of the notifier.

**GRAS Self-Determinations**

GRAS substances that do not go through the notification process are commonly referred to as “self-determined GRAS” or “self-GRAS” substances. GRAS self-determinations, like GRAS notifications, must be based on either:

1. use prior to 1958; or
2. scientific evidence of comparable quantity and quality as that needed to support a GRAS notice or a Food Additive Petition.

Regardless of which option the GRAS sponsor chooses, upon request of the FDA, the sponsor must make available all specific data supporting their GRAS conclusion. Further, as safety data made available at the time of a determination of GRAS status can change over time, under 21 CFR 170.30(l) the availability of new information may at any time require reconsideration of the GRAS status of a food ingredient. Additionally, FDA has the authority to act if the Agency disagrees with a GRAS position.

**Additional GRAS Considerations**

One advantage to the food industry of the self-determined GRAS and GRAS notification processes versus the FAP process is shorter time to market. The food industry is fast paced and competitive, with a strong focus on innovation driven by consumer preferences. The current FAP process is in general a much longer process than GRAS and can inhibit the industry’s ability to keep pace with technology and meet rapidly evolving consumer demands. A properly developed GRAS determination contains the same information as a FAP to support its use in food, and the shorter timeframe allows industry to more quickly respond to market demands for new and innovative products.

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9 U.S. Food and Drug Administration. GRAS Notice Inventory. [http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/](http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/)
GRAS also allows the food industry to more quickly harmonize with other recognized national and international standards (e.g., Codex and JECFA specifications). As such, the GRAS process provides producers with a mechanism to address situations that may otherwise be viewed as inadvertent technical barriers to trade.\textsuperscript{10}

Further, the GRAS notification and self-determined GRAS processes have their own specific advantages and disadvantages. The GRAS notification process informs the FDA and results in an acknowledgement (albeit not an approval) that the substance is safe and may be marketed. The disadvantage is that because it is public, there is no protection of investment and proprietary information made by the sponsor to determine the GRAS status. The primary advantage of the self-determined GRAS position is to develop a general recognition of safety by the qualified experts while protecting the sponsor’s proprietary information. The conclusion of the experts is unique to the individual sponsor and does not preclude a different sponsor from developing the same or a similar GRAS position.

IV. GRAS Guiding Principles

Following are several guiding principles for making a GRAS determination.

- Food additives and GRAS substances must demonstrate the safety of the substance on the basis “that there is reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.”\textsuperscript{11}
- Producers and users of food ingredients may use the GRAS notification process to provide the FDA with the information to support a GRAS claim.
- The data needed to support the safety of a food additive or a GRAS substance is the same, except the data needed to support a GRAS position must be publicly available.
- GRAS positions should be unbiased and free of conflicts of interest.

V. Considerations for a Robust GRAS Assessment

GRAS determinations must be based on sound science and unbiased by business pressures. To ensure that the GRAS assessment is robust, the sponsor should first determine the scope of safety review which includes the following factors.

\textsuperscript{10} The World Trade Organization (WTO) oversees the Agreement on Technical Barriers to Trade (TBT) “to ensure that regulations, standards, testing and certification procedures do not create unnecessary obstacles, while also providing members with the right to implement measures to achieve legitimate policy objectives, such as the protection of human health and safety, or the environment.” \url{http://www.wto.org/english/tratop_e/tbt_e/tbt_e.htm}

\textsuperscript{11} 21 CFR Part 107.3(i)
A. Selection of Experts

1. Criteria for Experts

The FFDCA and FDA’s implementing regulations require that the experts participating in the GRAS review must be qualified by training and experience to evaluate the safety of substances added to foods. However, neither Congress nor FDA deemed it necessary to establish specific criteria or a definitive checklist or test for experts to assess their qualifications.

In the absence of further specificity, the decision on expert selection should take into account the role of the experts in the review process and the sponsor’s obligation to ensure that the added substance meets the safety standard of reasonable certainty of no harm under conditions of intended use.

The primary work product of the expert(s) participating in the GRAS review process is to critically evaluate the prepared technical data package of the proposed GRAS substance for completeness and scientific accuracy and to determine if the GRAS status can be confirmed.

Therefore, it is vital that the experts selected have the specialized knowledge and independence to make the appropriate decision. Additionally, as the opinions of these experts must be representative of the scientific community and knowledgeable about the safety of substances, they are recognized as subject matter experts in their particular field(s)/discipline(s).

Due to the wide variation in the types of substances and intended uses, in practice, the decision on how many experts are needed and which specific disciplines should be directed by the nature of the substance, the intended use of the substance, and the proper assessment of safety. However, maintaining a process for selecting experts will help ensure consistency in approach and assure that excellent and independent opinions are obtained.

As a guideline, experts with the following areas of expertise are most often requested to serve on GRAS review panels: toxicology, pharmacology, chemistry, microbiology, biochemistry, metabolism, medicine, nutrition, exposure assessment, food technology and statistics.

Qualifications of experts may include, but are not limited to, the following:

- advanced degrees in chemistry, biology, food science, toxicology, pharmacology or other relevant biosciences;
- extensive experience in food safety risk assessment and/or equivalent areas with respect to food additives, specifications, impurities and/or exposure assessment;
• significant scientific publications in peer-reviewed journals and/or relevant publications;
• participation in national or international scientific organizations and committees, pertinent to the above disciplines and described tasks; and/or
• certifications in their field of expertise.

2. Conflicts of Interest

IFAC supports processes to minimize potential conflicts of interest when organizing GRAS reviews and/or opinions. Following are several considerations regarding conflict of interest.

• A particular strength of a GRAS opinion is that it is an independent determination by qualified experts. It is reasonable to expect that company employees will be relied upon for their technical expertise regarding a substance under review. However, employees should not participate in the final determination.

• When a qualified expert retained by a company is asked to complete a GRAS review, any prior relationship between the qualified expert and the company should not constitute a conflict of interest by definition.

• Financial compensation for an expert’s time to review a GRAS determination should not constitute a conflict of interest. It would be impossible to have qualified experts evaluate GRAS materials without some compensation being provided for their time.

B. Development of a Technical Data Package

The technical data package for the GRAS evaluation must contain all relevant information to adequately show that the substance under consideration is safe under the conditions of its intended use. Information on identity, manufacturing and safety should be included to enable the panel to perform an assessment of the substance and its intended use in foods.

The following general principles should be considered when developing the technical data package:

• The data presented should be comprehensive (including favorable and unfavorable information).

• The data elements included should be consistent with the appropriate FDA guidance documents available on the FDA website.12 The rationale FDA

provided therein on the level and type of data to include should be deliberately
considered and addressed accordingly.

The following outline and subsequent sections describe the type of information that
may be included in a technical data package submitted for a GRAS determination.
Depending on the nature of the substance and/or the focus of the GRAS
determination, not all of this information may be necessary or relevant; therefore,
this list should not be regarded as compulsory.

1. Identity of the Substance

The substance should be characterized as completely as possible to provide a
description of the substance and the following pertinent information, if
applicable, to define the material including but not limited to identity, purity and
method of manufacture.

a. Product description (examples):
   i. Common or usual name, other names used
   ii. Chemical name or Systematic/accepted name\(^\text{13}\)
   iii. INS number
   iv. General description of starting material
   v. CAS registry number (or Latin binomial, strain, type registry)
   vi. Molecular and structural formula

b. Manufacturing process:
   i. Raw materials
   ii. Process description (and flow diagram)
   iii. Processing aids/additives
   iv. In-process quality controls

c. Specifications for identity and purity and confirmation of food-grade status
   (as appropriate):
   i. A description of the substance (e.g., physical form, odor, color, and
      solubility and other relevant chemical & physical attributes including,
      ash content, moisture content, particle size distribution, melting point,
      density, refractive index, pH, etc.).
   ii. Conformance to established food grade specifications (e.g., FCC,
      JECFA, etc.),
   iii. Compositional profile, including:
      A. Purity assay/compositional analysis\(^\text{14}\)
      B. Impurity profile
         1. Heavy metals (e.g., lead)
         2. Pesticide residues
         3. Environmental contaminants

\(^\text{13}\) For substances of microbial origin, should include ATCC, DSMZ, etc.

\(^\text{14}\) Complexes derived from natural sources that are not chemically defined should be adequately characterized.
4. Extraction and processing by-products and residues
5. Unreacted raw materials
C. Other (e.g., assessment of potential presence of allergenic substances or sensitizers)
   iv. Analytical methodologies to measure specifications
   v. Certificates of Analysis of 3-5 non-consecutive lots of material demonstrating conformance to specifications

d. Stability data
   i. Degradation products/food matrix effects
   ii. Analysis of impurities and/or degradents (if needed)
   iii. Reevaluation, retest and/or expiration date

2. Intended Use of the Substance

   a. Proposed use of substance
      i. Food categories in which substance will be used (e.g., Codex General Standard for Food Additives categories)
      ii. Proposed typical use level and maximum use levels
      iii. Any self-limiting levels of use

   b. Functionality
      i. Description of the intended use/effect
      ii. Proposed use level

3. Safety and Toxicology of the Substance

   As noted previously, general recognition indicates a comprehensive review of published literature for determining the safety of the substance and any impurities, contaminants or degradation products as appropriate. Generally recognized toxicological data should be published in a peer-reviewed journal prior to being included in a GRAS notification. A recommended sequence to gathering the needed data follows:

   • Perform a comprehensive literature search to document history of use and identify the availability of published literature to support common knowledge element.

   A comprehensive literature search should include scientific databases (e.g., PubMed, Toxline, Agricola) and official safety reviews (e.g., JECFA). The review should include both positive and negative studies, if reported.

   The literature search should focus on the biochemical fate and toxicity of the substance and structurally-related substances. Inclusion of all relevant
data on pharmacokinetics, metabolism and enzyme induction is strongly encouraged.

The FDA “Concern Levels” should be considered when designing the criteria for the literature review. “Concern levels”, as determined by the agency, are “’relative measures of the degree to which the use of an additive may present a hazard to human health’. The concern level is based on the extent of human exposure (dose) and the toxicological effects on biological systems. There are three broad bands of concern levels. Concern level three represents the highest probable risk to human health. Concern level one represents the lowest probable risk. Concern level two is intermediate between high and low risk.”\(^\text{15}\)

Based on concern level, the expert needs to identify applicable studies needed to support the safety of the proposed GRAS substance considering the intended use. The substance should be well characterized with an in-depth understanding of the structure and the method of manufacture. Studies utilizing similar substances can be considered to augment the “strength of argument” to aid in the determination of the safety of the GRAS substance. Experts should have the appropriate background to understand the substance and be able to develop a scientific argument based on the weight of evidence to establish the safety of the substance.

- Review the studies identified in the literature search.

The literature search should be reviewed against the objectives, as defined, during the development of the scope of the safety review. The studies should be evaluated on the basis of quality and their applicability to the substance’s intended use. The quality of the studies should be balanced against the data requirements. For example:

- Are the studies conducted under Good Laboratory Practices?
  - If not, the results need to be justified as supporting information.
- Is the test article well characterized and representative of the substance under review?
  - If not, the applicability of the study should be explained.

In general, the totality of the available studies should be considered in the determination whether a specific endpoint is satisfied.

• Perform a gap analysis

Following evaluation of the literature review, the sponsor should identify any additional studies that may be needed to support the safety of the substance for its intended use (i.e., a gap analysis). The sponsor should conduct a thorough review of the substance by any regulatory bodies to identify potential limitations and additional data requirements that could impact the intended use.

• Commission studies to fill identified data gaps (if necessary)

To address the data gaps, the sponsor should commission carefully designed studies to demonstrate the safety of the substance for its intended use. Guidance from FDA, the Organisation for Economic Co-operation and Development (OECD) and the World Health Organization’s International Programme on Chemical Safety (IPCS) are available and should be referenced when designing and conducting toxicological studies for food ingredients. The qualifications of the laboratory must be identified and documented. It is expected that these studies would be published in an appropriate scientific venue such as a peer reviewed journal, conference proceedings, or other publicly available sources. For general guidelines on relevant toxicity studies, please see Appendix C.

Intake and Exposure Assessment

As an Industry Best Practice, intake and exposure assessments are developed using resources that provide information on food categories and dietary exposure. Information on food categories is provided by FDA, the Codex General Standard for Food Additives (GSFA) and the National Health and Nutrition Examination Survey (NHANES). Information on dietary exposure is provided by NHANES and other published sources.

Other sources of data can be used if properly justified. Many additional factors such as frequency, portion size, and food ingredient concentration are taken into account (i.e., Food Intakes of Sub-populations, Types of Food Intake Estimates (Chronic Intake, Acute Intake), Statistical Approaches to Data Analysis, Upper Percentile Estimates and Probabilistic Modeling).

20 NHANES can be effectively used for demographic populations to estimate the Intake of a Food Ingredient in a food category.
The Office of Food Additive Safety (OFAS), within FDA’s Center for Food Safety and Applied Nutrition (CFSAN), provides guidance\textsuperscript{21} for estimating exposure.

**Safety Assessment**

Safety assessment consists of hazard identification and characterization, exposure assessment, and risk characterization. Depending on the global regulatory status of the substance, the following information should be considered when making a safety assessment:

- Identify scientific basis (including history of use, if available) including:
  - All relevant national, regional, and international regulatory status of use of the substance or related substances in food or other applications (e.g., pharmaceuticals, dietary supplements, etc.).
  - Natural occurrence of the substance in foods.
  - Discussion of any record or indication of adverse effects.

- Safe strain lineage: For fermentation products, safety of the production strain remains the primary consideration in evaluating product safety, in particular, the toxigenic potential of the production strain.\textsuperscript{22,23}

4. Relevant studies on the substance or closely related compounds. These studies can include data on the biochemical fate and toxicity of the substance including relevant data on pharmacokinetics, metabolism and/or enzyme induction.

The safety assessment should be conducted by an expert with the necessary skills to properly evaluate the available safety data and the dietary exposure. The safety assessment should include information on susceptible populations. Any uncertainties in the safety assessment should be adequately addressed.

Generally, the acceptable daily intake (ADI) level is calculated from the no-observed-adverse-effect level (NOAEL) from the pivotal studies. Safety factors, which are to account for differences between animals and humans and differences in sensitivity among humans,\textsuperscript{24} may be applied to the NOAEL.


Typically a 100 fold safety factor is used; if properly justified, other safety factors may be used. The use of greater or lesser safety factors should be considered on a case-by-case basis, with consideration of food additive-specific factors, such as toxicokinetic parameters and chemical and physical properties. Regardless, there should be an adequate margin of safety when comparing the NOAEL to the estimated exposure.

VI. USDA and GRAS

The U.S. Department of Agriculture (USDA) will only consider substances that have undergone a safety assessment by FDA. USDA exercises discretion for proposed expanded uses of substances.

VII. Conclusion

The modern food industry is innovative and very competitive. The industry needs to respond quickly to changing consumer preferences with creative products. The Generally Recognized as Safe (GRAS) process provides a transparent, robust, effective and responsive system to address industry needs while protecting public safety. The GRAS process places the ultimate safety assessment of the ingredient on the sponsor of the GRAS determination and the user of the GRAS substance. GRAS recognition involves the evaluation of the publicly available science, by the experts who must reach a consensus to determine if a substance is GRAS for an intended use.

The United States has a long history of a safe and stable food supply. This is due to industry’s commitment to follow a robust and scientific process to ensure safety for the intended use. The GRAS process is one of the tools used by industry to ensure safety while fostering product innovation.
Appendix A – List of Acronyms

ADI – Acceptable Daily Intake
AOAC – Association of Official Analytical Chemists
ATCC – American Type Culture Collection
CAS – Chemical Abstracts Service
CFR – U.S. Code of Federal Regulations
CFSAN – Center for Food Safety and Applied Nutrition
DSMZ – German Collection of Microorganisms and Cell Cultures
FAO – Food Agriculture Organization
FAP – Food Additive Petition
FCC – Food Chemicals Codex
FDA – U.S. Food and Drug Administration
FEMA – Flavor and Extract Manufacturers Association
FFDCA – Federal Food, Drug and Cosmetic Act
GRAS – Generally Recognized As Safe
GSFA – General Standard for Food Additives
ICPS – International Programme on Chemical Safety
IFAC – International Food Additives Council
INS – International Numbering System
JECFA – Joint FAO/WHO Expert Committee on Food Additives
NHANES – National Health and Nutrition Examination Survey
NOAEL – No Observed Adverse Effect Level
OECD – Organisation for Economic Co-operation and Development
OFAS – Office of Food Additive Safety
TBT – Technical Barriers to Trade
USDA – U.S. Department of Agriculture
WHO – World Health Organization
WTO – World Trade Organization
Appendix B – Glossary

As used throughout this Guide, the terms below have the following meaning.

Certificate of Analysis
A document listing the test methods, specification and results of testing a representative sample from the batch to be delivered.

Color Additive
A color additive is a dye, pigment or other substance, which is capable of imparting color when added or applied to a food, drug, cosmetic, or to the human body. The legal definition can be found in Section 201(t) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and provides exclusions as well. Color additives for use in food, drugs, and cosmetics require premarket approval. Color additives for use in or on a medical device are subject to premarket approval, if the color additive comes in direct contact with the body for a significant period of time.

Common Use
Per 21 CFR Part 170.30(c) and 170.3(f), “common use in foods requires a substantial history of consumption for food use by a significant number of consumers.”

Conflict of Interest
A situation in which a person is in a position to derive personal financial benefit as a result of a particular action or decision in which the person has a significant role.

Food Additive
A food additive is defined in Section 201(s) of the FD&C Act as 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 characteristic of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use); if such substance is not GRAS or sanctioned prior to 1958 or otherwise excluded from the definition of food additives.

Food Contact Substance
Section 409 of the FD&C Act defines an FCS as any substance that is intended for use as a component of materials used in manufacturing, packing, packaging, transporting, or holding food if such use of the substance is not intended to have any technical effect in such food.

Food Ingredient
Any substance that is added to a food to achieve a desired effect.

Functionality
The intended effect(s) of a substance added to food.
GRAS Substance
"GRAS" is an acronym for the phrase Generally Recognized As Safe. Under sections 201(s) and 409 of the FD&C Act, any substance that is intentionally added to 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, or unless the use of the substance is otherwise excluded from the definition of a food additive. GRAS substances are distinguished from food additives by the type of information that supports the GRAS determination, that it is publicly available and generally accepted by the scientific community, but should be the same quantity and quality of information that would support the safety of a food additive.

Manufacture/Manufacturing Process
All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release and storage of food additives and GRAS substances and related controls.

Producer
A company that makes, sells and is ultimately responsible for a commodity (i.e., a food additive, GRAS substance, food or dietary supplement).

Production
Operations involved in the preparation of a food additive or GRAS substance from receipt of materials through processing and packaging of the food additive or GRAS substance.

Sponsor
A person or organization that provides funds for a project or activity (i.e., a GRAS determination).

Stability
Continued conformance of the food additive or GRAS substance to its specifications.
Appendix C – General Guidelines for Toxicity Studies

Following are general guidelines on the toxicity studies a sponsor may wish to consider to address any gaps identified through a literature search. General considerations for these studies include test substance characterization, experimental design for studies, metabolites, effects on nutrition and others. (For more detailed descriptions of these studies, refer to the FDA Redbook, Organisation for Economic Co-operation and Development (OECD) Guidelines, World Health Organization’s International Programme on Chemical Safety (IPCS), and/or other international guidelines.)

Genotoxicity/mutagenicity assays

A battery of short-term genetic toxicity tests are used to directly measure gene mutations and/or chromosomal effects. Genotoxicity tests are in vitro and in vivo tests designed to detect compounds that induce genetic damage.

Animal toxicity studies

A. Acute

The food ingredient supplier should determine if acute toxicity studies are useful for the safety assessment.

B. Short-term (subacute)

Short-term toxicity studies with rodents are generally conducted for 28 days. These types of studies may be used for bridging to other studies on similar materials.

C. Subchronic

Subchronic toxicity studies with rodents are generally conducted for 90 days but may be conducted for up to 12 months. A well designed subchronic study can provide significant data to evaluate specific effects.

D. Carcinogenicity/chronic toxicity

A carcinogenicity study may be combined with a chronic toxicity study to reveal information about a food ingredient’s potential to cause long-term toxicity, in addition to tumor development and evaluation. Addition of parameters for evaluation of chronic toxicity may include hematology, clinical chemistry, organ weights, and other general toxicity parameters, as well as determination of the highest dose with no adverse effects, to maximize the information collected in the carcinogenicity study. Combining both chronic toxicity and carcinogenicity endpoints allows judicious use of animals and other resources.
E. Reproduction/developmental

To evaluate reproductive effects, consideration should be given to a multi-generation reproductive study.

F. Special toxicological studies

Specially designed toxicological studies may be needed based on the interpretation of previous studies and to explore findings from previous studies or special endpoints that may have been indicated from previous studies, for example, target organs or systems, immunotoxicity, etc.

G. Information related to tolerance, metabolism, allergenicity, and nutritional effects on the general population or sensitive populations (infants, immunocompromised) should be included in the overall evaluation.