ANNOTATED GUIDE

A Guide to Submitting New or Modified Ingredient Definitions to AAFCO

GENERAL REVIEW GUIDANCE

The SRIS program and this review guidance closely follow the United States Food and Drug Administration (FDA) regulations and guidance for Generally Recognized as Safe (GRAS) conclusions. FDA's relevant published information can be helpful and is provided as references at the end of this guidance.

The role of the Expert Panel is to review the submitter's conclusion of generally recognized as safety for the intended use of a feed ingredient; to assure that the cited information is sufficient to demonstrate safety and support a new or modified AAFCO Feed Ingredient Definition.

The general recognition of safety of a substance for use in animal food may be based on the acceptance by the appropriate scientific experts and requires common knowledge, which form the basis for making a GRAS conclusion. Thereby the review of a SRIS submission, is based on pivotal safety data having been published in peer-reviewed journals or other recognized resources including textbooks and publications by respected global scientific and regulatory organizations. These resources may include US scientific journals or other peer-reviewed international journals, with the principles of the safety of the use of a proposed substance reflecting US conditions. Other examples of established references can include textbooks, National Research Council (NRC)[1] publications, Joint FAO/WHO Expert Committee on Food Additives (JECFA)[2] reviews and findings, European Food Safety Authority reviews and findings (as published in the EFSA journal), Flavor and Extract Manufacturers Association (FEMA)[3], GRAS reviews, published GRAS Notices, other published ingredient use rates, and other science-based reference books that are generally available and accepted. Additionally, data and information from published peer-reviewed journal articles that address safety in comparable use conditions or physiologically relevant to the target animals can be used as bridging information to address any data gaps to meet general recognition standards and acceptance. The safety assessment can also be corroborated by use of well-written scientific reports of adequately powered and well-controlled studies that were not published.

Under the FDA GRAS regulations 21 CFR 570, evidence of intended use (utility) is only required as part of the safety narrative when such information is pertinent to safety. Generally, thought of as the "if the product fails at its intended use" will there be harm to the animal principle. Examples of when utility-type data are needed would be: (a) a substance that is

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[1] NRC is the principal operating arm for the National Academies of Science, Engineering, and Medicine.

[2] JECFA is an international scientific expert committee administered jointly by the Food and Agricultural organization (FAO) and the World Health Organization (WHO) of the United Nations. JECFA conducts safety and risk assessments of substances added to food, such as food additives, flavorings, and veterinary drug residues.

[3] FEMA is Flavor and Extract Manufacturers Association, a food industry trade group based in the US. FEMA maintains a Flavor Ingredient Library based on GRAS conclusions it makes.

intended to provide an essential nutrient; e.g., a novel source of a vitamin or mineral; (b) an enzyme that impacts the availability of an essential nutrient (e.g. phytase as it will make phosphorous available); or (c) a substance intended to increase the safety of the feed such as an antimicrobial agent or a mycotoxin-detoxifying agent. Examples of GRAS substances that would not need scientific support of the intended use include: enzymes that degrade complex carbohydrates to increase the value of feed; live microorganisms that are commensals to that animal; flavors intended to alter the consumption of feed: and nutritional antioxidants. Data is not required to be published if used to simply support the rationale and conditions (not safety) of the intended use. However, it is encouraged that reviewers remember that under the law for GRAS requirements, utility is only required when associated with safety.

For SRIS reviews, submitters must additionally submit a proposed AAFCO ingredient definition with the submission. This is asked of the submitter beyond traditional GRAS. When evaluating this proposed definition, a justification of the definition should be represented in the safety data provided (which could include utility data). This is to ensure that the proposed levels of inclusion or use have been evaluated from a safety perspective.

Information to support the method of manufacture, as required in Part Two of the submission, requires sufficient detail to inform the safety review. However, as SRIS submissions will not be redacted if released under the Freedom of Information request, this section should not include confidential business information. Typical manufacturing processes used to make the subject GRAS substance should be published, e.g., as is the case for enzymes.

The expert panel review may raise questions to the submitter and a mechanism is in place for requesting supplementary information. If needed, the submission review will be placed on a temporary stop-clock while the information is gathered by the submitter to respond to the questions. The submission and review process are intended to be completed in one filing and are not intended to lead to submission returns and require re-filings. It is possible that if one or more issues identified during the review needs to be addressed, such issue(s) can be resolved within the SRIS specified timelines (less than 14 calendar days for questions or less than 30 calendar days for additional information requests) unless otherwise agreed to by SRIS, and the final decision can be made based on the totality of information available to the panel.

After the expert panel evaluation is complete, a recommendation is made by the panel to the AAFCO Ingredient Definition Committee (IDC) whether the safety conclusion made by the submitter is sound and that the ingredient, as described by the proposed definition, is suitable for inclusion in the AAFCO Official Publication (OP).

SUBMISSION REVIEW GUIDANCE

Below are the instructions that are provided to submitters of the SRIS submission; the bolded and italicized information provide additional explanatory guidance to the experts reviewing the submissions. The respective AAFCO Investigator in conjunction with the SRIS program administrators at Kansas State University's Olathe Innovation Campus (K-State Olathe) will conduct a general review of the submission to ensure suitability to file the submission such that it may be reviewed by the Expert Panel. This pre-filing review is performed to ensure that

the submission contains reasonable information under each of the six specific Parts, as stated in the guidance to the submitter, while also ensuring that the proposed substance and its intended use are appropriate for a substance to be evaluated under the SRIS program. Once filed, the submission will be forwarded to the panel of experts selected by the SRIS program administrators for the detailed review of the submission. Generally, after the specified review period, the expert panel will assemble, discuss their independent findings, and form a final opinion about the safety of the proposed intended use of the substance and the proposed AAFCO ingredient definition. Accordingly, results from the SRIS panel will be used to make a recommendation to the AAFCO IDC whether to include the ingredient definition in the AAFCO OP.

If the review of the submission by the expert panel raises questions, then the submitter will be allowed to address these questions through a timed response window as determined by the SRIS program administrators. Once the questions are adequately addressed by the submitter, the panelists will assemble, make a safety determination on the substance under the described conditions of use, and further provide a written recommendation to the AAFCO IDC. Based on the review of the full submission, the expert panel may provide suggestions on altering the DRAFT AAFCO definition and/or the common or usual name of the proposed substance; these proposed alterations may be finalized in alignment with the AAFCO investigator and the submitter. The written recommendation report will be provided to the submitter for review prior to submission to AAFCO IDC. The submitter will have a designated amount of time (14 calendar days) to review the results and choose to sign off on the review for forwarding to AAFCO IDC or choose to withdraw the submission.

The following guidance provides additional details (*in bold, italicized font*) to the "Guide to submitting new or modified ingredient definitions to AAFCO" as approved by the AAFCO membership in August 2025. This is intended to provide more specific expectations of how the submission should be organized and considerations for the review by the expert panels.

A Guide to Submitting New or Modified Ingredient Definitions to AAFCO

Jump to Section:

Part One – Signed Statements & Certification

In Part One of your submission packet, you will:

1. Provide a statement that the filing meets the definition of GRAS. Inform AAFCO that you are submitting a Generally Recognized as Safe (GRAS) conclusion in accordance with 21 CFR 570 Subpart E;
2. Provide your name and the name and address of your organization.
3. Provide the common name of the substance, using an appropriately descriptive term.
4. Describe the intended conditions of use of the substance, including stating whether the substance will be added to food and/or drinking water for animals, identifying the form in which provided, the levels of use in such foods, and the animal species for which these foods are intended (including, when appropriate, a description of a subpopulation expected to consume the substance); and the purposes for which the substance will be used;

   The intended use (the intended animal species, physiological status, and level of use) will inform the safety assessment.

5. Provide a Proposed AAFCO OP Chapter 6 Ingredient Definition

   This ingredient definition is the basis of the request and the contents of the submission are expected to support the definition. Based on the contents of the submission, it should be possible to assure the safe use of the ingredient for the intended use in food or drinking water for the target species. The safety data provided in the submission, in addition to further information including manufacturing specifications, intended use, etc. should be discussed in the panel recommendation document addressed to the IDC. It is critical that this definition be justified in the submission's safety data, which can be accomplished through treatment selection and possible utility data if directly correlated to the safety of the ingredient's use. It is equally important that the ingredient definition is justified within the Narrative of the submission.

6. State your view that the substance is not subject to the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act based on your conclusion that the substance is GRAS under the conditions of its intended use;

   This is intended to be included as a declarative statement that the substance does not require premarket approval because it is GRAS for its intended use. Justification of this statement should be based on scientific data included in Parts 2,3, 4, and 6, and narrated in Part 5 of the submission.

7. Provide the full data package in parts 2 through 6 of the submission, as well as copies of all the published data to be relied on;

8. Certify, to the best of your knowledge, the submission packet is a complete, representative, and contains a balanced discussion that includes unfavorable information, as well as favorable information, known to you and pertinent to the evaluation of the use of the substance;
9. State the name, title, and contact information of the person responsible for submitting the AAFCO ingredient definition. It must be signed by a responsible official of your organization, or by your attorney or agent.

Part Two – Identity, method of manufacture, specifications, and physical or technical effect.

In Part Two of your submission packet, you must include:

1. Scientific data and information that identifies the substance.
    a. Examples of appropriate data and information include the chemical name, applicable registry numbers (such as a Chemical Abstracts Service (CAS) registry number or an Enzyme Commission (EC) number), empirical formula, structural formula, quantitative composition, and characteristic properties.
    b. When the source of a substance is a biological material, you must include data and information sufficient to identify:
        i. The taxonomic source (*e.g.*, genus, species), including as applicable data and information at the sub-species level (*e.g.*, variety, strain);
        ii. The part of any plant or animal used as the source
        iii. Physical form of the substance; and
        iv. Any known toxicants that could be in the source.
2. A description of the method of manufacture of the substance in sufficient detail to evaluate the safety of the substance as manufactured;

> ***Typically, raw materials that are authorized for use in the AAFCO OP (chapter 6) are considered safe. Raw materials used in the ingredient's production that are not authorized animal feed ingredients in their own right, may need to have a safety assessment or reference to assure the safety of the final substance. The safety of such raw materials may be addressed though information on common use in animal food in the U.S. or elsewhere, specifications and corresponding certificates of analyses, and/or published information in support of the safety of use of such raw materials. Additionally, these raw materials should be of feed grade or higher quality. For microbially derived ingredients, pre-manufacturing molecular biology or bioengineering information may be included in this section.***

3. Specifications for material that is of appropriate grade for use in animal food supported by 3 to 5 batch analysis;

Specifications should be defined to provide assurances of consistency of the substance across non-consecutive, discrete production batches. These specifications should be relevant to the intended use (including utility) and safety of the substance. The specifications should be in reasonable alignment with and taking into consideration the data and information included in analyses reports on typically three to five non-consecutive batches should be included in the submission.

4. Summary statement to support stability of ingredient;

Stability may be supported by stability studies or reference to a similar authorized ingredient's stability. Summary information on both the stability of the substance as marketed and once added to relevant feed matrices for appropriate time periods and storage conditions should be provided.

5. Summary statement that validated analytical methods and/or citation of published methods were used to support testing;

All used analytical methods should be validated for the matrix, and a statement confirming that is needed. Reference to official published methods used for analyses or a confirmation statement that the analytical method is properly validated in the respective matrices should be included.

6. Utility data is only required when the intended use of the ingredient has an impact on the safety of the feed.

While utility data are only required when the intended use of the ingredient has an impact on the safety of the feed, it is helpful to include data to demonstrate the ingredient functions as intended in order to assess safety at the intended use level. Utility studies can be from generally available literature or can be based on reports of adequate and well-controlled studies that have not been published. In some situations, in vitro studies can be acceptable alternatives to in vivo studies, provided the assay metrics and conditions are reasonably representative of the potential effects and conditions in the animal. In the instances when in vitro assays are referenced, it is favorable that the treatments of interest are also reviewed in an in vivo manner to justify the data. While this may not be necessary in all circumstances (i.e. specific mechanism of action investigations) it is viewed favorably if the in vitro results relate to in vivo observations.

Part Three – Target animal & human exposures

In Part Three of your submission packet, you must provide data and information about exposure to the target animal and, if applicable, to humans consuming human food derived from food- producing animals.

This is a Draft Working Document

1. Target Animal Exposure
   For exposure to the target animal, you must provide:
   a. The amount of the substance that different target animal species are likely to consume in the animal food (including drinking water, if that is applicable) as part of the animal's total diet, including the intended use and all other sources in the total diet;

   This is commonly a simple mathematical calculation based on the directions for use of the ingredient and the animal species (and stage of growth). Intake estimates should be based on generally available information from reputed sources such as NRC publications and, typically from a maximum or worst case estimation basis;

   b. When applicable, the amount of any other substance that is expected to be formed in or on food because of the use of the substance (*e.g.*, hydrolytic products or reaction products) that are of potential safety concern; Justifiable verbiage or analytical method citations should be included for any quantitative data when applicable.
   When applicable, the amount of any other substance that is present with the proposed substance either naturally or due to its manufacture (*e.g.*, contaminants or by-products). Justifiable verbiage or analytical method citations should be included for any measured quantitative data when applicable.

   The potential contaminants, impurities, and toxicants per the product specifications included in Part Two of the submission should be considered here;

   c. The data and information you rely on to establish the amount of the substance and the amounts of any other substance in accordance with paragraphs a-c of this section that different target animal species are likely to consume in the animal food (including drinking water) as part of the animal's total diet.

   The final safety assessment (as found in the Narrative Part Five) should be based on the exposure estimates as found in this Part.

2. Potential for Human Food Exposure
   When the intended use is in food for food-producing animals, you must provide:
   a. The potential quantities of any residues that humans may be exposed to in edible animal tissues (***milk, meat, or eggs***), including:
      i. Residues of the substance;

ii. Residues of any other substance that is expected to be formed in or on the animal food from the use of the substance; and
iii. Residues from any other substance that is present with the substance whether naturally, due to its manufacture (*e.g.*, contaminants or by-products), or produced as a metabolite in edible tissues when the substance is consumed by a food-producing animal.

This section may typically be based on a mathematical calculation by species to the amount of ingredient fed over the specifically designated period (worst case scenario). It may be based on the understanding of the absorption, distribution, metabolism, and excretion of the ingredient, for example a novel form of an essential ingredient would be metabolized similarly to the currently authorized forms. It may also be supported by data generated from a residue study; however, it should be noted that a residue study or presentation of residue data is warranted only if the substances deposited in edible tissues are of toxicological or nutritional relevance.

b. The data and information you rely on to establish, in accordance with paragraph (a) of this section, the potential quantities of any residues that humans may be exposed to in edible animal tissues.

Part Four – Self-limiting levels of use

In Part Four of your submission packet, you must include data and information on self-limiting levels of use in circumstances where the amount of the substance that can be added to animal food is limited because animal food containing levels of the substance above a particular level would become unpalatable or technologically impractical.

It is not common for substances used as an animal food ingredient to have a self-limiting level of use within their intended level (or range) of inclusion. An example of self-limiting levels of use would be: (a) a product that includes salt; (b) a product that causes diarrhea at high inclusion levels causing animals to go off feed after a period of feeding; or (c) an ingredient that has a disagreeable taste.

Part Five – Narrative

In Part Five of your submission packet, you must include a narrative that provides the basis for your conclusion of safety, in which:

1. You must explain why the data and information in your submission provide a basis for your view that the substance is safe under the conditions of its intended use for both the target animal and, if applicable, for humans consuming human food derived from food-producing animals. In your explanation, you must address the safety of the substance, considering all animal food (including drinking water) as

part of the animal's total diet, considering any chemically or pharmacologically related substances in such diet. In your explanation, you must also address the safety of the substance regarding human exposure, considering all dietary sources and considering any chemically or pharmacologically related substances;

   a. In your explanation, you must identify what specific data and information that you discuss in accordance with paragraph 1 of this part are generally available, and what specific data and information that you discuss in accordance with paragraph 1. of this part are not generally available, by providing citations to the list of data and information that you include in Part Six of your submission.

2. You must explain the generally available data and information that you rely on to establish safety in accordance with paragraph 1 of this part (i.e., that you consider pivotal to the safety evaluation) and provide a basis for your conclusion that the substance is generally recognized, among qualified experts, to be safe under the conditions of its intended use for both the target animal and, if applicable, for humans consuming food derived from food-producing animals;
3. You must either:
   a. Identify, discuss, and place in context, data and information that are, or may appear to be, inconsistent with your conclusion of safety, regardless of whether those data and information are generally available; or
   b. State 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 safety.
4. For non-public, safety-related data and information (corroborative data) considered in reaching a conclusion of safety, you must explain how there could be a basis for a general conclusion of safety if qualified experts do not have access to such data and information.
5. Two separate conclusions must be provided as a part of the overall safety assessment: one specific to target animal safety and one for Human food safety. Within human food safety with regard to potential residues or associated with safety human gut microbiome should be provided as appropriate.

The panelists should ensure that the pivotal safety argument provided by the submitter is based on generally available and accepted information. Unpublished or proprietary information can be used as secondary or supporting evidence to corroborate the safety argument. The expert panel, based on the totality of evidence provided in the submission, including generally available and accepted pivotal safety information, will make a recommendation whether the described ingredient when used in accordance with Part One sections 4 and 5 (draft definition) is safe. Traditional Target Animal Safety studies are not required to establish the safety of the intended use of an ingredient, as it depends on the scientific understanding of the substance and structurally related substances, as well as their

history of use. For example, commensal live organisms that are supported by studies specific to the potential toxicity or pathogenicity of the microbial species is often the basis of the safety assessment. Similarly, microbially-produced enzymes, which are proteins, often are evaluated based on the comprehensive evaluation of the safety of the source organism including products derived therefrom together with a decision tree safety analysis. For microbially derived products, the concept of safe strain lineage of the production organisms should address relevant safety questions, together with molecular biology and sequencing information, the summary of which may be included in the manufacturing information included in Part Two, section 2 of this document. Target animal studies for nutritional ingredients should consider the nature of the substance and limitation on inclusion levels to avoid imbalances in the diet. As such, studies on macronutrients would normally evaluate a measure of digestibility, performance and routine blood parameters within nutritionally relevant inclusion levels. For ingredients present only at very low levels, internationally recognized safety assessment tools such as the threshold of toxicological concern (TTC) approach may also be pertinent. When addressing target animal safety in companion animals, euthanasia and tissue pathology is typically not recommended. If a study is necessary, it is typically a lengthy study in which animal, blood, and fecal assessments (as informed by the ingredient) are used as pivotal parameters. Generally, the professional training and experience of the expert panelists will guide in decision on the adequacy of data to support the safety. The safety assessment must conclude both the target animal safety and, when fed to production animals, the human food safety.

Part Six – List of supporting data and information in your submission

1. In Part Six of your submission packet, you must include a list of all of the data and information that you discuss to provide the basis for your review that the substance is safe under the conditions of its intended use in Part Five (1)(a);

This list should be organized by part, with the understanding that certain studies may be replicated between parts. This formatting is designed to aid the reviewer during the evaluation process to understand which data will be referenced within the specified part of the submission.

2. You must specify which data and information that you list in accordance with paragraph 1 of this part are generally available, and which data and information are not generally available.

You must provide copies of the reference materials that are used in the preparation of the submission. These copies are to be submitted in alphabetical order in a PDF separate from parts 1-6 of the submission. In the case that the file is too large to upload. The submission can be divided into two files based on first author's last name: file 1: A to M and file 2: N to Z.

Resources

FDA and others (International Cooperation for the Convergence of Technical Requirements for the Assessment of Feed Ingredients) have published guidance documents describing the information that may be considered when drafting GRAS conclusions. FDA Guidance for Industry (GFI) 221 provides some guidance and hyperlinks to other potentially useful guidance documents.

Additionally, FDA GFI 262 contains a general structure of a final study report of studies intended to address the utility and safety of animal food ingredients.

The following resources were identified as potentially valuable references to support your understanding of ingredient submissions if you desire to seek out additional guidance.

AAFCO Official Publication, Section 30. Enzymes, Enzyme Marketing Coordination document.

Federal Food Drug and Cosmetic Act, Section 201 Definitions (GRAS and Food Additives)

21 CFR 570 Subpart E Generally Recognized as Safe (GRAS) Notice
This document outlines key definitions as they pertain to GRAS as well as elements of GRAS submission to FDA which SRIS follows the requirements of.

21 CFR 570 Sub Part B

- 570.20 General principles for evaluating the safety of food additives.
- 570.30 Eligibility for classification as generally recognized as safe (GRAS).
- 570.35 Affirmation of generally recognized as safe (GRAS) status.

FDA GRAS Final Rule (148 pages)
This document provides the regulations but also the general thought process and answers to some regulatory issues.

Guidance for Industry 221. Recommendations for Preparation and Submission of Animal Food Additive Petitions
While this document pertains to Food Additive Petitions, it is often suggested for GRAS submissions as well.

FDA Guidance for Industry: Frequently Asked Questions About GRAS for Substances Intended for Use in Human or Animal Food October 2016

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

FDA Animal GRAS Notice Inventory (redacted Submissions and FDA responses)

Pariza, M.W. and M. Cook. 2010 Determining the safety of enzymes used in animal feed. Regulatory Toxicology and Pharmacology 56:332-342

Pariza, et. al. 2015. Determining the safety of microbial cultures for consumption by humans and animals Regulatory Toxicology and Pharmacology 73: 164-71.

Pariza, M.W. and E.A. Johnson. 2001 Microorganisms Evaluating the Safety of Microbial Enzyme Preparations Used in Food Processing: Update for a New Century Regulatory Toxicology and Pharmacology 33:173-186

International Cooperation for the Convergence of Technical Requirements for the Assessment of Feed Ingredients

- #01 – STABILITY TESTING OF FEED INGREDIENTS
- #02 – SUB-CHRONIC ORAL TOXICITY TESTING IN LABORATORY ANIMALS
- #03 HOMOGENEITY TESTING OF FEED INGREDIENTS
- #04 MANUFACTURING PROCESS AND SPECIFICATION
- #05 GENOTOXICITY TESTING
- #06 FEED INGREDIENTS ENVIRONMENTAL RISK ASSESSMENT APPROACH
- #07 IDENTIFICATION AND CHARACTERIZATION OF FEED INGREDIENTS – CHECK LIST
- #08 ADME EVALUATION IN THE CONTEXT OF RISK ASSESSMENT OF FEED INGREDIENTS
- #09 FEED INGREDIENTS ENVIRONMENTAL RISK ASSESSMENT (PHASE 2)